Clinical Development

KAE609

CKAE609A2202 / NCT03334747

A Phase 2, multi-center, randomized, open-label, dose-escalation study to determine safety of single (QD) and multiple (3 QD) doses of KAE609, given to adults with uncomplicated *Plasmodium falciparum* malaria

Statistical Analysis Plan (SAP)

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21-Jan-2020	Updates prior to DBL	Amendment 1	Corrected definition of fever temperature for other routes from 38.3 to 38.0	Section 2.3.2 and 2.8.3.2
			Added note for tail of KM plots	Section 2.1.1
			Added that treatment failure definitions are based on P. falciparum asexual counts	Section 2.1.1.1
			Extended definition of LCF and LPF with respect to fever definition for other routes	
			Adapted condition of parasite clearance by Day 7 from definition of cures at Day 15/29 and from definition of event date for KM	Section 2.1.1.1 + Section 2.7.2.1
			Adapted definition of Analysis Sets to be consistent with Table 5-9	Section 2.2
			Added non-PD criterion to definition of PK analysis set	Section 5.6, Table 5-9
			Removed category 'Mixed-infection' from demographic variable P. falciparum species, as mixed infections are not allowed	Section 2.3.2
			Removed shift tables	Section 2.8.2
			Adding note for handling Lab values beyond detection limit	
			Added 'New' to ECG criteria based on absolute values only	Section 2.8.3.1
			Harmonized definition of subjects excluded from FCT with respect to tables/figures	Section 2.7.2.3

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Adapted visit window for analysis timepoint for 4 hrs due to gap	Section 5.1.4 (Table 5-6)
			Clarified baseline derivation as assessments at treatment start datetime should be included	Section 2.1.1 & Section 5.1.4 (Table 5-7)
			Changed condition of clearance of initial infection for recrudescence/reinfection	Section 2.7.2.4/2.7.2.5
			Removed QTcB	Section 2.8.1.1/2.8.3.1
			Added derivation of study day for subjects that are randomized but not treated	Section 2.1.1
			Added HR to in-text table	Section 2.8.1.1
			Removed table for MH contributing to liver dysfunction	Section 2.3.1
			Changed threshold in step 2 (ii) to 500 such that algorithm fits to inclusion criterion 3	Section 2.13
			Added Lumefantrine	Section 2.9
			Added T1/2 to list of PK parameters	Section 2.9
			Removed visit window for time point 36 hrs for PK and adapted preceding and subsequent visit windows	Section 5.1.4, Table
		Protocol amendment	Adapted section according to protocol amendment; added new figure 1-1	Section 1.1
			Added two new treatment groups to list	Section 2.1.1
			Adapted sections according to protocol amendment	Section 2.15/3.2
			Added link to final list of prohibited medications	Section 5.2
07-Apr-	Updates	Addendu	Added subgroup of high baseline	Section 2.2.1

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
2020	after DBL	m 1	parasitaemia	
			[redacted]	
			Removed analysis on PPS	Section 2.3.2
			[redacted]	

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
bid	bis in diem/twice a day
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
IVR	Interactive Voice Response
IWR	Interactive Web Response
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
o.d.	Once Daily
OS	Overall Survival
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization
ETF	Early treatment failure
LPF	Late parasitological failure
LCF	Late clinical failure
SRC	Safety Review Committee
FCT	Fever clearance time
PCT	Parasite clearance time

1 Introduction

The purpose of the Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analysis which is planned in the protocol. The study has 6 cohorts: Cohort 1, 5, 6 with 2 arms and Cohort 2, 3, 4 with 3 arms each. Proceeding to next cohort depends on the interim safety review outcome done by the safety review committee (SRC) which will happen at predefined time points and is outlined in section 2.15 below. A single database will suffice for all the cohorts. The clinical study report will be prepared after the final database lock (DBL) at the end of all cohorts on the basis of this SAP. This single SAP will be used for the analysis of data collected for each cohort and the pooled analysis of all the cohorts together. The statistical method in this SAP will be used to execute a separated SRC TFL shells by [redacted] for Interim Safety review if required.

1.1 Study design

This will be a multicenter, open label, randomized, dose escalation study to evaluate the hepatic safety and tolerability of KAE609 in adult patients (≥18 years and ≥45 kg bodyweight) with uncomplicated malaria caused by *P. falciparum*.

Starting dose of KAE609 will be a single dose of 10 mg and following acceptable safety results in the 10 mg treatment arm, the dose of KAE609 will be increased stepwise up to a single dose of 225 mg and multiple doses of 50 mg (QD x 3 days) according to schedule below (Figure 1-1).

Based on the safety pattern observed in previous studies with KAE609, liver function test (LFT) parameters, if they rise, are expected to peak within 14 days of treatment. Hence, the decision to escalate to next cohort with higher doses will be based on the criteria as specified in the table below (Table 1-1):

Table 1-1 Decision criteria for dose escalation based on LFT results with KAE 609

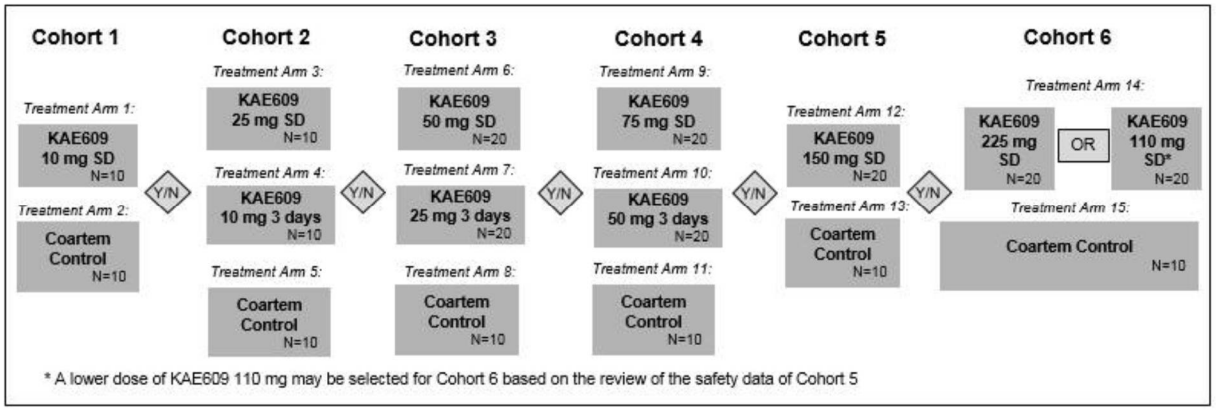
LFT parameter	Baseline	Maximum post baseline value	Decision to escalate to next cohort
ALT/AST	Within ULN	< 2 times ULN (from **Day 1 to Day 15**)	Escalate to next cohort after notification to safety review committee, after all the patients in the cohort have been followed for at least 14 days post treatment (study Day 15).
	> 1 to ≤ 1.5 ULN	< 2 times baseline (from **Day 1 to Day 15**)	
ALT/AST	Within ULN	≥ 2 to < 3 times ULN (from **Day 1 to Day 15**)	Escalate to next cohort based on review of liver safety (and any other relevant data) by safety review committee, after all the patients in the
	> 1 to ≤ 1.5 ULN	≥ 2 to < 3 times baseline (from **Day 1 to Day 15**)	

			cohort have been followed for at least 28 days post treatment (**Study Day 29**)
ALT/AST	Any baseline value	≥ 2 Grade (CTCAE grades) increase from baseline (**at any time point during the study**) in: - 2 patients in a 10 patient cohort (Cohorts 1 and 2) or - 3 patients in a 20 patient cohort (Cohorts 3 and 4, 5 and 6)	Suspend recruitment and initiate review of liver safety (and any other relevant data) by safety review committee. Any further progression of the study is based on the decision by the safety review committee

In consultation with the safety review committee, Novartis can suspend recruitment and trigger safety review any time based on safety signals including any potential Hy's law case.

