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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
23-09-2020	final in CREDI	N/A	N/A - First version	N/A
23-12-2020	Before FPFV	Data are not planned to collect Correct reference to be provided	Summaries for Protocol solicited medical history or medical history possibly contributing to liver dysfunction is removed Table 2-4 is updated with reference of section to 5.6	Section 2.3.1
		Urine pregnancy is not captured in CRF	Urine pregnancy summaries is deleted	Section 2.8.2
12-01-2021	Before FPFV	Child bearing status	Summary of females with child bearing status is deleted	Section 2.3.2
		Consistent analysis sets between DMC and CSR analyses	Table 2-8 is updated	Section 2.15
04-02-2021	Before FPFV	Additional ECG analysis requested by DMC committee for DMC review meetings		Section 2.8.3
11-11-2021	Before DMC#1	Analysis visit window for parasite count at 32 hours is to be corrected at 36 hours	Table 5-6 is updated	Section 5.1.4

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
27-12-2021	Protocol amendment	This SAP amendment is due to major amendment in protocol including change in objectives design, active comparator etc.	Title change	Section 1.1
			Study design is updated	
			Study objectives and endpoints are updated	Section 1.2
			Pooling strategies are further defined. Study treatment, Study Day, PCR-corrected ACPR are clarified.	Section 2.1
			[redacted]	Section 2.2.1, 2.13
			Treatment dispositions and compliance related analysis is simplified	Section 2.4.1
			Primary endpoint analysis is changed	Section 2.5
			Analysis of secondary endpoint is changed	Section 2.7.2
			Sample size section is modified	Section 3
18-01-2022		Non-compliance with food to be excluded from PPS and PK set	PD criteria for OTH04 is updated in Table 5-10	Section 5.8
		Impute missing concomitant medication date same as imputation of missing AE date	Delete imputation details for concomitant medication date	Section 5.1.3

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
09-10-2022		Address comments from the Novartis team and Medicines for Malaria Venture:	Stated the confidence interval level for individual cohorts if constructed. In the primary objective analysis, stated Cohort 2 to be analyzed mainly using descriptive statistics if Cohort 2 stops early;	Sections 2.1, 2.5, and 2.7.2;
			Added additional analysis for FCT by excluding patients who took anti-pyretic drugs prior to FCT;	
			Added a note that patients who take non-study anti-malarial medication due to repeated vomiting of study medication should be considered as treatment failure	Sections 2.5.4 and 2.7.2
			Added a bullet to consider a patient as PCR corrected 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 new infection at Day X using PCR genotyping or later if Day X is missing and another bullet to indicate that new infection at a visit causes PCR-corrected ACPR status unknown in later visits	Section 2.1.1.2
			Revised the Per Protocol set (PPS) to exclude new infections before Day 29	Sections 2.2 and 5.8

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Revised the analysis visit window for Day 29 in Table 5-6.	Section 5.1.4
			Added Table 5.13 to describe derivation Criteria of uncorrected ACPR and PCR- corrected ACPR and the sensitive analyses;	Section 5.7.4
24-06-2024		Address comments after the dry run for CSR	Changed the time to event/censoring from Day 41 to Day 43 in tail of KM plots	Section 2.1.1
			In the definition of uncorrected ACPR, deleted 'new infection' in the last bullet point; In the definition of PCR-corrected ACPR, added 'new infection' at the definition '□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/**new infection**'.	Section 2.1.1.2
			In the definition of corrected ACPR and uncorrected ACPR, add a patient who take non-study antimalaria medications during the treatment period is considered as non-responder .	
			In the definition of corrected ACPR, add that if the patient has parasite cleared by Day 7 but has negative PCR prior	

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			to Day X, the response is considered as missing/undetermined.	
			In PK analysis set, added two PK analysis subsets with different food compliance conditions for run-in cohorts and cohort 1 and cohort 2	Section 2.2
			For PCT and FCT censoring, added 'If the study medication is vomited in the same date as the use of antimalarial medication, the last vomiting time on the study medication date is imputed as time of antimalarial medication. Otherwise, the antimalarial medication time can be imputed using the middle day time (12:00).'	Section 2.7.2.4
			Changed the condition of clearance of initial infection from Day 15 to Day 7.	Section 2.7.2.5
			Included cohort 1 and cohort 2 separately for the treatment difference evaluation using a log-rank test	Section 2.7.2
			Changed the condition of clearance of initial infection from Day 15 to Day 7.	Section 2.7.2.6
			Added "Change from baseline will only be analyzed for Hemoglobin, RBC, platelets, TBIL, ALT, AST."	Section 2.8.2

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			For Post treatment QTcF/QTcB increase from baseline for cohort 1 and cohort 2, it will only be analyzed at common post-baseline timepoints (48H, Day 8, and Day 43)	Section 2.8.3
			Lower limit of the Day 29 visit is changed from Day 25 to Day 27	Section 5.1.4
			In Table 5-6, Added three more time points 51 h, 54h, 68 h for ECG and PK sampling	Section 5.1.4
			Added more prohibited medications, in particular related to Liver enzymes (ALT/AST) elevation and QTc prolongation	Section 5.3
			In Table 5-14, lower limit of parasite count required for inclusion criteria increased to 1,500 parasites/μL for cohorts 1 and 2;added • "received non-study concomitant antimalarial drugs during the treatment period" in the non-PD criteria for PPS; for the non-PD criteria for new infection, changed the occurrence time of new infection from Day 29 to Study Day 27; in the PK exclusion criteria caused by PD, removed the wording about food compliance	Section 5.8

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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
CDC	Centers for Disease Control and Prevention
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 parasitological 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 this Statistical Analysis Plan (SAP), is to describe the implementation of the statistical analysis, which is planned in the protocol (Version 01). The study has three age descending cohorts: Run-in, Cohort 1, and Cohort 2. Mock shells for the clinical study report (CSR) will be prepared according to the analysis plan specified in this SAP. Statistical outputs for the CSR will be generated after the final database lock (DBL) according to the mock shells and this SAP. A separate set of mock shells will be prepared and executed for DMCs based on this SAP.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

All CSR analyses will be carried out by using SAS, Version 9.4 or higher.

1.1 Study design

This will be a multicenter, open-label, randomized parallel-group, non-inferiority study in pediatric population with confirmed uncomplicated *P. falciparum* malaria.

The study has three age descending cohorts; Run-in Cohort, Cohort 1 and Cohort 2.

Run-in Cohort:

Male and female adolescent patients (≥12 and <18 years) with at least 35 kg weight will be enrolled in the Run-in cohort. 24 patients (up to 96 in case of dose/food adaptation) will be dosed starting with KAF156 400 mg and LUM-SDF 240 mg QD (once daily) for 2 days; 12 will be under fasted and 12 under fed conditions, in randomized fashion. In case of dose/food adaptation, the Run-in cohort may be repeated up to thrice with maximum of 96 (24 x 4) patients. Once the dose/dose-regimen is deemed optimal (based on safety and PK data review as available), Cohort 1 will start recruitment.

Cohort 1:

Male and female children with age 2 to <12 years will be enrolled in Cohort 1. Approximately 140 patients will be enrolled in this cohort in 1:1 ratio between KAF156/LUM-SDF and Coartem® groups. In case of Cohort 2 stops early, 80 more patients are planned to be randomized in Cohort 1 (1:1 ratio between KAF156/LUM-SDF and Coartem®) to achieve the required overall sample size for the Cohort 1 and 2, which is 220.

Cohort 2:

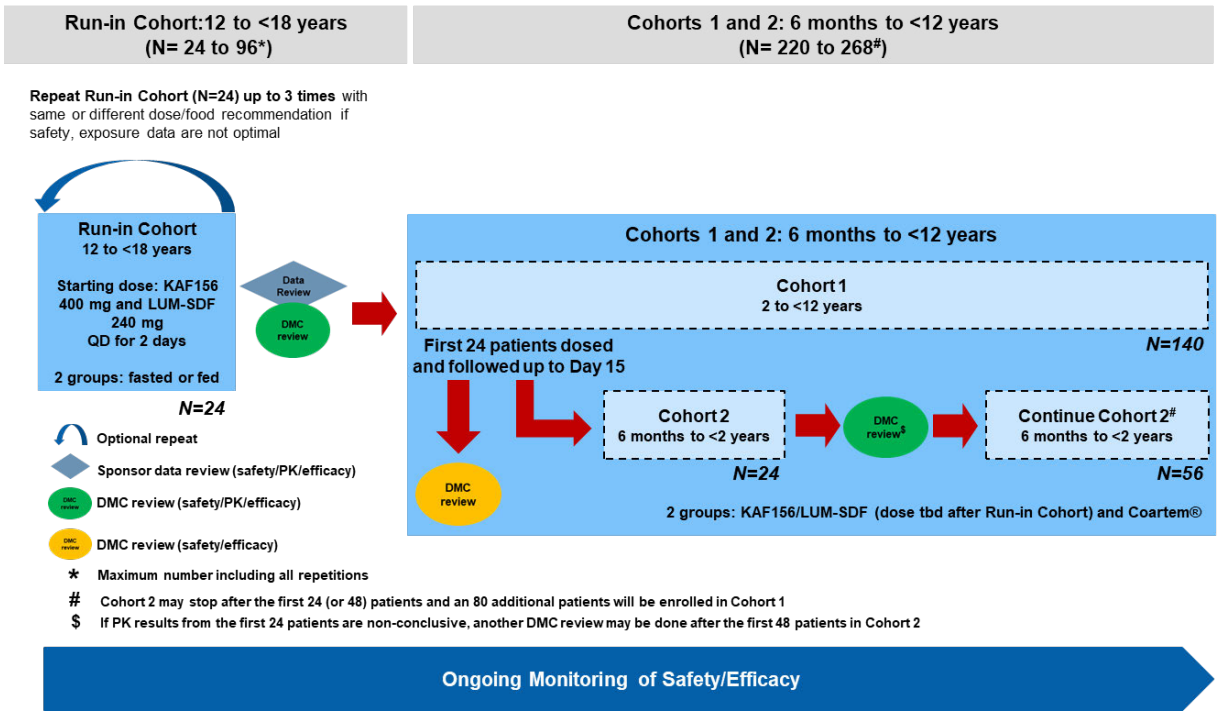
Male and female children with age 6 months to <2 years will be randomized in Cohort 2.

Approximately 80 patients (may stop at 24 or 48 patients if dose not optimal) may be enrolled in this cohort. First 24 patients from the age group of 6 months to < 2 years will be randomized. If the dose is deemed optimal (based on safety, PK and efficacy data review as available), then the remaining 56 patients in the cohort will be randomized so that there are approximately 80 treated patients aged 6 months to < 2 years old. In case results (PK, safety and efficacy data) from the initial 24 patients are non-conclusive, another DMC review may be scheduled after

the first 48 patients of Cohort 2 have been dosed and followed up to Day 15. In case that the dose is not optimal (based on safety, PK and efficacy data review as available) , the enrollment for this cohort will be terminated. The 80 patients allocated to Cohort 2 will be re-allocated to Cohort 1.

Overall total sample size in Cohort 1 and Cohort 2 will be ranging from 220 to 268 in case of Cohort 2 early termination after either 24 or 48 patients.

Figure 1-1 Study Design



At screening, within each cohort, eligible patients will be randomized into one of the two treatment groups in 1:1 ratio (fasted and fed patients in the Run-in Cohort; KAF156/LUM-SDF and Coartem® in Cohorts 1 and 2)

Randomization is stratified according to Table 1-1 to achieve the balanced treatment allocation within /age group/a country.