Based on the pre-specified criteria (Table 3-1) and the review of the liver safety data by a safety review committee, the recruitment in Cohort 5 may be stopped and a lower dose of KAE609 i.e. 110 mg may be selected for Cohort 6. The study could be stopped after Cohort 5 if there is no added advantage for dosing the patients with 225 mg single dose from the perspective of future clinical development of KAE609 and its subsequent use in clinical practice.

Figure 1-1 Study KAE609A2202 diagram



Given the expected sub-therapeutic efficacy of the doses of KAE609 in the first 2 cohorts, a smaller number (N=10) of patients will be included (10 mg Single Dose (SD), 25 mg SD and 10 mg 3 Days) to detect potential LFT increases. In the subsequent cohorts a higher number (N=20) of patients will be included. All patients will be followed up for 4 weeks with close monitoring in an inpatient setting for at least the first 3 days (Study Day 4) for efficacy and safety followed by outpatient monitoring up to Study Day 29.

Patients will be randomized to KAE609 vs Coartem in a ratio of 1:1 in cohort 1. In cohort 2, SD KAE vs QD KAE609 vs Coartem will be randomized in the ratio of 1:1:1. In Cohorts 3

and 4 the SD KAE609 vs QD KAE609 vs Coartem will be randomized in the ratio of 2:2:1. In Cohorts 5 and 6 the SD KAE609 vs Coartem will be randomized in the ratio 2:1. There are no stratification factors in this study.

Visits to assess safety and efficacy will be scheduled during the follow-up period as described in the assessment schedule table in protocol.

The safety of entire study will be monitored by the Safety Review Committee.

1.2 Study objectives and endpoints

Table 1-2 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s) • To characterize hepatic safety aspects of single- and multiple ascending doses of KAE609 in adult malaria patients	**Endpoint(s) for primary objective(s)** • At least 2 CTCAE grades increase from baseline in ALT or AST during the 4 week study period
Secondary Objective(s) • To evaluate overall safety and tolerability of KAE609. • To assess key PK parameters following treatment with KAE609. • To assess the efficacy of KAE609 in patients with uncomplicated *falciparum* malaria. • To assess recrudescence after single and multiple doses of KAE609	**Endpoint(s) for secondary objective(s)** • Standard safety/tolerability assessments (AE incidence and severity, vital signs, ECG, laboratory abnormalities) • PK parameters such as AUC, Cmax, Tmax, T½ etc. • PCR-Uncorrected adequate clinical and parasitological response (ACPR) and PCR-Corrected ACPR at Days 15 and 29 (i.e., 14 and 28 days post-dose) Parasite and Fever Clearance Times (PCT and FCT) before rescue medication is given • Incidence rate of recrudescence at Day 29
[redacted]	

2 Statistical methods

2.1 Data analysis general information

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

At the end of trial, full statistical analyses will be performed by cohort and treatment group. Coartem data from all cohorts will also be pooled.

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

Data analyses required for the study SRC meeting will be analyzed by the third party vendor ([redacted]). The outline of the SRC Review analysis plan is presented in the SRC charter and will be detailed in the SRC TFL shells. A separate SAP for SRC is not needed since the statistical methods for SRC are same as those in this SAP.

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

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

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

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

Since the randomization is not stratified, statistical analysis will not be stratified. For pooled analyses, coartem patients will be pooled from all the cohorts and compared with patients from different KAE doses.

2.1.1 General definitions

Study treatment: KAE609 is the investigation treatment whereas Coartem® will serve as control. They are referred to as study treatments in the document.

Summary results will be presented by cohort and treatment group. Besides, a pooled Coartem group from all cohorts will be presented from all tables as applicable. The following abbreviated treatment group labels will be used as the column headers in the CSR outputs:

- KAE609 10 mg SD

- KAE609 10 mg QD 3 days
- KAE609 25 mg SD
- KAE609 25 mg QD 3 days
- KAE609 50 mg SD
- KAE609 50 mg QD 3 days
- KAE609 75 mg SD
- KAE609 150 mg SD
- KAE609 225 mg SD or KAE609 110 mg SD
- Coartem
- Pooled Coartem

Baseline: The last measurement made prior to and including administration of the first dose of study treatment. Note this may include measurements taken on the day of randomization (e.g. lab, ECG, vital signs). 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. 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.

For assessments collected on or after Day 1, 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.

At the end of trial, full statistical analyses will be performed by cohort and treatment group. Coartem data from all cohorts will also be pooled.

Tail of KM plots: Since the tail of KM plots after the day of last planned assessment is not reliable due to small numbers of patients at risk, the time to event will be truncated to the planned last day (Day 29) regardless of censoring.

2.1.1.1 Definition for treatment failures

All definitions of treatment failures are based on *P. falciparum* asexual counts.

Early treatment failure (ETF)

Patients will be classified as ETF upon meeting any of the following criteria:

- Clinical decline or lack of improvement (per Investigator) at 24 hours after first dose of treatment.

- Development of any clinical complications (described in the WHO definition of complicated/severe malaria (WHO Guidelines 2010) in the presence of parasitaemia (based on microscopy) within 72 hours of the first dose of treatment
- Parasitaemia > 75 000/µL based on microscopy at or after 12 hours post first dose
- Parasitaemia ≥ baseline based on microscopy with or without fever at 36 hours after the first dose of treatment
- Any parasitaemia based on microscopy with fever, 48 hours post first dose
- Parasitaemia > 100/ µL based on microscopy with or without fever, 72 hours post first dose

Late Clinical Failure (LCF)

Patients will be classified as LCF upon meeting any of the following criteria:

- Development of danger signs or severe malaria on any day between Study Day 5 and Study Day 29 in the presence of parasitaemia based on microspcopy without previously meeting any of the criteria of ETF.
- Presence of parasitaemia based on microspcopy and fever (i.e. axillary temperature ≥ 37.5ºC or other routes >= 38°C) on any day between Study Day 5 and Study Day 29 without previously meeting any of the criteria of ETF.

Late Parasitological Failure (LPF)

Patients will be classified as LPF upon meeting the following criterion:

- Presence of parasitaemia based on microspcopy on any day between Study Day 5 and Study Day 29 and no fever (i.e. axillary temperature < 37.5ºC or other routes < 38°C) without previously meeting any of the criteria of ETF or LCF.

Adequate Clinical and Parasitological Response (ACPR):

Absence of parasitaemia based on microspcopy on Study Day 29 irrespective of axillary temperature, without previously meeting any of the criteria of ETF, LCF, or LPF.

Uncorrected ACPR at Day X where X=15 and 29

- A patient is considered as non-responder at Day X if the patient experiences an ETF, LCF or LPF from Day 5 to Day X.
- A patient is also considered as non-responder if the parasitaemia is not cleared by Day X unless the patient discontinues the study prior to Day X without ETF, LCF, or LPF in which case the response is considered as missing.

- A patient is considered as responder (Uncorrected ACPR) at Day X if the patient is not classified as a non-responder at Day X and the patient has a malaria blood film showing absence of parasitaemia at Day X or later if Day X is missing.
- The response for a patient is considered as missing/undertermined if the patient is not classified as a non-responder and the malaria blood film result at Day X is missing and not followed by a subsequent negative result.

PCR-corrected ACPR at Day X where X=15 and 29

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

Note - The outcome of PCR-corrected ACPR and uncorrected ACPR at a given day is categorized as responder or non-responder to distinguish from failure used in early treatment failure, late clinical failure or late parasitological failure. With this notation, ACPR rate is the proportion of responders.

A patient with presence of parasitaemia at more than 7 days after the first dose is considered as non-responder for uncorrected ACPR. We reclassify such a patient as responder for PCR-corrected ACPR if presence of parasitaemia at more than 7 days after the first dose is due to new infection. Whether the presence of parasitaemia after 7 days is due to recrudescence or new infection is determined and provided by the central laboratory.

The above defintions of ACPRs are purely based on the malaria blood film and PCR results without consideration for taking concomitant anti-malaria drugs. In statistical analyses, some

responses may be overriden for patients who take concomitant anti-malaria drugs (see Sections 2.5 and 2.7).

Fever Clearance time (FCT), defined as time from the first dose until the first time the axillary body temperature decreased below and remained below 37.5°C axillary or 38.0°C oral/tympanic/rectal for at least a further 24 hours.

Parasite clearance time (PCT), 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 (RAN) : All patients who are randomized and not misrandomized if identified from IRT and who did not experience any important protocol deviation related to informed consent.

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 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.

Safety set (SAF set) : 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.

Per-protocol set (PPS) : PPS will be comprised of patients in FAS who

- did not have any important protocol deviations
- took at least 80% of assigned 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. Except for patients who are assigned to Coartem treatment, this requires that all patients take all KAE609 dosages as assigned. For Coartem, the patient needs to take at least 5 doses of study drug to have taken 80%.
- did not take other antimalarial medications prior to Study Day 29 for reasons other than rescue medication given for *P. falciparum* related treatment failure, and
- met at least one of the following criteria: (a) classified as treatment failure before Study Day 8 (see Section 2.1.1.1), (b) absent from parasitaemia at Study Day 29, or (c) had valid PCR evaluations at baseline and at the time point with parasitaemia if parasitaemia is present at Study Day 8 or later.

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

PK analysis set : All subjects in the safety analysis set who had evaluable PK parameter data and with at least 80% compliance to study medicationand who did not experience any important protocol deviation as mentioned in Table 5-9.

2.2.1 Subgroup of interest

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

- Sex (male vs female)
- Patients with baseline parasitaemia >= 10000/μL

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 primary system organ class (SOC) and preferred term (PT) of the MedDRA dictionary. A separate 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 but before the first dose of study medication is administered are collected in the adverse event panel and will be summarized separately from adverse events.

The Medical History conditions captured on the eCRF “Protocol solicited events ” will be tabulated separately.

History of use of alcohol will also be summarized.

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 presented descriptively and tabulated (n, mean, standard deviation, median, minimum, and maximum for continuous variables; n and percent for categorical variables) by cohort and treatment group, as well as overall, using Randomized set. If many patients(Overall > 5%) are excluded from FAS, summary will also be provided for the FAS.

Following demographic variables will be summarized

- Age and age categories (<65 vs ≥65 yrs)
- Sex (male, female)
- Subject child bearing status (able to bear children, premenarche, post menopausal, sterile of child bearing age)
- Race
- Ethnicity

- 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 the number and percentage of patients for categories (<37.5, 37.5 to <39, ≥39) (°C) for *(axillary)* and < 38.0°C, 38.0 to <39.8, ≥ 39.8 for other routes)
- Presence of Falciparum species: (P. Falciparum asexual forms, P. Vivax, P. Ovale, P. malariae, P. Knowlesi, n (%))
- P. falciparum asexual forms density per micro ltr. and the number and percentage of patients for categories (<500, 500 to <2,000, 2,000 to <5,000, 5,000 to <15,000, 15,000 to <50,000, ≥50,000 parasites /μL)

2.3.3 Patient disposition

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

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

Randomized set will be used.

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

2.4.1 Study treatment / compliance

Number and percentage of doses taken will be presented by cohort and treatment group. The percentage will be calculated based on the planned number of doses per treatment group.

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

For example, planned number of doses is 1 for 'KAE609 10 mg and 6 for Coartem in cohort 1, etc.

Percentage of doses taken will be calculated as $\frac{\text{actual number of doses administered}}{Planned\ number\ of\ doses}$ x 100

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

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

Average daily dosage and total dosage (in mg) of each study drug (KAE609, Coartem) will be summarized by cohort and treatment group.

$$\text{Average daily dosage} = \frac{\text{sum of actual doses taken in mg}}{actual\ number\ of\ days\ of\ treatment}$$

For Coartem, the tablets taken by patient are converted into mg based on the strength of tablet separately for the two active components of the drug, i.e., artemether and lumefantrine.

Note- If a patient vomited the original dose but did not vomit the replacement dose, the patient is considered as fully dosed. Doses that were vomited are excluded from the analyses although all patients who took at least one dose of study drug regardless of vomit or not are included in the Safety set.

Safety set will be used.

2.4.2 Prior, concomitant and post therapies

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

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

Note – The only rescue medication considered in this study is Coartem. All other antimalarial drugs are prohibited and if taken then it will be considered as PD. If Coartem is used after discontinuation of study drug due to early treatment failure, late clinical failure or late parasitological failure then it should be considered as resue medication,. Rescue medication will be captured along with other concomitant medications by the investigators under rescue medication category.

Any patient on KAE609 who does not need rescue medication up to Study Day 28 will be given Coartem as post therapy at the end of the study (Study Day 29) and will be followed as per standard medical care.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 cohort and treatment by ATC class and preferred term (PT).

Number and percentage of the patients receiving prohibited prior and concomitant drugs will be summarized. Details regarding prohibited drugs are mentioned in Table 5-9. PK related prohibited medications(the drugs which are prohibited only within first 7 days from first dose) and non-PK related prohibited medications will summarized separetly.
Safety set will be used.

2.5 Analysis of the primary objective

The primary objective is to characterize hepatic safety aspects of single and multiple ascending doses of KAE609 in adult malaria patients for treatment of uncomplicated malaria caused by *P. falciparum*.

2.5.1 Primary endpoint

The primary variable is the occurrence of at least 2 CTCAE grades increase from baseline in ALT or AST during the 4 weeks study period.

2.5.2 Statistical hypothesis, model, and method of analysis

The study is a Phase II safety study in African patient population aiming to rule out high incidence of abnormal LFT reported in a couple of earlier studies. As the significance of safety related results is determined by both the frequency of the event and the severity of the event, there is no pre-defined hypothesis. The following analyses will be performed using the SAF set:

- Proportion of patients with occurrence of the primary variable by cohort and treatment group and the 95% confidence interval based on the exact CI (Pearson-Clopper method).
- 2-sided Fisher exact test for each KAE609 treatment group compared to the pooled Coartem.

These results along with patient narratives will be assessed to make decision about whether a KAE609 dosage regimen is safe for further development.