Table 1-1 Stratified randomization scheme

Cohort	Stratification factor
Run-in cohort	Country
Cohort 1	Age group (6 to <12 years and 2 to <6 years) and Country
Cohort 2	Country

Patients will be admitted to the hospital on Day 1. They will be dosed according to predefined dosing regimen 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 8-1, Table 8-2, Table 8-3) in the protocol. If malaria symptoms re-emerge outside the scheduled study visits, patients will be instructed to contact the investigator.

1.2 Study objectives and endpoints

The study objective and end points are included in below table.

Table 1-2 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the efficacy of of KAF156 combined with LUM-SDF compared to Coartem® (non-inferiority trial) for the treatment of uncomplicated malaria caused by *P. falciparum* in children 6 months to <12 years.	• PCR-corrected adequate clinical and parasitological response (ACPR) at Day 29 (i.e., 28 days post-dose) (Cohorts 1 and 2 pooled).
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To investigate the effect of food on lumefantrine bioavailability in patients 12 to <18 years old (Run-in Cohort).	• LUM PK parameters such as AUC, Tmax and Cmax (Run-in Cohort).
• To investigate the effect of food on KAF156 bioavailability in patients 12 to <18 years old (Run-in Cohort).	• KAF156 PK parameters such as AUC, Tmax and Cmax (Run-in Cohorts).
• To evaluate safety and tolerability of KAF156/LUM-SDF in pediatric patients (6 months to <18 years old).	• Standard safety/tolerability assessments: AE/SAE incidence and severity, laboratory abnormalities and electrocardiogram (ECG) abnormalities.
• To assess PK of KAF156 and lumefantrine in pediatric patients (6 months to <12 years old) .	• KAF156 and lumefantrine: PK parameters such as AUC, Cmax (LUM Cmax for Cohorts 1 and 2) C168 h and Tmax.
• To further evaluate the efficacy of KAF156 combined with LUM-SDF by assessing uncorrected and corrected ACPR at different time points as well as fever- and parasite-clearance times.	• PCR-corrected adequate clinical and parasitological response (ACPR) at Day 15, Day 29 (Run-in Cohort) and Day 43, and the uncorrected ACPR at Day 15, Day 29, and Day 43. • Incidence rate of recrudescence and new infection (i.e., reinfection) at Days 15, 29 and 43. • Parasite and fever clearance times (PCT and FCT).
[redacted]	[redacted]
[redacted]	[redacted]

Objective(s)	Endpoint(s)
[redacted]	[redacted]

2 Statistical methods

2.1 Data analysis general information

Data will be analyzed by Novartis using SAS version 9.4 according to the data analysis presented in section 12 of the study protocol, which is also available in Appendix 16.1.1 of the CSR. Detailed information is given in the following sections.

Data analyses required for the study Data Monitoring Committee (DMC) will be analyzed by Novartis (Trial statistician/trial programmer for Run-in Cohort and independent statistician/ independent programming team for Cohort 1 and 2). The outline of the DMC analysis outputs is presented in the DMC charter and will be detailed in a separate mock shell 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. This SAP covers the methods for: DMC meetings, planned interim assessment, 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 (for selected parameters), 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 (if required) 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. PK summaries will be presented up to 3 significant digits except CV% , which will be rounded up to 1 digit after decimal.

The dose level/regimen of treatment groups in the run-in cohort may be adjusted after the first 24 patients in the cohort have been dosed. Once it has been adjusted, it becomes a different treatment group. The treatment group will be labeled to include both the full dose level of the study drugs, duration of treatment (no. of doses such as QDx2) and food intake designation (See Section 2.1.1). Cohort 1 and Cohort 2 will be pooled together for the analysis if dose regimen is considered to be similar and Cohort 2 does not stop early. In case of Cohort 2 stops early, Cohort 1 will be recruited with more patients to match the required sample size and hence Cohort 1 will be analyzed separately from Cohort 2; in this situation, Cohort 2 will be analyzed mainly using descriptive statistics. Selected efficacy and safety endpoints will be analyzed on

Cohort 1 and Cohort 2 pooled together. If at least one dose regimen is considered similar among the 3 cohorts, data will be summarized by treatment group for all 3 cohorts pooled in addition to summary by cohort and treatment group. In that case, statistical analysis will in general include a pooled cohort in addition to each cohort.

If Cohort 2 does not stop early, confidence level for comparison with Coartem (if provided) will be based on the 95% level for Cohorts 1 and 2 pooled and the 95% level for individual cohort. If Cohort 2 stops early, confidence level for comparison with Coartem (if provided) will be based on the 95% level for Cohort 1 and the 95% level for Cohort 2.

Note: similar doses among different cohorts are based on the equivalent adult dose according to the current planned weight range (see Table 6-4 in the protocol). However, they may be reassessed based on PK exposures at the end of study.

All post-text tables will be generated using Microsoft Word cell-based format so that they can be easily cut and pasted to create intext tables for the CSR. For the run-in cohort, some treatment groups may consist of doses that are not optimal. All such treatment groups will also be displayed in the post-text tables along with the ones that are the optimal. However, only those treatment groups containing the optimal dose for the run-in cohort are important for displaying in the intext tables. Therefore, post-text tables will display all cohorts including the pooled cohort (if applicable) and all treatment groups under a cohort side by side as columns. Within each cohort, the 2 treatment groups will be displayed side by side.

Although randomization is stratified using country and age category per Table 1-1 statistical analysis will not be stratified accordingly due to small sample sizes in each country/age category. For pooled analyses, study cohort will be used as stratum.

2.1.1 General definitions

Study treatment: KAF156, Lumefantrine solid dispersion formulation (LUM-SDF) are part of investigation treatments. Coartem® is used as standard of care (SOC). They are referred to as study treatments in the document.

Treatment group name will be used in statistical analyses and outputs. Abbreviated treatment group description that concatenates drug code, dosage, no. of doses, and food intake in the form of “KAFxxxmg/LUMyyymg- QD x X food intake” will be used as the column headers in the CSR outputs. If all the treatment groups are not accommodated within a page of a post text table, the names may be shortened such as by deleting the unit “mg”.

For example, the initial treatment groups in Run-in Cohort will be displayed as:

- KAF400mg/LUM240mg- QDx2-Fed
- KAF400mg/LUM240mg-QDx2-Fasted

As per study design, other dose combinations of KAF/LUM with different food recommendation may also be used. It is also possible to use treatment for 3 days. Treatment groups for each of the combinations will be used accordingly.

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 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 collected more than once for a day in the treatment phase for some variables, the study day calculation is based on the treatment start date and time.

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

Study day =Integer (datetime of assessment – datetime of first dose of study treatment)/(60*60*24) + 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 patients may come to visit earlier or later than the targeted day and 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/censoring will be reset to Day 43 if it's greater than 43. This principle will be used for relevant tables using the KM method.

Body temperature: Body temperature is measured using different routes (oral/rectal/tympanic/axillary), which will lead to variations in the readings. Therefore, all the temperature readings will be standardized with respect to axillary equivalent as follows for the reporting purpose:

Body temperature (Axillary temperature) = Other routes (oral/tympanic/rectal equivalent)-0.5^{o}C

For body temperature, date and time of measurement should be collected as per the protocol. However, the current CRF captures only the date but not time due to which actual body temperature collection time will be missing in the clinical database for Run-in and its repeats cohorts. This technical glich in the database will be corrected before the initiation of Cohort 1. For the statistical analysis of body temperature data, planned time will be considered as actual time of collection where the actual time is missing.

Non-rescue medication: Non-study concomitant antimalarial drugs without experiencing treatment failure.

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 parasitaemia.
- Parasitaemia on Day 3 higher than Day 1 count irrespective of axillary temperature.
- Parasitaemia on Day 4 with axillary temperature ≥ 37.5°C.
- Parasitaemia 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 parasitaemia without previously meeting any of the criteria of early treatment failure.
- Presence of parasitaemia 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.
- Missing body temperature assessment in presence of parasitemia will be classified as LCF.

Late Parasitological Failure (LPF)

- Presence of parasitaemia 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.

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 parasitaemia/parasite in the assessments 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. Note that if a patient takes non-study antimalaria medications during the treatment period, the patient is considered as non-responder.

- 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/undetermined if the patient is not classified as a non-responder prior to Day X 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 initial 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. Note that if a patient takes non-study antimalaria medications during the treatment period, the patient is considered as non-responder.
- 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 negative results at Day X based on microscopy and PCR genotyping.
- 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.
- 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 new infection **at** Day X using PCR genotyping or later if Day X is missing.
- The response for a patient is considered as missing/undetermined (e.g., due to missing PCR data or miss blood smear data) 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/new infection.
  - The patient has parasite cleared by Day 7 but has a new infection/negative PCR prior to Day X, ie, new infection/negative PCR at a visit causes PCR-corrected ACPR status unknown in later visit(s).

Note - In the context of derivation of ACPR status at Day X, the 'Day X' is referred to as the Day X analysis visit. For e.g., ACPR status at Day 29 is referred to as the ACPR status at Day

29 analysis visit. Analysis visit X will be derived using the day actual visit as defined in Tables 5-5 and 5-6. Unscheduled visits will be considered for deriving analysis visit. Assessments 'prior to Day X' will be identified using study day of assessments prior to Day X. 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 parasitaemia after 7 days is considered as non-responder for uncorrected ACPR. We reclassify such patient as responder for PCR- corrected ACPR at the visit if recurrence of parasitaemia after 7 days is due to new infection and a patient did not take rescue medication. A new infection at a visit causes PCR-corrected ACPR status unknown at later visit(s). Whether the recurrence of parasitaemia after 7 days is due to recrudescence or new infection is determined and provided by the central laboratory. Negative PCR will be handled similarly to new infection and categorize the patient as PCR corrected responder.

The above definitions 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 overridden for patients who take concomitant anti-malaria drugs (see Sections 2.5 and 2.7).

Fever Clearance is defined (in patients with temperature of ≥ 37.5°C -axillary equivalent at baseline) as the time of the first measurement of at least 2 consecutive temperatures of < 37.5°C 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 randomized into the study.

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 parasitaemia count is greater than 0. Following the intent-to-treat principle, patients will be analyzed according to the treatment group assigned to at randomization.

Unless otherwise specified, misrandomized patients will be excluded from the FAS.

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.

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. For the PK run-in cohort, all patients to receive the same dose in either fasted or fed condition.

Per-protocol set (PPS)

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

- did not have any important protocol deviations affecting efficacy
- took at least 80% dosages 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 to take partial dosages.
- did not take non-study medications with anti-malaria activity prior to Day 29 visit unless experiencing any treatment failure (ETF, LCF, LPF) (e.g new infections between Day 8 and Day 29), and PCR corrected ACPR status at Day 29 is defined, ie, at least one of the following criteria is met:
    a. classified as treatment failure before Day 8 (see Section 2.1.1)
    b. had parasitaemia present on Day 8 or later without parasite clearance before (eg., parasite present Day 15 and parasite was not cleared before Day 15).
    c. absent from parasitaemia at Day 29 or later,
    d. had a recrudescence if parasitaemia is present from Day 8 to Day 29, or
    e. had a new infection at Day 29 visit or later

Food noncompliance in the Run-in cohort is considered as important PD. Important protocol deviations for exclusion from PPS are specified in Table 5-14 and will be identified by the clinical team before the database lock.