2.5.3 Handling of missing values/censoring/discontinuations

No missing value of the primary variable is expected since the analysis is based on the SAF set and all patients in the SAF set should provide safety observation as they are hospitalized for the first 3 days. No missing data imputation will be done in this study.

2.5.4 Supportive analyses

In the past KAE609 studies, peak LFT occurred during the first 2 weeks after dose administration. For patients who discontinued the study during the first 2 weeks after dose administration, their peak LFT may not be observed. Analyses in Section 2.5.2 will be performed by excluding those patient(s) who discontinued the study before Study Day 15 and did not experience at least 2 CTCAE grades increase from baseline in ALT or AST.

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)

Descriptive statistics for each secondary variable will be provided by cohort and treatment group. Statistical comparison with Coartem will not be performed due to small sample size for each treatment group.

2.7.1 Secondary endpoints

All efficacy analyses are secondary. Secondary efficacy variables include:

- PCR-corrected ACPR at Study Days 15 and 29;
- Uncorrected ACPR at Study Days 15 and 29;

- Proportion of patients with parasitaemia at 12, 24, and 48 hours after the first dose of study drug;
- Parasite clearance time (PCT), 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;
- Fever clearance time (FCT), defined as time from the first dose until the first time the axillary body temperature decreased below and remained below 37.5°C axillary or 38.0°C oral/tympanic/rectal for at least a further 24 hours;
- Proportion of patients with ETF;
- Proportion of patients with LCF;
- Proportion of patients with LPF;
- Incidence rate of recrudescence and reinfection at Study Day 29.

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 and method of analysis are presented in the following sub-sections by topic.

2.7.2.1 PCR-corrected ACPR and uncorrected ACPR

At each visit, the ACPR rate with 95% confidence intervals will be provided using the Pearson-Clopper method for each treatment group by cohort.
PCR corrected/uncorrected ACPRs at Day 29 will be summarized descriptively by the following subgroups

- Sex (male vs female)

Handling of missing values/censoring/discontinuations

Data will be handled as follows:

- Patients with presence of parasitaemia which was determined to be reinfection on Day 8 or later will be counted as responders for PCR corrected ACPR and as non-responder for PCR uncorrected ACPR from the day of test
- Patients with presence of parasitaemia which cannot be determined to be recrudescent or reinfection due to missing PCR corrected/uncorrected data will be counted as non-responders from the day of test
- Patients with 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
- Patients who received non rescue anti-malarial medication will be considered in the analysis as if they had not taken the anti-malarial drug.

In addition, PCR-corrected and uncorrected ACPR rate will be calculated and plotted using the Kaplan-Meier method for each treatment group by cohort in the FAS.

2.7.2.1.1 Analysis of PCR-corrected ACPR 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 29, See Section 2.1). The event time is the first time when the patient becomes a non-responder based on PCR-correction. If a patient parasite is not cleared at all, Day 7 is considered as the event time.

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

Rule for censoring:

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

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

2.7.2.1.2 Analysis of uncorrected ACPR using Kaplan-Meier method

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

Event = PCR-uncorrected non-responder during the study (same as at Day 29, See Section 2.1). The event time is the first time when the patient becomes a non-responder without PCR-correction. If a patient parasitaemia 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 will be censored at the first time of anti-malaria medication;
- other patients will be censored at the time of last parasitemia assessment.

2.7.2.2 Treatment failure related parameters

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

- proportion of patients with parasitaemia at 12, 24, and 48 hours after treatment
- proportion of patients with ETF
- proportion of patients with LCF
- proportion of patients with LPF

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

Handling of missing values/censoring/discontinuations

Patients whose outcome status cannot be determined due to incomplete/missing data will be excluded from analysis. Especially, the denominator is the number of patients who experience treatment failure or have malaria blood film result at Day 29 for LCF and LPF. Patients with ETF will be excluded from the analysis of LCF and patients with ETF or LCF will be excluded from the analysis of LPF.

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

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

PCT will be calculated based on uncorrected parasite counts.
PCT, and FCT will be summarized descriptively by the following subgroup

- Sex (male vs female)

Handling of missing values/censoring/discontinuations

Patients without parasite clearance for whatever reason will be censored at the time of last parasite assessment.

Patients who did not have fever at baseline 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.

In case that a patient receives rescue medication before (parasite or fever) clearance, the time to event will be censored at the first use of rescue medication.

2.7.2.4 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 Study Day 29 will be estimated by Kaplan-Meier method based on the subset of FAS patients who have clearance of initial infection before Day 15. Time to recrudescence will be calculated from the time of first study medication to the date of first event if a patient experiences the event and be censored at the time of last parasite

assessment if a patient does not experiences the event. Patients who experienced a new infection will be censored at the first time of new infection.

2.7.2.5 Time to event analysis for reinfection

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

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

Time to event (reinfection) will be calculated from the time of first study medication to the date of first event if a patient experiences the event and will be censored at the time of last parasite assessment if a patient does not experience the event. Patients who experienced recrudescence will be censored at the first time of recrudescence.

Handling of missing values/censoring/discontinuations

The patient will be censored at the time of last parasite assessment if a patient does not experience the event. Undertermined treatment failures due to missing PCR data will be considered as censored at the time of treatment failure.

2.8 Safety Analysis

All safety parameters will be analyzed by cohort and treatment group based on the safety.

2.8.1 Adverse events (AEs)

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

Adverse events will be summarized by presenting, for each cohort and 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 (CTC 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 the 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 death, serious adverse events, severe malaria, other significant adverse events leading to treatment discontinuation and adverse events leading to dose adjustment.

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

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

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

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

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

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

The adverse events will be summarized for the following subgroup.

- Sex (male vs female)

Algorithms for date imputations is provided in Appendix 5.

2.8.1.1 Adverse events of special interest / grouping of AEs

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

-Drug code = KAE609

-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 percentage 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 (QT interval corrected for heart rate according to Fredericia) abnormalities will be summarized. Only QTcF and HR will be summarized for the intext table. QTcF will be summarized in post-text tables and will be presented in the listing. (see Sections 2.8.2 and 2.8.3.1).

Table 2-1 List of safety topics of interest

Safety Topic Of Interest	SOC	MedDRA Code	MedDRA Term	MedDRA Level	MedDRA Qualifier
QTc prolongation	Investigations	20000001	Torsade de pointes/QT prolongation	SMQ	Broad
Adrenal gland disorder	Endocrine disorders	10001353	Adrenal gland disorders	HLGT	
	Investigations	10001339	Adrenal cortex tests	HLT	
	Metabolism and nutrition disorders	10014412	Electrolyte and fluid balance conditions	HLGT	
	Vascular disorders	10011954	Decreased and nonspecific blood pressure disorders and shock	HLGT	
	Investigations	10001373	Adrenal medulla tests	HLT	
Hepatotoxicity	Hepatobiliary disorders	20000006	Drug related hepatic disorders-comprehensive search	SMQ	Broad
Phototoxicity	Skin and subcutaneous tissue disorders	10072982	Photosensitivity and photodermatosis conditions	HLT	
	Skin and subcutaneous tissue disorders	10052566	Rashes, eruptions and exanthems NEC	HLT	
	Skin and subcutaneous tissue disorders	10054786	Skin burning sensation	PT	
	Skin and subcutaneous tissue disorders	10037087	Pruritus	PT	
	Skin and subcutaneous tissue disorders	10015151	Erythemas	HLT	
Anemia	Blood and lymphatic system disorders	20000029	Haematopoietic erythropenia	SMQ	Broad
	Blood and lymphatic system disorders	10002055	Anaemias haemolytic NEC	HLT	
	Blood and lymphatic system disorders	10002052	Anaemias haemolytic immune	HLT	