PK analysis set

Run-in Cohort

PK Analysis set: All the subjects in the safety analysis set who have at least one evaluable PK concentration. A profile is considered evaluable for that period if following conditions are satisfied:

- Participants took at least 80% dosages of randomized study medication
- If a patient vomited the original dose but did not vomit the replacement dose
- Participants with no protocol deviations (PD) that may have an impact on the PK data

PK analysis set-partial food compliance: all subjects in the PK analysis set who are compliant to meal criteria (within 30 minutes of drug administration and took at least 70% of the standard meal) on any of the two dosing days.

PK analysis set-Full food compliance: all subjects in the PK analysis set who are compliant to meal criteria (within 30 minutes of drug administration and took at least 70% of the standard meal) on both dosing days.

Note that meal non-compliance for the run-in cohorts is identified using the PD (protocol deviation) code OTH04.

Cohort 1 and Cohort 2

PK Analysis set: All the subjects in the safety analysis set who have at least one evaluable PK concentration. A profile is considered evaluable for that period if following conditions are satisfied:

- Participants took at least 80% dosages of randomized study medication
- If a patient vomited the original dose but did not vomit the replacement dose
- Participants with no protocol deviations (PD) that may have an impact on the PK data

PK analysis set-partial food compliance*: all subjects in the PK analysis set who are compliant to meal criteria (within 1 hour (±5min) of drug administration and took at least 70% of light meal) on both Days 2 and 3.

PK analysis set-Full food compliance*: All subjects in the PK analysis set who are compliant to meal criteria (within 1 hour (±5min) of drug administration and took at least 70% of light meal) on all three dosing days.

*: In breastfed subjects, the % is not considered (as it cannot be assessed) and breastfeeding within the +/- 1 hr (+/- 5 min) of dosing is considered as meeting the criteria for both standard and light meal.

Note that meal non-compliance for Cohort 1 and Cohort 2 is identified using PD code OTH04A.

2.2.1 Subgroup of interest

The following subgroups will be used for descriptive summary of the selected efficacy and safety analyses in all cohorts pooled. 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)

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 if considered necessary.

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 FAS and PPS. If there are patients in the SAF excluded from FAS, summary will also be provided for the SAF.

Following demographic variables will be summarized

- Age and age categories (6 months to < 2 yrs, 2 to <6 yrs, 6 to <12 yrs, 12 to <18 yrs)
- Sex (male, female)
- Race (White, black, Asian, native American, pacific islander, unknown, other)
- Ethnicity
- Body weight and weight categories (5 to <10, 10 to <15, 15 to <25, 25 to <35, 35 to <55, 55 to <75, and ≥75 kg)
- 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 equivalent to axillary method (<37.5, 37.5 to <38.5, ≥38.5) (°C)
- Falciparum species: (P. Falciparum asexual forms, [redacted], 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)

[redacted]

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 or discontinued the treatment and study (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, compliance, rescue medication, concomitant therapies)

2.4.1 Study treatment / compliance

Number and percent of patients with study drug vomiting and successfully receiving replacement dose will be presented by treatment group. A patient is called as receiving successful replacement dose if the patient does not vomit the replacement dose.

Overall compliance for each study drug will be calculated separately using following formula: (sum of full doses taken/ sum of planned doses) x100 %. For KAF/LUM, compliance for combined dose will be the average compliance of both drugs. Compliance will be categorized by < 80 % and ≥80 % of planned doses taken and summarized by treatment group.

For e.g., if a patient from KAF 400/LUM 480 QD x 2 took 400 mg of KAF on Day 1 and 200 mg of KAF on Day 2 then overall compliance for KAF is 600/800x100% which is equal to 75%. If the patient receives 480 mg of LUM on both days, then the overall compliance for LUM is 100%. The average compliance for KAF/LUM combination for this patient is (75%+100%)/2 = 87.5%

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 rescue 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 related to the primary objective

The primary objective is to demonstrate the non-inferiority (NI) of a KAF156 and LUM-SDF combination to Coartem® for treatment of uncomplicated malaria caused by *P. falciparum* in children 6 months to < 12 years old. The NI margin (Δ) has been set to 10%.

Patients from Cohorts 1 and 2 will be pooled together. In case that Cohort 2 stops early, such as after the first 24 patients, the study objectives will be assessed based on Cohort 1 data alone since there will be enough statistical power for Cohort 1 alone (refer to Section 3.1.1) while Cohort 2 will be analyzed mainly using descriptive statistics.

2.5.1 Primary endpoint

The primary efficacy variable is the PCR corrected Adequate Clinical and Parasitological Response (ACPR) at Day 29 (i.e. 28 days post-dose) (see Section 2.1) (Cohorts 1 and 2 pooled).

2.5.2 Statistical hypothesis, model, and method of analysis

The statistical null hypothesis is that the difference in PCR-corrected ACPR rate at Day 29 between KAF156 and LUM-SDF combination and Coartem® is at most -10% with the alternative hypothesis that it is greater than -10%. The statistical hypothesis will be evaluated using the lower limit of two-sided 95% confidence interval (CI) for the difference between two treatment groups.

If Cohort 2 does not stop early, two-sided 95% CI for the difference between two treatment groups will be provided for Cohorts 1 and 2 pooled using Mantel-Haenszel estimate of the common risk difference stratified by cohort (see SAS manual version 13.2 Pages 2681-2682, 2014). If the lower limit of 2-sided 95% CI for the difference is greater than -10%, the null hypothesis will be rejected.

In case that Cohort 2 stops early, such as after the first 24 patients, two-sided 95% CI for the difference between two treatment groups will be provided for Cohort 1 alone using the Wilson

uncorrected method. If the lower limit of 2-sided 95% CI for the difference is greater than -10%, the null hypothesis will be rejected.

The statistical hypothesis testing will be evaluated based on the PPS.

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

Parasite assessments obtained within the 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 Sensitivity analyses

- The primary efficacy analysis will be repeated on the FAS using the statistical methods 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 parasitaemia which cannot be determined to be recrudescent or new infection due to missing PCR data will be counted as non-responders (from the day of test)
  - Missing/undetermined 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 with new infection before Day 29 will be considered 1) not achieving PCR-corrected ACPR at Day 29 in one analysis and 2) and achieving PCR-corrected ACPR at Day 29 in another analysis
  - Patients who received non-study related anti-malarial medication without having reappearance of the parasites will be considered in the analysis as if they had not taken these drugs. This is because such cases will be very unlikely as administration of such medicines are expected only in case of the reappearance of the parasites. Note- Patients who take non-study anti-malarial medication due to repeated vomiting of study medication should be considered as treatment failure.

    Note: These patients did not experience any treatment failure (ETF, LCF, 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 recrudescence or as responder for PCR corrected ACPR if they received rescue medication to treat a new infection on Day 29 visit.
- Patients who received non anti-malaria medication with potential anti-malarial activity without having reappearance of the parasites will be considered in the analysis as if they had not taken these drugs. This is because such medications will have minimal effect on efficacy.

- Although the objective of Run-in cohort is to investigate the food effect on bioavailability of KAF156 and lumefantrine, analyses related to primary and other secondary variables will be performed in Run-in cohort by treatment group, unless otherwise specified.

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 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 antimalarial medication for other infections [redacted] will be censored at the first time of antimalarial 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.

An asymptotic two-sided 95% CI for the difference in proportion of responders between two treatment groups 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_k = Kaplan-Meier estimate for the treatment 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_k= estimated standard error for the treatment 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, $\alpha = 0.05$.

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 efficacy endpoints

Secondary efficacy variables include:

1. PCR-corrected ACPR at Days 15, Day 29 (Run-in Cohort) and 43;
2. Uncorrected ACPR at Days 15, 29, and 43;
3. Proportion of patients with parasitaemia 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 body temperature decreased below and remained below 37.5°C (axillary equivalent) 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 new infection 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. There is no adjustment for multiplicity since these endpoints are supportive in this study.

2.7.2.1 PCR-corrected ACPR and uncorrected ACPR

Analysis will be performed on PPS and FAS.

If Cohort 2 does not stop early-

At each visit, the ACPR rate with 95% confidence intervals will be provided using Clopper-Pearson method for each treatment group by cohort. Two-sided 95% CI for the difference between two treatment groups will be provided using Wilson's uncorrected method by cohort. Two-sided 95% CI for the difference between two treatment groups will be provided for Cohorts 1 and 2 pooled using Mantel-Haenszel estimate of the common risk difference stratified by cohort (see SAS manual version 13.2 Pages 2681-2682, 2014).

If Cohort 2 stops early –

At each visit, the ACPR rate with 95% CIs will be provided using Clopper-Pearson method for each treatment group for Cohort 1 and 95% CIs for the Cohort 2; two-sided 95% CI for the difference between two treatment groups will be provided for Cohort 1 only using Wilson's uncorrected method. Handling of missing values/censoring/discontinuations

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

- For PCR-corrected ACPR, presence of parasitaemia which were determined to be new infection from Day 8 and before Day 29 are excluded from the PPS, however, new infections at Day 29 or after Day 29 but before Day 43 are included in the PPS. At Day 43, 2 analyses will be performed, these new infections are considered as non-responders in one analysis and as responders in another analysis. For FAS, similar 2 analyses will be performed, new infections prior to a visit will be considered non-responders in one analysis and as responders in another analysis.
- For the PCR-corrected ACPR, the patient who is not classified as PCR-corrected nonresponder at earlier timepoint, and the PCR data is missing will be excluded from the PPS based analysis; however, for FAS, the patient will be considered as non-responder from the day of test.
- New infection at a visit means no recrudescence at prior visits (e.g., new infection at Day 43 means no recrudescence).
- Missing/undetermined 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, for the FAS; however, such patients will be excluded from the PPS based analysis.
- Patients who received non-rescue anti-malarial medication before Day 29 will be excluded from the PPS; however, for the FAS, they will be considered in the analysis as if they had not taken the antimalarial drug. Note- Patients who take non-study anti-malarial medication due to repeated vomiting of study medication should be considered as treatment failure.

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 and PPS (see Section 2.5.4 and Section 2.7.2.2).

2.7.2.2 Analysis of uncorrected ACPR rate using Kaplan-Meier method

Analysis will be performed on the FAS and PPS.

If Cohort 2 does not stop early-

The proportion of patients with uncorrected ACPR at Day 29 and Day 43 and 95% CI will be estimated using the Kaplan-Meier method (Stepniewska and White 2006 and WHO 2015) stratified by Cohort. For each cohort, an asymptotic two-sided 95% CI for the difference in proportion of responders between two treatment groups will be calculated from the z-test statistic distribution based on the variance of individual proportion using the Greenwood

formula (See Section 2.5.4.1). For pooled cohorts 1 and 2, an asymptotic two-sided 95% CI for the difference in proportion of responders between two treatment groups will be calculated.

If Cohort 2 stops early-

The proportion of patients with uncorrected ACPR at Day 29 and Day 43 and 95% CI will be estimated using the Kaplan-Meier method (Stepniewska and White 2006 and WHO 2015) by Cohort except Cohort 1 along with an asymptotic two-sided 95% CI for the difference in proportion of responders between two treatment groups. For Cohort 1, an asymptotic two-sided 95% CI for each treatment group along with between treatment difference in proportion of responders will be calculated

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 received non-rescue anti-malaria medication (i.e., receiving antimalaria treatment without reappearance of parasites) will be censored at the first time of anti-malaria medication.
- Other patients will be censored at the time of last parasitemia assessment.

Appendix Table 5-21 provides a comparison of treatment outcome assignments for both uncorrected and PCR-corrected ACPR in FAS and PPS for various specific scenarios.

2.7.2.3 Treatment failure related parameters

Following is the list of treatment failure related variables-

- proportion of patients with parasitaemia 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. Which means that the proportion of patients with an endpoint will be based upon the patients who experience treatment failure or have malaria blood film result at Day 43 for LCF and LPF.

For the above variables, proportion and confidence intervals will be calculated using the exact confidence interval as follows:

If Cohort 2 does not stop early, then 95% CIs will be provided for each treatment group by cohort. In addition, Cohorts 1 and 2 will be pooled together and 95%CI will be provided for each treatment group.

If Cohort 2 stops early, then 95% CIs will be provided for each treatment group by cohort except Cohort 1. For Cohort 1, 95% CI will be provided for each treatment group.

2.7.2.4 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. If the study medication is vomited in the same date as the use of antimalarial medication, the last vomiting time on the study medication date is imputed as time of antimalarial medication. Otherwise, the antimalarial medication time can be imputed using the middle day time (12:00). The between treatment difference will be evaluated exploratorily using a log-rank test separately by cohort and stratified by cohort for pooling Cohorts 1 and 2 if cohort 2 does not stop early; otherwise log-rank test will be performed for Cohorts 1 and 2 separately.

Additional analysis for FCT will be performed by excluding patients who took anti-pyretic drugs (ATC2 code as N02 or M01) prior to FCT.

2.7.2.5 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 by Day 7.

Time to event (recrudescence) will be calculated from the time of first study medication to the date of first event if a patient experiences the event and is censored at the first use of non-study antimalarial medication for purpose other than recrudescence or at the time of last parasite assessment otherwise. Undetermined treatment failures due to missing PCR data will be considered as censored at the time of treatment failure. The between treatment difference will be evaluated exploratorily using a log-rank test separately by cohort and stratified by cohort for Cohorts 1 and 2 pooled if cohort 2 does not stop early; otherwise for Cohorts 1 and 2 separately.

2.7.2.6 Time to event analysis for new infection

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

Incidence rates of new infection 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 by Day 7.

Time to event (new infection) will be calculated from the time of first study medication to the date of first event if a patient experiences the event and is censored at the first use of non-study antimalarial medication for purpose other than new infection or at the time of last parasite assessment otherwise. Undetermined treatment failures due to missing PCR data will be considered as censored at the time of treatment failure. The between treatment difference will be evaluated exploratorily using a log-rank test separately by cohort and stratified by cohort for Cohorts 1 and 2 pooled if cohort 2 does not stop early; otherwise for Cohorts 1 and 2 separately.

2.7.2.7 Subgroup analysis for selected efficacy variables

PCR corrected/uncorrected ACPRs at Day 29, PCT, and FCT will be summarized descriptively by the following subgroups using pooled Cohort 1 and 2 if Cohort 2 does not stop early. If Cohort 2 stops early, then these subgroup analyses will be performed only in Cohort 1

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

2.8 Safety analyses

All safety analyses will be performed using the safety set. Safety data for each cohort will be summarized separately. If Cohort 2 does not stop early, then safety analyses will also be performed on Cohort 1 and 2 pooled together. If there exists a similar treatment regimen of KAF-LUM dose combination among the Run-in Cohort, Cohort 1 and Cohort 2, selected safety analysis may also be presented on pooled cohorts

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 on or after the first dose of study medication) 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 frequency.

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

2.8.1.1 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.

2.8.1.2 Subgroup analysis for AEs

The adverse events and SAEs will be summarized by the following subgroups using pooled Cohort 1 and 2 if Cohort 2 does not stop early. If Cohort 2 stops early, then these subgroup analyses will be performed only in Cohort 1.

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

Algorithms for date imputations is provided in Appendix 5.

2.8.1.3 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 TMS.ECRS 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 adverse 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)

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, visit and treatment group. Maximum change from baseline during study will also be reported. 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, chloride, and total protein, albumin, INR, Thyroid Stimulating hormone (TSH), Thyroxine Free T4.

Change from baseline will only be analyzed for Hemoglobin, RBC, platelets, TBIL, ALT, AST.

Box plots for hematology and biochemistry parameters will be provided using normalized values, by dividing a value by its upper normal limit. Normalized values are used in the box plots since lab units and normal ranges could vary according to each site and also according to a certain age group. All lab values outside the normal ranges (High/Low) will be highlighted. The lab parameters without the normal reference rages will be excluded from this plot.

Summary with frequency and percentage of patients with liver related events as defined in Table 2-1 will be provided by treatment:

Table 2-1 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

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.

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

2.8.3 Other safety data

2.8.3.1 ECG and cardiac imaging data

Average triplicate ECG measurements will be used for the summary.

The following quantitative variables will be summarized: heart rate, RR interval, PR interval, QRS interval, QT interval, QTcF (QT interval corrected for heart rate according to Fredericia) and QTcB (QT interval corrected for heart rate according to Bazett) for each timepoint and maximum post baseline value.

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

To assess the dynamics of QTc, HR and body temperature, patients with notable QT, HR and fever (≥37.5 °C, axillary equivalent) by timepoint will be provided. Notable criteria is provided below.

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).

Post treatment max QTcF/QTcB increase from baseline will be calculated for each patient and 2-sided confidence intervals for the difference between the 2 treatment groups will be calculated based on two sample t-test using the 80% confidence level for the run-in cohort.

Post treatment QTcF/QTcB increase from baseline at common post-baseline timepoints (48H, Day 8, and Day 43) will be calculated for each patient and 2-sided confidence intervals for the difference between the 2 treatment groups will be calculated based on two sample t-test using the 90% confidence level for Cohorts 1 and 2.

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
  - > 90th percentile defined in Table 2-2
  - < 10th percentile defined in Table 2-2
- 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 2-2 Heart rate cut-offs (beats/minute) based on centile charts

Age Range#	10th percentile	90th percentile
Birth	107	148
0 – <3m	123	164
3 – <6m	120	159
6 – <9m	114	152
9 – <12m	109	145
12 – <18m	103	140
18 – <24m	98	135
2 – <3y	92	128

Age Range#	10th percentile	90th percentile
3 – <4y	86	123
4 – <6y	81	117
6 – <8y	74	111
8 – <12y	67	103
12 – <15y	62	96
15 – <18y	58	92

Age ranges given in years (y) and months (m). "Birth" refers to the immediate neonatal period.
Reference: Lancet. 2011 March 19; 377(9770): 1011–1018. doi:10.1016/S0140-6736(10)62226-X.

Analysis will also be performed on all parameters by age categories (6 months to < 2 yrs, 2 to <6 yrs, 6 to <12 yrs, 12 to <18 yrs).

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

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.

For DMC review meetings, following additional analysis will be provided;

- QRS - Increase from baseline >25% and (80<= QRS<=100 ms) and Increase >25% and (100< QRS<=120 ms)
- Heart rate - <50 bpm, 51-60 bpm, 61-80 bpm, 81-100 bpm, and >100 bpm

2.8.3.2 Vital signs

The following quantitative variables will be summarized: Body height (cm) in Cohort 2, 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

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 2-3 below.

Table 2-3 Criteria for notably abnormal vital signs

Vital sign		Criteria
Systolic blood pressure [mmHg]	High	≥ 95th percentile of the age and height group[1]
	Low	≤ 5th percentile of the age and height group[1]
Diastolic blood pressure [mmHg]	High	≥ 95th percentile of the age and height group[1]
	Low	≤ 5th percentile of the age and height group[1]

Vital sign		Criteria	
Body temperature [°C]	High	≥ 37.5°C (*axillary equivalent*)	
Pulse rate [bpm] [2]	High	1-<6 months	> 160
		6-<12 months	>150
		12-<18 months	> 140
		18-<24 months	> 135
		2-<3 years	> 128
		3-<4 years	> 123
		4-<6 years	> 117
		6-<8 years	> 111
		8-<12 years	> 103
		12-<15 years	> 96
		≥ 15 years	> 92
	Low	1-<6 months	<120
		6-<12 months	<110
		12-<18 months	< 103
		18-<24 months	< 98
		2-<3 years	< 92
		3-<4 years	< 86
		4-<6 years	< 81
		6-<8 years	< 74
		8-<12 years	< 67
		12-<15 years	< 62
		≥ 15 years	< 58
Weight	High	increase from baseline of ≥ 2 BMI-for-age percentile categories[3]	
	Low	decrease from baseline of ≥ 2 BMI-for-age percentile categories[3]	

bpm=beats per minute; NHLBI= National Heart, Lung, and Blood Institute.

[1] Fourth Report on Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics 2004; 114; 555 (see section 5.6 for detailed computation)

[2] Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011; published online March 15. DOI:10.1016/S0140-6736(10)62226-X.

[3] BMI-for-age percentiles categories (P3, P5, P10, P25, P50, P75, P85, P90, P95, P97) are obtained from the WHO Growth Charts, which may be accessed from GPS II growth_data (where TESTCD=BMI' and YEAR_CHG=WHO2006 and WHO2007).

Body mass index-for-age (BMI-for-age) (who.int)

2.9 Pharmacokinetic endpoints

The PK objectives are to assess PK parameters of KAF156 and lumefantrine in fasted or fed pediatric patients and to investigate the effect of food on lumefantrine PK and KAF156 PK in a Run-in Cohort of patients 12 to <18 years old.

PK parameters such as AUCinf, AUClast, AUC0-t, C168h, Cmax and Tmax (if feasible), will be used to evaluate these objectives, if available.

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), coefficient of variation, (CV %), median, minimum, and maximum, etc. CV% geo-mean will be calculated using this formula; (sqrt (exp (variance for log transformed data)-1))*100.

In the study, rich PK data will be collected from the Run-in Cohort whereas Cohort 1 and 2 will provide sparse PK samples. A separate PK analysis will be performed for each Cohort.

Parameters will be reported for the Run-in Cohort using non-compartmental method of analysis (using Phoenix 6.4 or higher).

Two-sided 90% confidence intervals for AUC, Cmax and Tmax PK parameters of KAF156 and LUM-SDF will be calculated by cohort, day 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. Two-sided 90% confidence intervals for geometric mean ratio for KAF156 and LUM-SDF between fed vs fasted will be provided for Run-in cohort

A descriptive statistic for concentration at all nominal time points including 168 hours post dose would also be reported for all the patients.

PK parameters/ PK concentration will also be explored graphically. PK parameters/ PK concentration in Cohorts 1 and 2 will be summarized by age subgroup and body weight subgroup as per section 2.3.

PK data may be pooled for population pharmacokinetics analysis and the broad principles outlined in the Food and Drug Administration (FDA) Guidance for Industry: Population Pharmacokinetics would be followed. Additionally, PK exposure from the first few patients in each treatment group may be compared across the treatment groups and with the historical data to ensure that exposures are within the acceptable safety and efficacy.

Analyses will be performed using the PK analysis set, PK analysis set-partial food compliance, and PK analysis set-full food compliance (see Section 2.2 for the definition).

Note that in the PK analysis set-partial food compliance for the run-in cohorts, only the PK concentrations from the dosing day, where subjects are compliant to the meal criteria, will be included in the analysis.

2.10 PD and PK/PD analyses

A scatter plot of KAF156 and lumefantrine day 8 concentrations will be produced. The dots on this plot will be colored according to the cure status (both PCR-corrected and uncorrected ACPR29), which will allow the assessment whether patients with lower concentrations have higher failure rate.