Gastrointestinal disorders (e.g., nausea, vomiting, diarrhea)	Gastrointestinal disorders	20000140	Gastrointestinal nonspecific symptoms and therapeutic procedures	SMQ	Broad
Semen discoloration (yellow)	Reproductive system and breast disorders	10013358	Spermatogenesis and semen disorders	HLT	
	Investigations	10016462	Fertility analyses	HLT	
Hypoglycemia	Metabolism and nutrition disorders	90000029	Hypoglycemia (Standard)	NMQ	Narrow
Development of clinical resistance to KAE609 in P. vivax and P. falciparum	Infections and infestations	10035499	Plasmodia infections	HLT	
	Investigations	10033903	Parasite identification and serology	HLT	
	General disorders and administration site conditions	90000022	Lack of efficacy (PSUR) [Standard]	NMQ	Broad

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, cohort, and treatment group. Change from baseline will only be summarized for patients with both baseline and post baseline values and will be calculated as:

change from baseline = post baseline value – baseline value

The following laboratory parameters will be analyzed for hematology test group: hemoglobin, platelets, white blood cell count, Reticulocytes, 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 clinical chemistry 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, uric acid, gamma glutamyltransferase (GGT), magnesium, phosphate, chloride, haptoglobin, total protein, albumin, INR and LDH.

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

Table 2-2 Liver-related events

Parameter	Criterion
ALT	>3xULN; >5xULN; >8xULN;>10xULN
AST	>3xULN; >5xULN; >8xULN >10xULN;
ALT or AST	>3xULN; >5xULN; >8xULN >10xULN;
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
ALP	>2xULN, >3xULN
ALP & TBL	ALP >3xULN & TBL >2xULN
(ALT or AST) & TBL & ALP	ALT or AST >3xULN & TBL >2xULN & ALP <2xULN **(Hy's Law)**

To support the primary endpoint, the number and percentage of patients with at least 2 CTCAE grades increase from baseline in ALT or AST at any time during the study will be provided by cohort and treatment. This safety endpoint will be analyzed using the method specified in Section 2.5.2.

Peak ALT/AST and peak TBL will be ploted using eDISH (evaluation of Drug Induced Serious Hepatotoxicity) method and Modified eDISH (mDISH) method, see Lin, *et. al.* (2012).

If required for SRC, maximum increases in ALT or AST during the first 2 weeks (Day 1 to Day 15) will be categorized based on the Protocol Table 3-1 as follows:

- 2: ≥2 CTCAE grades increase from baseline in either ALT or AST
- 1: 1 CTCAE grades increase from baseline if baseline value is normal or ≥ 2 times baseline value if baseline value is above normal in either ALT or AST
- 0: otherwise.

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+
- New dipstick glycosuria ≥ 1+

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

Urine pregnancy data will be summarized by visit.

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

2.8.3 Other safety data

2.8.3.1 ECG and cardiac imaging data

The following quantitative variables will be summarized for averaged triplicate ECG: heart rate, RR interval, PR interval, QRS interval, QT interval and QTcF. Summary statistics for change from baseline will be presented for ECG variables by timepoint and treatment group.

QT intervals will be summarized categorically by computing the number and percentage of patients at each time point and at the maximum post baseline value for the following categories:

- QT, QTcF
  - New > 450 and ≤ 480 ms
  - New > 480 and ≤ 500 ms
  - New > 500 ms
  - Increase from baseline of > 30 ms to ≤ 60ms
  - Increase from baseline of > 60 ms
- HR
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm
- 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
  - New > 120 ms

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

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

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

2.8.3.2 Vital signs

The following quantitative variables will be summarized: Weight (kg), Temperature (^{o}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 notable vital sign abnormalities

Vital sign (unit)	Notable abnormalities
Systolic blood pressure (mmHg)	≥ 180 mmHg/≤ 90 mmHg with increase/decrease from baseline of ≥ 20 mmHg
Diastolic blood pressure (mmHg)	≥ 105 mmHg/≤ 50 mmHg with increase/decrease from baseline of ≥ 15 mmHg
Pulse (beats/min)	≥ 120 bpm/≤ 50 bpm with increase/decrease from baseline of ≥ 15 bpm
Temperature (^{o}C)	>=37.5 (axillary) or >=38.0 (other routes)
Weight	decrease > 7% from baseline increase > 7% from baseline

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

2.9 Pharmacokinetic endpoints

PK concentrations below the limit of quantification will be treated as zero in summary statistics and for the calculation of pharmacokinetic parameters by non-compartmental `method of analysis. Descriptive statistics of pharmacokinetic parameters will include arithmetic and geometric (means, standard deviation (SD), median, minimum and maximum, etc). Parameters such as AUCinf, AUClast, AUC0-t, Cmax, T1/2 and Tmax will be reported

using non-compartmental method of analysis (using Phoenix 6.4 or higher). 2-sided 90% confidence intervals for $AUC_{0\text{-}24h}$, Cmax and Tmax PK parameters of KAE609 and Lumefantrine will be calculated by cohort and treatment group using normal or log-normal approximation as applicable.

All the 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.

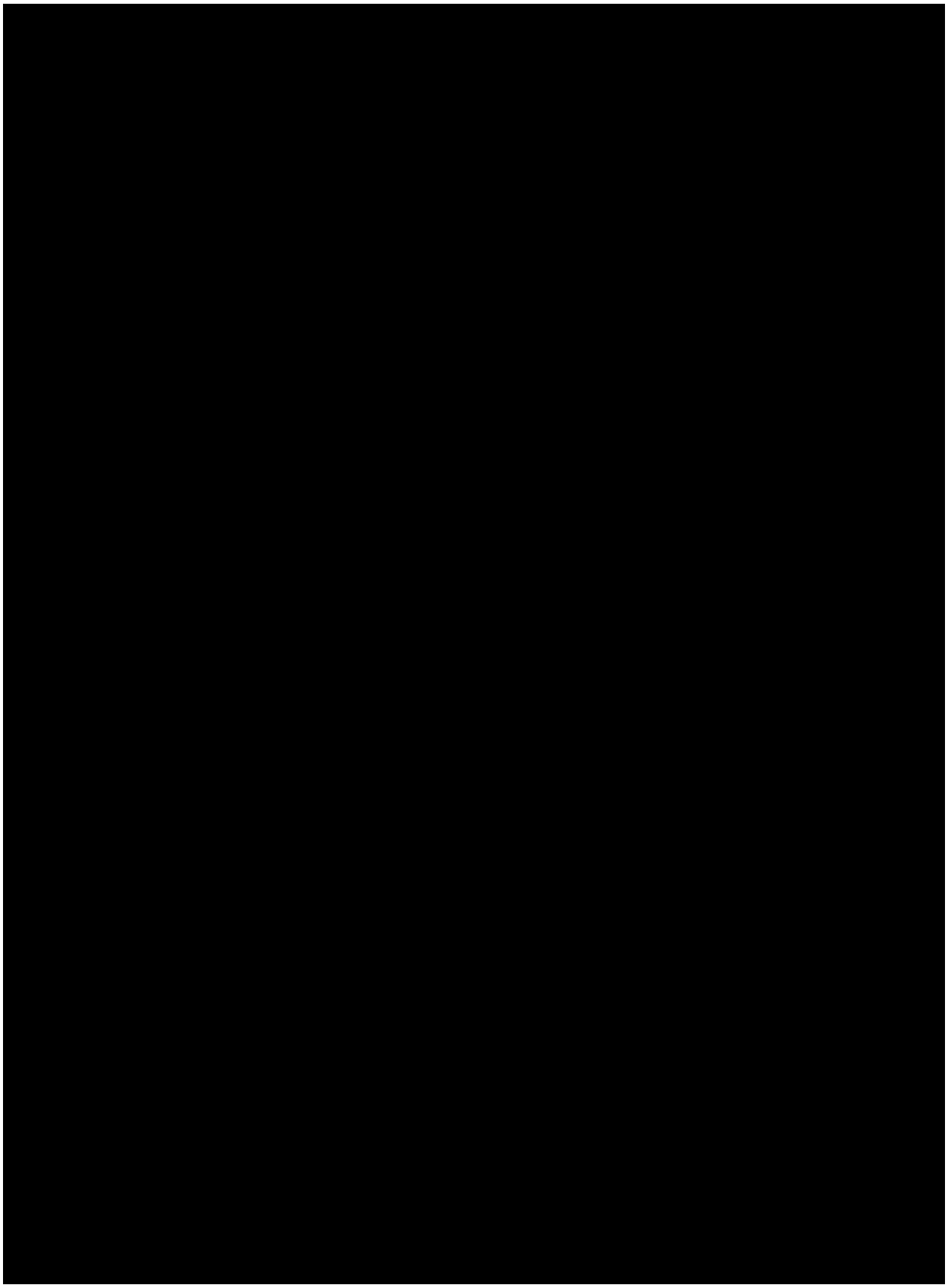
[redacted]