In addition, the PK and PD data obtained in the study may be pooled together with data from other studies and exploratory exposure-response modeling may be performed. An exploratory exposure-response analysis for safety outcomes such as QTc may also be conducted. These analyses may not be part of the CSR and may be reported separately.

2.11 Patient-reported outcomes

NA

2.12 Biomarkers

NA

[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 2-4 and Table 2-5. Descriptive statistics will be provided by cohort regardless of whether Cohort 2 stops early or not.

Table 2-4 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 (Cohort 1, 2)
Medical history	X	X	-	-	-	-	-	-
Demographics 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 parasitaemia at 12, 24, and 48 hours after treatment;	X	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	-	-	-	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 (Cohort 1, 2)
Proportion of patients with late clinical failure	X	X	-	X	-	-	-	X
Proportion of patients with late parasitological failure (LPF)	X	X	-	X	-	-	-	X
Incidence rate of recrudescence at Days 15, 29 and 43	X	-	-	-	-	X	X	X
Incidence rate of reinfection at Days 15, 29 and 43	X	-	-	-	-	X	X	X
[redacted]								
Scatter plot of KAF156 and lumefantrine day 8 concentrations with ACPR29	-	-	-	-	-	-	X	X
[redacted]								

Table 2-5 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 (Cohort 1, 2)
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 changes from baseline	-	X	X	X	X
Liver abnormalities	X	X	-	-	X
ECG abnormality	X	X	-	-	X
QTc change from baseline	-	X	X	X	X
Vital signs change from baseline	-	X	X	-	X
Notable vital signs abnormality	X	X	-	-	X
Drug concentrations	-	X	X	X	X
PK parameters	-	X	X	-	X

2.15 Interim analysis

Safety/efficacy/PK data for each Cohort will be analyzed after first 24 patients in each Cohort. The results for the run-in cohorts will be communicated to relevant internal and external people who will contribute to the selection of effective and safe dose for next Cohort or continuation of the same Cohort. The results for Cohorts 1 and 2 will be limited to DMC only.

DMC analysis: DMC analyses will be performed at the following timepoints

- After the first 24 patients in the Run-in Cohort (12 to <18 years) have been treated and followed up for at least 2 weeks,
- After the first 24 patients in Cohort 1 (2 to <12 years) have been treated and followed up for at least 2 weeks,
- After the first 24 patients in Cohort 2 (6 months to <2 years) have been treated and followed up for at least 2 weeks. In case results (PK, safety and efficacy data) from the initial 24 patients are non-conclusive, another DMC review may be scheduled after the first 48 patients of Cohort 2 have been dosed and followed up to Day 15.
- After the Run-in Cohort is repeated for a different dose group or an earlier ad-hoc safety review is triggered in case 5 SAEs (irrespective of relationship) or 3 SAEs with a suspected relationship are reported.

The 24 patients are the targeted number in each group/cohort. The actual number may be slightly different.

Below is the outline of the data required for the DMC review in Table 2-6

Table 2-6 Specification of data outputs for DMC data review

Output	Analysis set	Periodic data review	
		After first 24 patients in each Cohort/group	Periodic safety data review
Baseline			
Patient disposition	Randomized	Yes	Yes
Recruitment by country and center	Randomized	Yes	Yes
Demographic characteristics	FAS	Yes	Yes
Background disease characteristics	FAS	Yes	Yes
Safety			
Concomitant medications/significant non-drug therapies	Safety	Yes	Yes
All adverse events and Serious adverse events	Safety	Yes	Yes
General, and liver, specific safety laboratories (categorical analysis)	Safety	Yes	Yes
Vital signs (clinically notable)	Safety	Yes	Yes
ECG	Safety	Yes	Yes
Early treatment failures	Safety	Yes	Yes
Efficacy			
Parasite clearance time (PCT)	FAS	Yes	As needed
PCR uncorrected ACPR at Day 15	FAS	Yes	No
PCR uncorrected ACPR at Day 29	FAS	As available*	No
PCR uncorrected ACPR at Day 43	FAS	As available*	No
KAF156 and luLumefantrine (C6hr, AUC,, AUC, H168 concentration)	PK	Yes	As needed

FAS: Full analysis set

*Data may not be available for all patients for a data/DMC review

3 Sample size calculation

3.1.1 Primary endpoint(s)

The primary objective is to evaluate the efficacy of KAF156 combined with LUM-SDF by demonstrating non-inferiority to Coartem® in PCR corrected ACPR at Day 29 for treatment of uncomplicated malaria caused by *P. falciparum* in children 6 months to < 12 years old. The NI margin (Δ) has been set to 10%. There is no historical Coartem® trial that compared Coartem® with placebo in PCR corrected ACPR at Day 29 to justify the NI margin statistically. The 10% NI margin in PCR corrected ACPR at Day 29 is based on clinical judgement as a NI margin of 10% to 12.5% is commonly used in other infection diseases (e.g., FDA 2018 guidance for

Complicated Urinary Tract Infections, FDA 2020 guidance for Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia, EMA 2014 Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections, etc.).

The statistical null hypothesis is that the difference in PCR-corrected ACPR rate at Day 29 between KAF156 and LUM-SDF combination and Coartem® is at most -10% with the alternative hypothesis that it is greater than -10%. The non-inferiority of KAF156 and LUM-SDF combination in PCR corrected ACPR rate at Day 29 will be evaluated based on the per-protocol analysis set using Cohorts 1 and 2 pooled if Cohort 2 does not stop early or using Cohort 1 data alone if Cohort 2 stops early.

Cohort 2 does not stop early

The statistical hypothesis will be evaluated using the lower limit of 2-sided 95% confidence interval (CI) for the difference between two treatment groups using Cohorts 1 and 2 pooled based on Mantel-Haenszel estimate of the common risk difference stratified by cohort (see SAS manual version 13.2 Pages 2681-2682, 2014). If the lower confidence limit is greater than -10%, the null hypothesis will be rejected. That means the non-inferiority will be established at -10%.

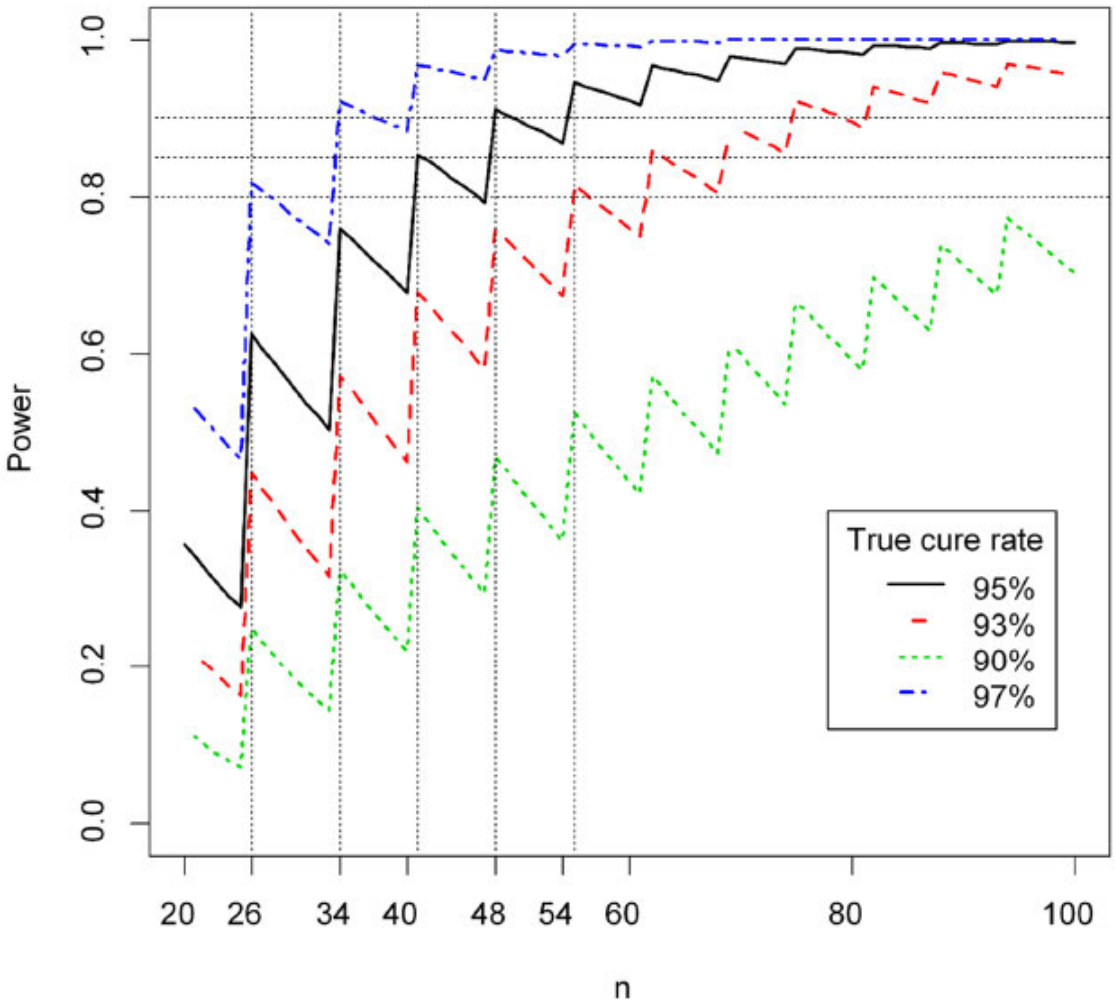
Assuming that the true response rate in PCR corrected ACPR at Day 29 is 95% for both treatment groups, a sample size of 92 patients per group will have at least 87% power to reject the null hypothesis that the response rate for KAF156 and LUM-SDF combination is at least 10% lower than Coartem® at 1-sided alpha of 2.5% (nQuery 8.4 module PTE0-1/Two Group Test of non-inferiority in Proportions).

Assuming that about 16% of patients will be excluded from the per-protocol analysis set, about 220 patients overall will be randomized in 1:1 to the 2 treatment groups to yield 92 evaluable patients per treatment group in pooled Cohorts 1 and 2. The number of evaluable patients in the PPS may be reduced further due to other unforeseen issues, such as COVID19. In this case, additional number of patients will be randomized to match the requirement of PPS.

Cohort 2 stops early

In case that Cohort 2 stops early after 24 patients, the statistical hypothesis will be tested using Cohort 1 data alone. Therefore, the 80 patients that are allocated to Cohort 2 will be re-allocated into Cohort 1 so that about 220 patients are randomized in Cohort 1 to achieve at least 87% power to demonstrate the non-inferiority in patients with 2 to 12 years old.

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



3.1.2 Secondary endpoint(s)

Run-in Cohort

The main objective in the Run-in Cohort is to investigate the food effect in terms of fold increase in exposure for fed vs fasted. The sample size will be justified based on the precision for estimating the fold increase in LUM exposure for fed vs fasted. The fold increase will be estimated using the geometric mean ratio between fed and fasted groups with the precision defined by the half-width of 90% confidence interval for the geometric mean ratio.

It is well known that the distribution of PK parameters, such as AUC or Cmax, is best described by log normal distribution. The geometric mean ratio along with its 90% confidence interval will be calculated first using log value and then anti-log transformed to ratio. The relevant historical data for sample size calculation are the standard deviations of log values. In the phase

2 study CKAF156A2202 Part A, the standard deviations from sparse PK samples of lumefantrine for KAF156 400 mg/LUM-SDF 960 mg QD 2 days (under fasted) were:

- 0.69 for log Cmax of last dose
- 0.77 for log AUC0-24h of last dose
- 0.63 for log concentration at 168 hours.

For log Cmax, assuming that the common standard deviation is 0.69, a sample size of 8 patients per group will provide an 80% probability that the half-width of 2-sided 90% confidence interval for the difference of two log means will be ≤ 0.693 or 2 in terms of ratio (nQuery MTC1-1). The probability will be increased to 90% if the sample size is 9 patients per group.

For log AUC0-24h, assuming that the common standard deviation is 0.77, a sample size of 10 patients per group will provide an 80% probability that the half-width of 2-sided 90% confidence interval for the difference of two log means will be ≤0.693 or 2 in terms of ratio (nQuery MTC1-1).

For log concentration at 168 hours, the required sample size is smaller for the same half-width and probability since its standard deviation is smaller.

Considering that about 20% of patients may be excluded from PK analysis, 24 patients will be randomized in the Run-in Cohort to yield about 9 to 10 evaluable for the analysis of the above LUM PK parameters.

Power consideration for PK checking after the first 24 patients in Cohort 2

After about 24 patients have been randomized in Cohort 2, PK checking along with safety and efficacy will be evaluated to see if the dose level of KAF156 and/or LUM-SDF is appropriate for this age group. Since lower lumefantrine concentration at 168 hours is associated with higher recrudescence in Coartem® (WWARN Lumefantrine PK/PD Study Group, 2015), lumefantrine concentration at 168 hours will be the key PK parameter to be checked. Difference in lumefantrine concentration at 168 hours between the 2 treatment groups (KAF156 and LUM-SDF combination divided by Coartem®) will be evaluated using the geometric mean ratio and its 90% confidence interval between the 2 groups. In the KAF156A2202 Part A, the SD of log lumefantrine concentration at 168 hours was 0.63 and 0.51 for KAF156 400 mg/LUM-SDF 960 mg QDx2 group and Coartem®, respectively. Therefore, it's assumed that the common SD for KAF156 and LUM-SDF combination and Coartem® in this study is 0.57 (average of 0.63 and 0.51). Assuming that there is no difference in lumefantrine concentration at 168 hours between the two treatment groups, a sample size of 10 patients per group will provide 80% power to reject the null hypothesis that the lumefantrine concentration at 168 hours is at least 50% lower in the KAF156 and LUM-SDF group than in the Coartem® group at 1-sided alpha of 5% (nQuery 8.4 Module MTE0-1/Two Group t-test of Non-Inferiority in Means). To adjust for potential non-evaluable lumefantrine concentration at 168 hours, the PK checking will be performed after approximately 24 patients have been randomized and reached the visit at Day 8.

Power consideration for safety (QTcF effect) in the first 24 patients in Run-in Cohort

Mean and median max QTcF changes from baseline were similar between the POC study KAF156X2201 with KAF156 alone and KAF156A2202 Part 'A' with LUM-SDF (internal data), which indicated that lumefantrine may not contribute to additional QTcF changes when in combination with KAF156. Therefore, we hypothesized that increase in lumefantrine exposure under fed condition may not further increase QTcF. The purpose of QTcF checking for the first 24 patients in the Run-in cohort is to ensure that there is no unacceptable increase in QTcF with food intake. A QTc increase of > 20 ms for a drug compared to placebo is listed as a serious concern in ICH E14 (2005). Hence, a NI margin of 20 ms is selected for comparing the 2 treatment groups in QTcF changes for the first 24 patients in the cohort. Considering that about 15% patients may not be evaluable for QTc change, about 10 patients per treatment group will be considered for the power calculation. In CKAF156A2202 study, the SD for maximum change from baseline to any post baseline was about 20 ms in the 8 arms. Assuming a SD of 20 ms and there is no difference in QTcF change between the 2 treatment groups, there is an 80% power to show that the treatment group with fed does not increase QTcF more than 20 ms compared to the treatment group under fasting using 2-sided 80% confidence interval (i.e., the upper limit of 2-sided 80% confidence limit for the difference between two treatment groups (fed Vs fasted) in mean maximum QTcF change is less than 20 ms) (nQuery Advisor 7.0 module MTE0-1).

4 Change to protocol specified analyses

None

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The study drug administration 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 administration 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 Table 5-3 will be used

Table 5-1 AE/Treatment Date Abbreviations

	Day	Month	Year
Partial Adverse Event Start Date	<not used>	AEM	AEY

	Day	Month	Year
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			
	TRTSTD	Before	Indicates AE start date prior to Treatment Start Date
	TRTSTD	After	Indicates AE start date after Treatment Start Date
		Uncertain	Insufficient to determine the relationship of AE start date to Treatment Start Date
Imputation calculation			
	Blank	NC /	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

Partial AE start date	Treatment start date	Relationship with TRTSTD	Imputation Calculation	Imputed Date
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 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 27 and Day 33 respectively, with narrow window 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 assessments 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 all 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		[redacted]
		Vital signs/ Chemistry/ Hematology/ Urinalysis	Thyroid function	
Baseline	1	Up to Day 1	Up to Day 1	
Day 2	2	Day 2	NA	
Day 3	3	Day 3	NA	
Day 4	4	Day 4	NA	
Day 5	5	Day 5 - 6	NA	
Day 8	8	Day 7 - 11	NA	
Day 15	15	Day 12 - 26	Day 2 - 29	
Day 29	29	Day 27 - 33	NA	
Day 43/End of study	43	Day 34 and above	Day 30 and above	

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

Analysis Visit	Analysis timepoint	Analysis window for assessment group			
		Parasite count/Temperature*	ECG	PK (Run-in)	PK (Cohorts 1&2)
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	> 0 - 2 hrs	NA
	3 hrs	NA	>0 – 4.5 hrs	> 2 – 3.5 hrs	>0 – 4.5 hrs
	4 hrs	NA	NA	>3.5 – 4.5 hrs	NA
	5 hrs	NA	NA	>4.5 – 5.5 hrs	NA
	6 hrs	>0 - 9 hrs	>4.5 - 15 hrs	>5.5 - 7 hrs	>4.5 – 15 hrs
	8 hrs	NA	NA	>7 – 16 hrs	NA
	12 hrs	>9 - 18 hrs	NA	NA	NA
Day 2	24 hrs	>18 hrs to 33 hrs	>15 – 25.5 hrs	>16 – 24.5 hrs	>15 – 25.5 hrs
	25 hrs	NA	NA	>24.5 – 26 hrs	NA
	27 hrs	NA	>25.5 – 28.5 hrs	>26 - 27.5 hrs	>25.5 – 28.5 hrs
	28 hrs	NA	NA	>27.5 – 28.5 hrs	NA
	29 hrs	NA	NA	>28.5 – 29.5 hrs	NA
	30 hrs	NA	>28.5 - 39 hrs	>29.5 - 31 hrs	>28.5 – 39 hrs
	32 hrs	NA	NA	>31 - 40 hrs	NA
	36 hrs	>33 – 42 hrs	NA	NA	NA
Day 3	48 hrs	>42 – 60 hrs	>39 – 49.5 hrs	>40 – 60 hrs	>39 – 60 hrs
Day 4	51 hrs	NA	>49.5 - 52.5 hrs	NA	>49.5 - 52.5 hrs
	54 hrs	NA	>52.5 – 61 hrs	NA	>52.5 – 61 hrs
	68 hrs	NA	>61 – 70 hrs	NA	>61 – 70 hrs
	72 hrs	>60 hrs to Day 4	>70 hrs to Day 5	>60 – 120 hrs	> 60 hrs
Day 5	NA	Day 5 - 6	NA	NA	NA
Day 8	168 hrs	Day 7 – 11	Day 6 -25	>120 hrs	NA

Day 15	NA	Day 12 - 26	NA	NA	NA
Day 29	NA	Day 27 - 33	NA	NA	NA
Day 43/End of study	NA	Day 34 and above	Day 26 and above	NA	NA

*Temperature should be checked every 6 hours until no fever. Since temperature is used for treatment failure also, the same window of parasite count is used.

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. If ECG is repeated, the higher value (worse case) of average triplicate between the scheduled and the repeated will be used for each measurement. Note, in such situations, the value used for analysis may be from the scheduled visit for some measurements but from repeated visit for other measurements.
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 Table of prohibited medication with respective ATC codes

Category	General classification	ATC code	Product name
Drug-drug interaction	ANALGESICS	N02CC06	Eletriptan
		N02CA01	Dihydroergotamine
		N02CA02	Ergotamine
		N02AB03	Fentanyl
	ANESTHETICS	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
		R06AX13	Loratadine
	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
	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 DIURETICS	C03XA02	Conivaptan
PSYCHOSTIMULANTS	N06BA09	Atomoxetine
UROLOGICALS	G04BD07	Tolterodine
	G04BD10	Darifenacin
	G04BE03	Sildenafil
	G04BE09	Vardenafil
Antibiotics/ Antiinfectives/ ANTIBACTERIALS	D06AX	Erythromycin
	D10AF	
	J01FA	

		S01AA	
	ANTIFUNGALS/ANTI-INFECTIVES AND ANTI-SEPTICS/ ANTIAD-RENAL PREPARATIONS	D01AC	Ketoconazole
		G01AF	
		H02CA	
		J02AB	
	ANTIINFECTIVES	J02AC	Itraconazole
	DRUGS FOR ACID RE-LATED DISORDERS	A02BA	Cimetidine
	ANTIBIOTICS/ ANTIBAC-TERIALS/ ANTIMYCO-BACTERIALS/ ANTI-INFECTIVES	D06AX	Rifampin
		J01XX	
		J04AB	
		J04BA	
		S01AA	
	PSYCHOLEPTICS/ AN-TIEPILEPTICS	N03AA	Phenobarbital
		N05CA	
	BILE AND LIVER THER-APY/ DIURETICS/ PREP-ARATIONS FOR TREAT-MENT OF WOUNDS AND ULCERS/ ANTIINFLAM-MATORY AND AN-TIRHEUMATIC PROD-UCTS/ PSYCHOLEP-TICS/ PSYCHOANALEP-TICS/ UNSPECIFIED HERBAL AND TRADI-TIONAL MEDICINE/ Ho-meopathic preparation	A05AW	HYPERICUM PER-FORATUM
		C03XW	
		D03WX	
		M01AW	
		N05CM	
		N06AW	
		N06AX	
		V90	
		V91	
Liver enzymes (ALT/AST) elevation	ANTIHYPERTENSIVES	C02AB	ALPHA-METHYL-DOPA
	ANTIARRHYTHMICS	C01BD	AMIODARONE
	ANTIHYPERTENSIVES	C02KX	BOSENTAN
	ANALGESICS/ANTIEPI-LEPTICS/PSYCHOLEP-TICS	N02BG	
		N03AF	
		N05AX	CARBAMAZEPINE
	MUSCLE RELAXANTS	M03CA	DANTROLENE
	DRUGS USED IN ADDIC-TIVE DISORDERS/ AN-	N07BB	
		P03AA	DISULFIRAM

TIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS		
ANTIPSORIATICS/	D05BB	
ANTINEOPLASTIC	D11AX	
AGENTS	L01XF	ETRETINATE
ANTIFUNGALS/ ANTIMYCOTICS/ ANTIINFECTIVES	D01AC J02AC S01AX	FLUCONAZOLE
DRUGS USED IN DIABETES	A10BB	GLYBURIDE
ANESTHETICS	N01AB	HALOTHANE
ANTITHROMBOTIC	B01AB	
AGENTS/ VASOPROTECTIVES/	C05BA S01XA	HEPARIN
LIPID MODIFYING AGENTS	C10AA	Hmg coa reductase inhibitors
ANTIMYCOBACTERIALS	J04AC	ISONIAZID
ANTIFUNGALS/ ANTIINFECTIVES AND ANTISEPTICS/ CORTICOSTEROIDS FOR SYSTEMIC USE/ ANTIMYCOTICS	D01AC G01AF H02CA J02AB	KETOCONAZOLE
BETA BLOCKING AGENTS	C07AG	LABETALOL
VITAMINS/ PERIPHERAL VASODILATORS/	A11HA C04AC	
LIPID MODIFYING AGENTS	C10AD	NICOTINIC ACID
ANTIBACTERIALS	J01XE	NITROFURANTOIN
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	M01A	NSAIDS
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS/ TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	M01AA M02AA	PHENYLBUTAZONE
ANTIEPILEPTICS	N03AB	PHENYTOIN
ANTITHYROID PREPARATIONS	H03BA	PROPYLTHIOURACIL
ANTIVIRALS	J05AE	PROTEASE INHIBITORS
INTESTINAL ANTIINFECTIVES/ ANTIBIOTICS/ GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS/ ANTIBACTERIALS	A07AB D06BA G01AE J01EB J01EC S01AB	SULFONAMIDES
ANTIFUNGALS/ ANTIINFECTIVES AND ANTISEPTICS	D01AE D01BA G01AX	TERBINAFINE
ANTIDEPRESSANTS	N06AX	TRAZODONE

	DRUGS USED IN DIABETES	A10BG	TROGLITAZONE
	ANALGESICS/ ANTIEPILEPTICS/ PSYCHOLEPTICS	N02CX N03AG N05AX	VALPROIC ACID
	DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES/ UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	R03WA V90	EPHEDRA
	BILE AND LIVER THERAPY/ HERBAL DIGESTIVES/ UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	A05AW A09WA V90	GENTIANA LUTEA
	BILE THERAPY/ HERBAL DIGESTIVES/ ANTIGOUT PREPARATIONS/ ANALGESICS/	A05AW A09WA M04AC N02BG V90	GERMANDER
	DRUGS FOR CONSTIPATION	A06AB V90	SENNA ALEXANDRINA
	OTHER GYNECOLOGICALS	G02CX V90	SCUTELLARIA
	ANTINEOPLASTIC AGENTS/ ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	L01 M01AX	SHARK CARTILAGE
	VITAMINS	A11CA	VITAMIN A NOS
	ANABOLIC STEROIDS	A14A A01AD N01BC	ANABOLIC STEROIDS
	STOMATOLOGICAL PREPARATIONS/ ANESTHETICS	R02AD S01HA S02DA	COCAINE
	PSYCHOANALEPTICS	N06BA	ECSTASY
	ANESTHETICS/ ANALGESICS	N01AX N02BG	PHENCYCLIDINE
	Solvents and diluting agents, incl. irrigating solutions	V07AB	CARBON TETRACHLORIDE
	ANESTHETICS	N01AB	CHLOROFORM
	tertiary carboxylic acid amides	V07AY	DIMETHYLFORMAMIDUM
	ANTINEOPLASTIC AGENTS	L01XX V03AX	HYDRAZINE
	ANESTHETICS	N01AB	TRICHLOROETHYLENE
QT prolongation and proarrhythmia	OTHER DERMATOLOGICAL PREPARATIONS/ ANTINEOPLASTIC AGENTS/	D11AX L01XX V03AX	ARSENIC

	V91	
ANTI-ACNE PREPARATIONS/ ANTIBACTERIALS/ ANTIINFECTIVES	D10AF J01FA S01AA	AZITHROMYCIN
IMMUNOSUPPRESSANTS/ ANTIPROTOZOALS	L04AX P01BA	CHLOROQUINE
ANTIEMETICS AND ANTINAUSEANTS/ PSYCHOLEPTICS	A04AD N05AA	CHLORPROMAZINE
ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE/ GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS/ ANTIBACTERIALS/	D06AX G01AA J01MA S01AE S03AA S03AA	CIPROFLOXACIN
PSYCHOANALEPTICS	N06AB	CITALOPRAM
PSYCHOANALEPTICS	N06DA	DONEPEZIL
ANTIEMETICS AND ANTINAUSEANTS/ PSYCHOLEPTICS	N05AD A04A	DROPERIDOL
ANTIFUNGALS FOR DERMATOLOGICAL USE/ ANTIMYCOTICS/ ANTIINFECTIVES	D01AC J02AC S01AX	FLUCONAZOLE
ANALGESICS/ DRUGS USED IN ADDICTIVE DISORDERS	N02AC N07BC	METHADONE
ANTIEMETICS AND ANTINAUSEANTS	A04AA	ONDANSETRON
ANESTHETICS	N01AX	PROPOFOL
ANESTHETICS	N01AB	SEVOFLURANE
PSYCHOLEPTICS	N05AC	THIORIDAZINE
ANTINEOPLASTIC AGENTS	L01EX	VANDETANIB
DRUGS USED IN BENIGN PROSTATIC HYPERTROPHY	G04CA	ALFUZOSIN
UROLOGICALS/ ANTIPARKINSON DRUGS/ Antidotes	G04BE N04BC V03AB	APOMORPHINE
PSYCHOLEPTICS	N05AH	ASENAPINE
PSYCHOANALEPTICS	N06BA	ATOMOXETINE
ANTIMYCOBACTERIALS	J04AK	BEDAQUILINE
ANTINEOPLASTIC AGENTS	L01ED	CRIZOTINIB
PSYCHOLEPTICS	N05CM	DEXMEDETOMIDINE
ANTIVIRALS FOR SYSTEMIC USE	J05AG	EFAVIRENZ
ANTIEPILEPTICS	N03AX A12CX D11AX	FELBAMATE LITHIUM

MINERAL SUPPLEMENTS/ PSYCHOLEPTICS	N05AN V04CX	
CALCIUM CHANNEL BLOCKERS	C08CA	NICARDIPINE
ANTIHYPERTENSIVES/ UROLOGICALS	C02KX G04BE	VARDENAFIL
ANTINEOPLASTIC AGENTS	L01EC	VEMURAFENIB
ANALGESICS/ PSYCHOLEPTICS/ ANXIOLYTICS/ ANTIDEPRESSANTS	N02CX N05BX N06AX	VENLAFAXINE
ANTINEOPLASTIC AGENTS	L01XH	VORINOSTAT

Note: Use ATC Code (4th level code - ATC4) and Preferred term (CMDECOD) for merging to get information about medications as we do not have 5th level code (ATC5) information in the database.

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 5.0

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 5.0 (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 5.0 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 Computation of Blood Pressure Percentiles for Arbitrary Sex, Age, and Height

Below algorithm is described in the Appendix B of the following reference: The Fourth Report on Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics 2004; 114; 555.

- To compute the systolic blood pressure (SBP) percentile of a boy whose age is y years and height =h inches with SBP = x mmHg:

  - Convert the height of *h* inches to a height Z-score relative to boys of the same age (as per data tables provided Table 5-11 and Table 5-12; this is denoted by Z_{ht}. For age < 2 years, age is recorded in the CRF with month as the unit and will be converted into year with 1 decimal, the corresponding height Z score can be calculated using months (see Table 5-11).
  - Compute the expected SBP (μ) for boys of age *y* years and height *h* inches given by

    $$\mu = \alpha + \sum_{j=1}^{4} \beta_j (y-10)^j + \sum_{k=1}^{4} \gamma_k (Z_{ht})^k$$

    where, regression coefficients are given in the 3rd column of Table 5-10.
  - Then convert the boy's observed SBP (x) to a Z-score (Z_{BP}) given by

    $$Z_{BP} = \frac{(x-\mu)}{\sigma}$$

    where, σ is given in the 3rd column for standard deviation row of Table 5-10.
  - To convert the bp Z-score to a percentile (P), compute P = $\phi(Z_{BP})$ x 100%

    where $\phi(Z)$ = area under a standard normal distribution to the left of Z.

- Likewise, to compute percentiles for SBP for girls, diastolic blood pressure (DBP) (K5) for boys, and DBP (K5) for girls, use the regression coefficients from the 4th, 5th, and 6th columns of Table 5-10.

For example, a 12-year-old boy, with height at the 90th percentile for his age-sex group, has a height Z-score = 1.28, and his expected SBP (μ) is

μ = 102.19768 + 1.82416 (2) + 0.12776 (2^2) + 0.00249 (2^3) –0.00135 (2^4) + 2.73157 (1.28) –0.19618 (1.28^2) –0.04659 (1.28^3) + 0.00947(1.28^4) = 109.46 mmHg.

Table 5-10 Regression coefficients from Blood Pressure Regression Models

Regression Coefficients From Blood Pressure Regression Models*

Variable Name	Symbol	Systolic BP		Diastolic BP5	
		Male	Female	Male	Female
Intercept	α	102.19768	102.01027	61.01217	60.50510
Age					
Age–10	β_1	1.82416	1.94397	0.68314	1.01301
$(Age–10)^2$	β_2	0.12776	0.00598	-0.09835	0.01157
$(Age–10)^3$	β_3	0.00249	-0.00789	0.01711	0.00424
$(Age–10)^4$	β_4	-0.00135	-0.00059	0.00045	-0.00137
Normalized height					
Zht	γ^1	2.73157	2.03526	1.46993	1.16641
Zht^2	γ^2	-0.19618	0.02534	-0.07849	0.12795
Zht^3	γ^3	-0.04659	-0.01884	-0.03144	-0.03869
Zht^4	γ^4	0.00947	0.00121	0.00967	-0.00079
Standard deviation	σ	10.7128	10.4855	11.6032	10.9573
ρ†		0.4100	0.3824	0.2436	0.2598
n (persons)		32,161	31,066	24,057	23,443
n (*visits*)		*42,074*	*41,017*	*29,182*	*28,794*

BP, blood pressure; Diastolic BP5, diastolic measurement at Korotkoff 5.

* The coefficients were obtained from mixed-effects linear regression models.

† The value of ρ represents the correlation between BP measurements at different ages for the same child after correcting for age and Zht. This computation was necessary because some studies contributing to the childhood BP database provided BP at more than one age.

Computation of Z-score for height:

As per the recommendation from Centers for Disease Control and Prevention (CDC) use WHO growth charts for 0 to < 2 years of age and CDC growth charts for age ≥2 years. Accordingly, convert the given height into corresponding Z-score as per Table 5-11 and Table 5-12 given for the growth standards using the following formula.

$$Z_{ht} = \frac{(\frac{height}{median})^L - 1)}{L * S}$$

where, median, L, S (i.e. CV) are provided in the Table 5-11 for age up to 2 years and in Table 5-12 for age 2-20 years; height in centimeters.