2.11 Patient-reported outcomes

NA.

[redacted]

[redacted]



2.14 Overview of analysis methods

An overview of statistical analyses and methods applied to efficacy variables and safety variables are given in Table 2-4 and Table 2-5.

Table 2-4 Overview of analysis methods for baseline data and efficacy variables

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

Variable(s)	Summary statistics for binary/ categorical data	Listings	95% CI for each treatment group	Summary statistics for continuous data	Time-to-event data analysis K-M	Graphs
Incidence rate of recrudescence at Days 29.	X	-	-	-	X	X
Incidence rate of reinfection at Days 29	X	-	-	-	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	Between treatment comparison
At least 2 CTCAE grades increase from baseline in ALT or AST	X	X	-	-	X*
AE	X	X	-	-	-
SAE	X	X	-	-	-
severe malaria	X	X	-	-	-
Adverse events of special interest	X	X	-	-	-
Hematology change from baseline	-	X	X	-	-
Clinical chemistry change from baseline	-	X	X	-	-
Liver abnormalities	X	X	-	X[1]	-
ECG change from baseline	-	X	X	X[2]	-
ECG abnormality	X	X	-	-	-
Vital signs change from baseline	-	X	X	-	-
Notable vital signs abnormality	X	X	-	-	-
Drug concentrations	-	X	X	X[3]	-
PK parameters		X	X		
[redacted]					

* For comparison with pooled Coartem. 95% confidence interval will be provided.
[1] eDISH and mDISH plot.
[2] Spaghetti plot.
[3] Time vs Concentration line plot.

2.15 Interim safety review

Safety laboratory data and adverse events will be monitored continuously throughout the study using data management's data review reports.

If there are no significant LFT elevations observed in a cohort at Day 15 (see Table 1-1), the next cohort with escalated KAE609 doses will start after informing the safety review committee about the findings.

If any significant LFT elevation is observed at Day 15 in any patient(s) in a cohort (see Table 1-1), a comprehensive safety data review will be performed after all the patients in the cohort have been followed up for 28 days post-treatment.

The safety review committee can pause recruitment and trigger safety review any time based on safety signals. An earlier review of the safety data by the safety review committee/Novartis in the middle of a cohort would be initiated based on occurrences of LFT elevations in the cohort as specified below:

- The number of patients meeting the primary safety endpoint in a treatment arm is at least 2 in Cohorts 1 and 2 or at least 3 in Cohorts 3, 4, 5 and 6.

Data management's data review reports will be provided to the safety review committee and the appropriate Novartis relevant internal and external people who will make decision about whether a KAE609 dosage regimen is safe and can be escalated to the higher dosage. Although the randomization data are not included in the data management system, the study drug (KAE609 QD 1 day, KAE609 QD 3 days, Coartem) and dosage taken by each patient is available in the dosage records. No formal interim safety analysis by treatment group will be performed.

In case that more comprehensive safety analyses by treatment group are needed at the end of cohort or in the middle of cohort, formal interim safety analyses of selected safety or efficacy parameters by treatment group will be provided as described in the safety review charter.

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

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

Output	Analysis set	Periodic safety review
Baseline		
Demographic characteristics	FAS	Yes
Background disease characteristics	FAS	Yes
Safety		
Concomitant medications/significant non-drug therapies	Safety	Yes
Relevant medical history/current medical condition	Safety	
All adverse events and Serious adverse events	Safety	Yes
Newly occurring liver enzyme abnormalities (categorical analysis)	Safety	Yes
Clinical chemistry shift table based on CTC grade	Safety	Yes
ALT & AST meeting specified criteria during first 2 weeks	Safety	Yes
eDISH and mDISH plots	Safety	Yes

3 Sample size calculation

The incidence of patients experiencing at least 2 CTC grade increase from baseline in ALT or AST is not consistent among KAE609 patient/human challenge studies:

- 3 out of 8 (37.5%) patients in a Study with KAE609 at 10 mg QD.
- 4 out of 11 (36.4%) in a Study with KAE609 at 75 mg QD.
- 1 out of 25 (4%) in a Study with KAE609 at 10 to 30 mg QD.
- 1 out of 21 (4.8%) in a study with KAE609 at 30 mg QD X3.

3.1 Single arm approach

Figure 3-1 and 3-2 present the probability of observing at least 2 and 3 safety events, respectively, in a treatment group by various sample sizes and true event rates to assess the operational characteristics for the proposed sample sizes.

Given the proposed sample sizes in the treatment groups within each cohort, the probability of observing at least 2 safety events in 10 patients or 3 safety events in 20 patients is at least 80% if the true event rate is ≥ 30% and less than 5% if the true event rate is ≤ 3%. Specifically:

- For a sample size of 10 patients per treatment group, the probability of observing ≥ 2 safety events is greater than 80% if the true event rate is ≥ 30% and less than 5% if the true event rate is ≤ 3% (Figure 3-1).
- For a sample size of 20 patients per treatment group, the probability of observing ≥ 3 safety events is greater than 90% if the true event rate is ≥ 30% and less than 5% if the true event rate is ≤ 3% (Figure 3-2).

Figure 3-1 Probability of observing at least 2 safety events by sample size and true event rate

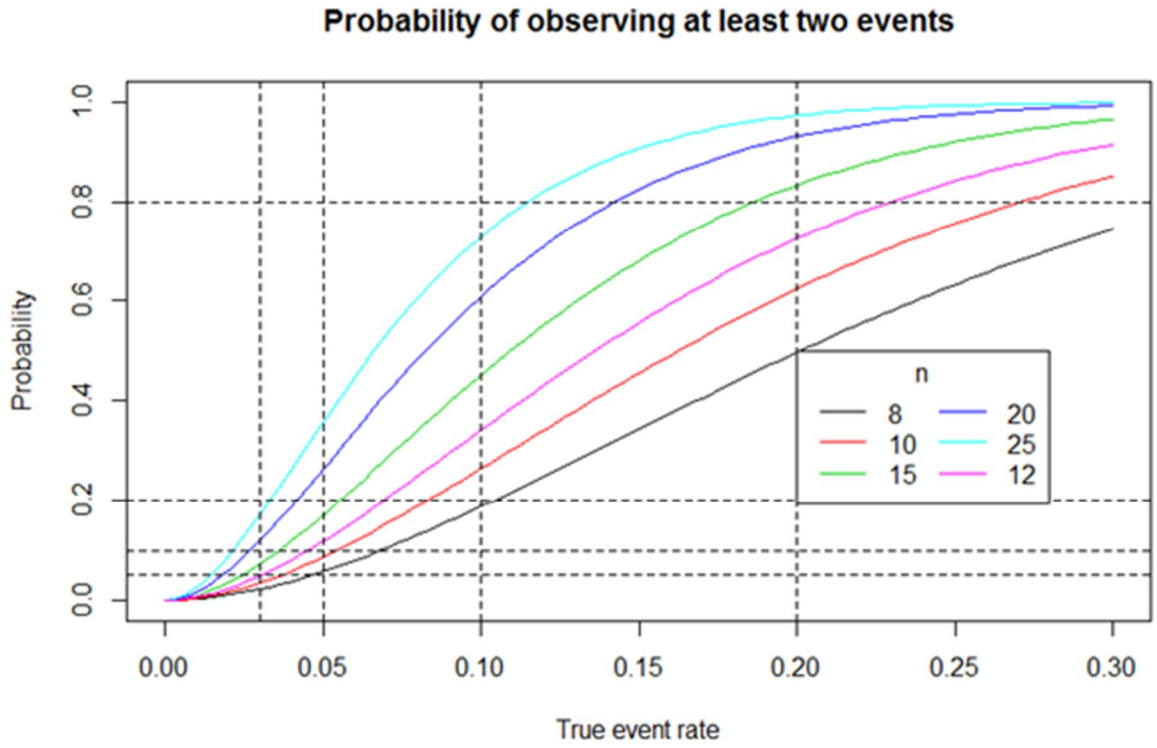
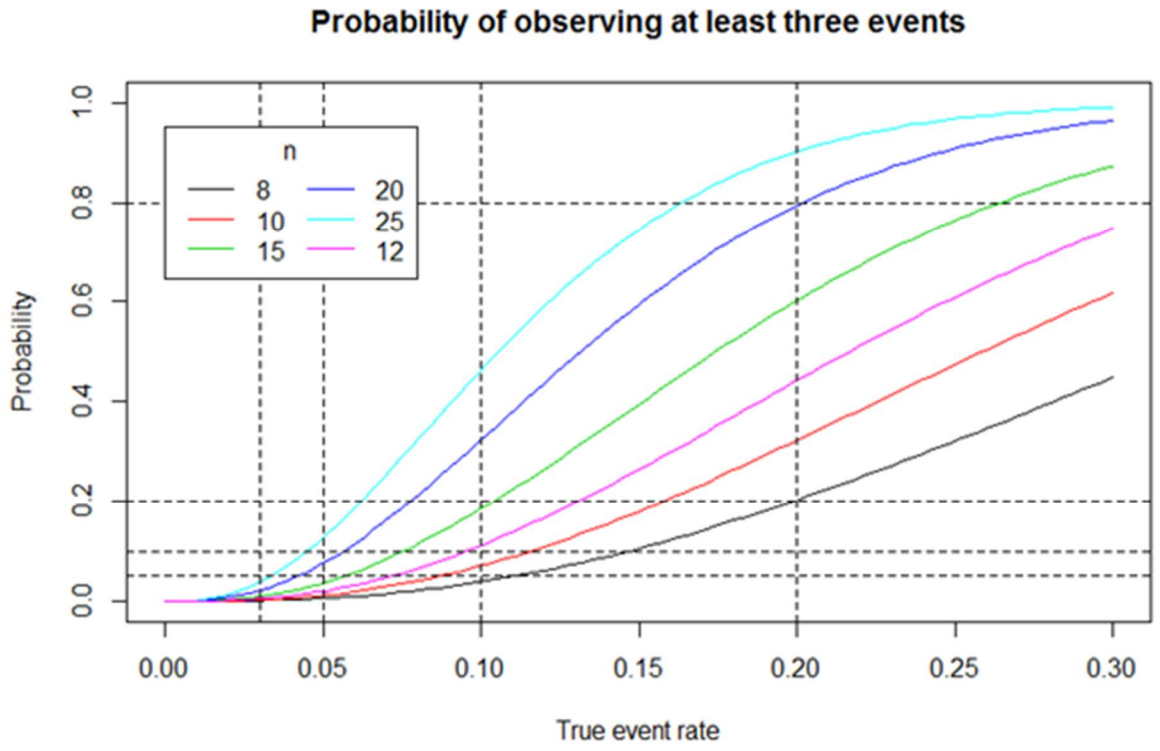


Figure 3-2 Probability of observing at least 3 safety events by sample size and true event rate



3.2 Power for comparison of KAE609 with Coartem

The comparison between KAE609 doses/regimen with Coartem will help interpretation of liver enzyme elevations in the individual KAE609 treatment arms. In the Pyramax Phase II/III trials (EMA 2012), the incidence of patients experiencing Grade 2 ALT was 3.4%, which was higher than other comparators including Coartem. The incidence rate of adults and adolescents experiencing at least 2 CTC grade increase from baseline in ALT or AST in Coartem is about 3%. To assess the power for between treatment comparisons, a Coartem incidence rate of 5% is also considered.

Table 3-1 Power for comparison with Coartem based on 2-sided Fisher exact test

KAE609 true incidence rate	Coartem® true incidence rate	n for KAE609	N for Coartem®	Power for 2-sided testing		
				5% level	10% level	20% level
50%	3%	10	10	50%	70%	77%
		10	20	86%	91%	95%
		10	30	91%	95%	97%
		10	40	94%	97%	99%
		10	50	93%	97%	99%
		10	60	94%	98%	99%
50%	3%	20	10	78%	84%	92%

		20	20	94%	97%	99%
		20	30	99%	99%	>99%
		20	40	99%	>99%	>99%
		20	50	>99%	>99%	>99%
		20	60	>99%	>99%	>99%
50%	5%	10	10	43%	63%	72%
		10	20	80%	86%	92%
		10	30	85%	92%	95%
		10	40	90%	94%	97%
		10	50	89%	94%	97%
		10	60	90%	95%	97%
50%	5%	20	10	71%	77%	86%
		20	20	89%	94%	97%
		20	30	96%	98%	99%
		20	40	98%	99%	>99%
		20	50	99%	99%	>99%
		20	60	99%	99%	>99%
40%	3%	10	10	28%	50%	54%
		10	20	70%	78%	87%
		10	30	77%	87%	91%
		10	40	84%	91%	95%
		10	50	82%	90%	95%
		10	60	83%	92%	95%
40%	3%	20	10	49%	61%	80%
		20	20	81%	88%	94%
		20	30	93%	94%	98%
		20	40	96%	97%	99%
		20	50	96%	98%	99%
		20	60	98%	99%	99%
40%	5%	10	10	23%	43%	50%
		10	20	61%	71%	81%
		10	30	69%	80%	86%
		10	40	77%	85%	91%
		10	50	73%	84%	92%
		10	60	76%	87%	91%
40%	5%	20	10	43%	53%	71%
		20	20	72%	81%	89%
		20	30	86%	90%	95%
		20	40	91%	93%	97%
		20	50	93%	95%	98%
		20	60	94%	96%	98%

Based on PASS 2011

Given the sample size of 10 to 20 per arm within a cohort, the power to detect treatment difference is low even with large treatment differences using a 2-sided statistical significance

level of 5%. If the true rate is 50% for KAE609 and 3% for the Coartem, the power to detect between treatment difference is about 80% using a 2-sided test at the 20% significance level for n= 10 per arm or at the 10% significance level for n= 20 for KAE609 and 10 for Coartem.