Table 5-3 Table for WHO standard Length-for-age growth chart for age 0 to to 2 years

		Boy		Girl	
Month	L	Median (cm)	S (CV)	Median (cm	S (CV)
0	1	49.8842	0.03795	49.1477	0.0379
1	1	54.7244	0.03557	53.6872	0.0364
2	1	58.4249	0.03424	57.0673	0.03568
3	1	61.4292	0.03328	59.8029	0.0352
4	1	63.886	0.03257	62.0899	0.03486
5	1	65.9026	0.03204	64.0301	0.03463
6	1	67.6236	0.03165	65.7311	0.03448
7	1	69.1645	0.03139	67.2873	0.03441
8	1	70.5994	0.03124	68.7498	0.0344
9	1	71.9687	0.03117	70.1435	0.03444
10	1	73.2812	0.03118	71.4818	0.03452
11	1	74.5388	0.03125	72.771	0.03464
12	1	75.7488	0.03137	74.015	0.03479
13	1	76.9186	0.03154	75.2176	0.03496
14	1	78.0497	0.03174	76.3817	0.03514
15	1	79.1458	0.03197	77.5099	0.03534
16	1	80.2113	0.03222	78.6055	0.03555
17	1	81.2487	0.0325	79.671	0.03576
18	1	82.2587	0.03279	80.7079	0.03598
19	1	83.2418	0.0331	81.7182	0.0362
20	1	84.1996	0.03342	82.7036	0.03643
21	1	85.1348	0.03376	83.6654	0.03666
22	1	86.0477	0.0341	84.604	0.03688
23	1	86.941	0.03445	85.5202	0.03711

Reference:

https://www.cdc.gov/growthcharts/who/boys_length_weight.htm

https://www.cdc.gov/growthcharts/who/girls_length_weight.htm

Note – Table 5-11 to be accessed from the GPS II growth_data (where TEST='BODY LENGTH' and YEAR_CHG=WHO2006)

Table 5-12 Table for CDC growth standard height-for-age growth charts for age 2 - 20 years

	Boy			Girl		
Age(year)	L	Median (cm)	S (CV)	L	Median (cm)	S (CV)
2	0.941524	86.4522	0.040322	1.072449	84.97556	0.040791

3	-0.39092	95.27359	0.040534	0.541981	94.21336	0.042018
4	0.827637	102.5105	0.041344	0.225706	101.0339	0.04326
5	1.266367	109.1751	0.042593	-0.05773	107.9566	0.044277
6	1.137443	115.6609	0.043673	-0.21907	115.0055	0.044964
7	0.753244	122.0305	0.044403	-0.21021	121.7617	0.045461
8	0.455268	128.1237	0.045127	-0.07928	127.8263	0.045968
9	0.415687	133.7345	0.046217	0.084148	133.1304	0.046884
10	0.505564	138.8234	0.04761	0.284749	138.2112	0.048705
11	0.487939	143.7304	0.048938	0.74429	144.2609	0.050524
12	0.420919	149.3088	0.049948	1.303045	151.4866	0.048599
13	0.81624	156.4099	0.050333	1.242968	157.3437	0.043859
14	1.670433	164.1418	0.048945	0.956572	160.4777	0.041022
15	2.20518	170.1393	0.04589	0.89557	161.898	0.040084
16	2.113023	173.6101	0.043086	0.941146	162.569	0.039821
17	1.724738	175.341	0.041408	0.999506	162.9238	0.039732
18	1.399999	176.185	0.040644	1.047571	163.1308	0.039687
19	1.229163	176.6179	0.040391	1.083315	163.259	0.039657
20	1.167279	176.8492	0.04037	1.108046	163.3383	0.039636

Reference: https://www.cdc.gov/growthcharts/data/zscore/statage.csv

Note – Table 5-12 to be accessed from the GPSII growth_data (where TEST='HEIGHT' and YEAR_CHG=CDC2000)

5.7 Statistical models

5.7.1 Primary analysis

The primary analysis of PCR-corrected 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.

1. For exploratory purpose, 2-sided 95% confidence intervals for the difference in ACPR at Day 29 between two KAF156/LUM-SDF treatment groups with optimal dose will be constructed for Cohorts 2 and 3 using the Wilson uncorrected method.

Wilson uncorrected method:

Let

a = # responders in the fed arm

c = # non-responders in fed arm

m = sample size of the fed arm (a+c)

b = # responder in the fasted arm

d = # non-responders in the fasted arm

n = sample size of the fasted arm (b+d)

$\theta = \pi_1 - \pi_2$ is the difference between two arms

$\hat{\theta} = \frac{a}{m} - \frac{b}{n}$ is estimated difference between two arms

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.

5.7.2 Key secondary analysis

NA

5.7.3 Other secondary/exploratory 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 cohort using Mantel-Hanszel estimate

For PCR corrected and uncorrected ACPR rates, the between treatment difference will be evaluated using a Mantel-Haenszel estimate of the treatment difference in responder rates stratified by cohort 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 between treatment difference will be evaluated using a Wilson uncorrected method using PROC FREQ with RISKDIFF (CL= NEWCOMBE) option in the TABLES statement.

Difference in parasite clearance (fever clearance) rate using log-rank test

For parasite clearance and fever clearance rates, the between treatment difference will be evaluated using log-rank test using PROC LIFETEST with STRATA <treatment > and TEST <treatment > statements. For pooled time to event data from cohort 1 and 2, stratified log-rank test will be performed using GROUP = <cohort> option in STRATA statement.

Confidence interval for Post treatment max QTcF/QTcB increase from baseline

For maximum increase in QTcF/QTcB from baseline, 2-sided 100*(1-α) % confidence intervals (CI) for the difference between the 2 treatment groups will be calculated using PROC TTEST by assuming normality of data.

Confidence interval for geometric mean ratio

For PK parameters, such as $AUC_{0\text{-}24h}$, Cmax, the values for individuals will be converted into $\log_e$ scale. Mean difference and corresponding 2-sided 100*(1-α) % confidence intervals (CI) will be calculated using PROC TTEST by assuming normality of data on log scale. The geometric mean, the lower and upper confidence limits will be calculated by exponentiating the difference, and lower and upper confidence limit that were derived using log data.

5.7.4 Summary of treatment outcome assignment

The below table provides treatment outcome assignments for both uncorrected and PCR-corrected ACPR at a given Day, say D where D can be 15, 29, or 43, for various specific scenarios.

Table 5-13 Derivation Criteria of uncorrected ACPR and PCR- corrected ACPR

Criteria	PP Analysis Set (PPS)		ITT Analysis Set	
	Treatment Outcome uncorrected ACPR	**Treatment Outcome PCR-adjusted ACPR**	**Treatment Outcome uncorrected ACPR**	**Treatment Outcome PCR-adjusted ACPR**
1. Completed up to Day (D) without re-emergence (new infection/ recrudescence) of parasites after initial clearance	Responder	Responder	Responder	Responder
2. Missing assessment on Day (D), but parasite free (No *P. falciparum* asexual parasites) after Day (D).	Responder	Responder	Responder	Responder
3. Missing assessment on Day (D), new infection (confirmed by PCR result) at first assessment after Day (D).	Non-responder	Responder	Non-responder	Responder
4. Early treatment failure from Day 2 to Day 4.	Non-responder	Non-responder	Non-responder	Non-responder
5. Late clinical failure from Day 5 to Day 7.	Non-responder	Non-responder	Non-responder	Non-responder
6. Receive non-study anti-malarial medication during the treatment period	Excluded from PPS	Excluded from PPS	Non-responder	Non-responder
7. Recrudescence before or on Day (D) (thus on or after Day 8 to [D])	Non-responder	Non-responder	Non-responder	Non-responder
8. New infection/PCR negative on Day (D).	Non-responder	Responder	Non-responder	Responder
9. New infection/PCR negative before Day (D) (thus on or after Day 8 to before (D))	If D <=29, excluded from PPS; If D=43, Non-responder	If D <= 29, excluded from PPS; if D=43, non-responder/	Non-responder	Non-responder/ responder/KM-censoring

		responder/KM-censoring;		
10. Re-emergence before or on Day (D) but PCR result is indeterminate or missing.	Non-responder	Excluded from PPS if D <=29 or non-responder/KM-censoring if D=43	Non-responder	Non-responder/KM-censoring
11. Missing assessment on Day (D), recrudescence (confirmed by PCR result) at first assessment after Day (D).	If D=29, excluded from PPS; if D=15, non-responder/KM-responder; NA for D=43	If D=29, excluded from PPS; if D=15, non-responder/ KM-responder; NA for D=43	Non-responder/ KM-responder	Non-responder/ KM-responder
12. Other *Plasmodium* species on Day (D) (in the absence of *P. falciparum*).	Responder	Responder	Responder	Responder
13. Other *Plasmodium* species before Day (D) (in the absence of *P. falciparum*).	If taking non-study drug prior to D29, excluded from PPS; otherwise, responder/ KM-censoring	If taking non-study drug prior to D29, excluded from PPS; otherwise, Responder/ KM-censoring	Responder/ KM-censoring	Responder/ KM-censoring
14. Other *Plasmodium* species before or on Day (D) (in the presence of *P. falciparum*), PCR-analysis result missing or indeterminate.	Handled as the Criteria 10, 12, and 13	Handled as Criteria 10, 12, and 13	Handled as Criteria 10, 12, and 13	Handled as Criteria 10, 12, and 13
15. Prematurely study discontinued from the study without parasite re-emergence before Day (D) and received SoC.	If discontinue before D29, excluded from PPS; if D=43,	If discontinue before D29, excluded from PPS; if D=43, non-	Non-responder/KM-censoring	Non-responder/KM-censoring

	Non-responder/KM-censoring	responder/KM-censoring		
16. Missing assessment on Day (D), no more assessments thereafter.	If D <= 29, excluded from PPS; Otherwise: non-responder/ KM-censoring	If D <= 29, excluded from PPS; Otherwise: non-responder/KM-censoring)	Non-responder/ KM-censoring	Non-responder / KM-censoring
17. Prematurely discontinued from the study before Day (D) and no record of SoC.	Same as Criterion 16	Same as Criterion 16	Same as Criterion 16	Same as Criterion 16

Note: '/' indicates separate analysis, e.g., 'non-response/KM-censoring' indicates one analysis considering outcome as non-responder and another analysis using KM method considering outcome as censored
NA: Not applicable; SoC: Standard of care
If a scenario meets multiple criteria, the worst case (non-responder) is used.

5.8 Rule of exclusion criteria of analysis sets

Table 5-14 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 (INCL05)	• Not randomized • Misrandomized if identified from IRT
FAS	NA	• Not in Randomized set • Baseline parasitaemia count is 0 or missing • No study drug taken
PPS	• Parasite specie is other than Plasmodium falciparum OR mixed infection (INCL03) • Baseline plasmodium falciparum parasite count <1000/uL or ≥150000/uL (INCL04) at the time of prescreening for the Run-in; plasmodium falciparum parasite count < 1,500 or ≥ 150,000 /uL parasites/µL at the time of pre-screening for Cohorts 1 and 2 • No fever within the past 24 hours at baseline (INCL06) • Prohibited non-antimalarial medications that may have effect on efficacy if received before the Day 29 visit without being falciparum treatment failures (COMD001A) • Only for Run-in Cohort, do not fully comply with the food guidelines according to randomization (with OTH04 either day)	• Not in FAS; • <80% of randomized study medication taken • Received non-study concomitant antimalarial drugs during the treatment period • Received non-study concomitant antimalarial drugs after the treatment period between Day 4 and 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, have a new infection prior to study Day 27 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 or new infection at Day 43
SAF	NA	• Not in Randomized set • No study drug taken
PK	• Patients who received concomitant prohibited medication which may have an impact on PK exposure	• Not in SAF • No evaluable pharmacokinetic parameter data • Compliance is <100% of randomized study medication taken

6 Reference

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