If there are at least 2 cohorts at the end of study and the patients treated with Coartem are pooled from all cohorts, the power to detect treatment difference is greatly increased. In case that the study proceeds to the end with 4 cohorts for a total of 40 patients treated with Coartem, the power to detect treatment difference using 2-sided test at the 5% significance level is 77% and 91% for n=10 and 20 patients treated with KAE609, respectively, if the true rate is 40% for KAE609 and 5% for the Coartem. In case that the study proceed to the end with 6 cohorts for a total of 60 patients treated with Coartem, the power to detect treatment difference using 2-sided test at the 5% significance level is 76% and 94% for n=10 and 20 patients treated with KAE609, respectively, if the true rate is 40% for KAE609 and 5% for the Coartem.

4 Change to protocol specified analyses

NA.

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 missing dates, rules specified in Tables 5-1 to 5-3 will be used

Table 5-1 AE/Treatment Date Abbreviations

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

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

Table 5-2 Imputation algorithm

	AEM MISSING	AEM < TRTM	AEM = TRTM	AEM > TRTM

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

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

Table 5-3 Imputation algorithm legends

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

Few examples are shown in Table 5-4.

Table 5-4 Example scenarios

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

5.1.3 Concomitant medication date imputation

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

5.1.3.1 Prior therapies date imputation

Start date: The same rule which is applied to the imputation of AE/concomitant medication start date will be used with the exception that: for scenario (B) the start date will be replaced by the randomization date -1.

End date:

- Imputed date = min (reference end date, DEC 31 of the year), if month and day are missing.
- Imputed date = min (reference end date, last day of the Month), if day is missing.

where reference end date will be randomization date.

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date. If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

5.1.3.2 Post therapies date imputation

Start date:

- If Day is missing, then impute to the max (reference start date, first day of the month).
- Day and month are missing then impute to the max(reference start date, Jan 1)
- Reference start date will be last date of study treatment administration + 1.

End date: No imputation.

5.1.3.3 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 15 visit is set to be Day 14 and Day 16 respectively, according to the protocol visit schedule since this is the primary analysis timepoint.
- The following rules are used to determine the window for other visits post baseline:
  - "Lower limit" = "upper limit of prior applicable visit" + 1.
  - "Upper limit" = "target day of current visit" + integer part of ("target day of next applicable visit" – "target day of current visit")/2 with the exception of Day 29

- No upper limit for Day 29 visit
- Upper limit of Day 11 is one day before the lower limit of Day 15

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 the collected data regardless of used in the by visit analyses.

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

Analysis Visit	Target Day	Analysis window for assessment group		
		Vital signs/ Chemistry/ Hematology	Urinalysis	Pregnancy
Baseline	1	Up to Day 1	Up to Day 1	up to day 1
Day 2	2	Day 2	Day 2-3	NA
Day 3	3	Day 3	NA	NA
Day 4	4	Day 4	NA	NA
Day 5	5	Day 5 - 6	Days 4-13	NA
Day 8	8	Day 7 – 9	NA	NA
Day 11	11	Day 10 – 13	NA	NA
Day 15	15	Day 14 – 16	Day 14 – 16	NA
Day 22	22	Day 17 – 25	NA	NA
Day 29/End of study	29	Day 26 and above	Day 17 and above	Day 2 and above

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

Analysis Visit	Analysis timepoint	Analysis window for assessment group			
		Temperature/ Parasite count	ECG		PK
			KAE609	Coartem	
Baseline	0 hrs	up to 0 hrs	up to < 0 hrs	up to < 0 hrs	NA
Day 1	1 hrs	NA	NA	NA	>0 to 1.5 hrs
	2 hrs	>0 to 3 hrs	NA	NA	>1.5 to 3 hrs
	4 hrs	>3 to 6 hrs	>0 to 8 hrs	NA	>3 to 5 hrs
	6 hrs	NA	NA	>0 to 37 hrs	>5 to 7 hrs
	8 hrs	>6 to 10 hrs	NA	NA	>7to 10 hrs
	12 hrs	>10 to 18 hrs	>8 to 18 hrs	NA	>10 to 18 hrs
Day 2	24 hrs	>18 to 30 hrs	>18 to 38 hrs	NA	>18 to 38 hrs
	36 hrs	>30 to 42 hrs	NA	NA	NA
Day 3	48 hrs	>42 to 54 hrs	NA	NA	>38 to 49 hrs

	50 hrs	NA	NA	NA	>49 to 51 hrs
	52 hrs	NA	>38 to 56 hrs	NA	>51 to 54 hrs
	56 hrs	NA	NA	NA	>54 to 58 hrs
	60 hrs	>54 to 66 hrs	>56 to 66 hrs	NA	>58 to 64 hrs
	68 hrs	NA	NA	>37 hrs to Day13	>64 to 70 hrs
Day 4	72 hrs	>66 hrs to Day 4	>66 hrs to Day 16	NA	>70 hrs to Day 6
Day 5	NA	Day 5-6	NA	NA	NA
Day 8	NA	Day 7 – 9	NA	NA	Day 7 – 9
Day 11	NA	Day 10 – 13	NA	NA	NA
Day 15	NA	Day 14 – 16	NA	NA	NA
Day 22	NA	Day 17 – 25	NA	NA	NA
Day 29/end of study	NA	Day 26 and avove	Day 17 and above	Day 14 and above	NA

Table 5-7 Rules for flagging variables

Timing of measurement	Type of data	Rule
Baseline	All data	The last measurement made prior to and including 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	All data	The measurement closest to the target day/time will be used. In the event that two measurements are taken equally apart (e.g. 1 day before target date and 1 day after) 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 that two measurements are taken equally apart, the first one will be used.
Post-baseline safety	Notable abnormalities (e.g. lab, ECG, VS)	The most extreme measurement in the window will be used. Note this means a patient can have a notably high and notably low measurement within a window

5.2 Prohibited medications

Table 5-8 Table of prohibited medications with respective ATC codes

Prohibited medication	ATC code	Drug	Comments
Antimalarials other than the study drug and rescue medication (Coartem)	P01BA	Aminoquinolines	Have not included codes for plain arthemether and arthemether/lumefantrine combination
	P01BB	Biguanides	
	P01BC	Methanolquinolines	
	P01BD	Diaminopyrimidines	
	P01BE	Artemisinin and derivatives, plain	
	P01BX	Other antimalarials	
	P01BF02	artesunate and mefloquine	
	P01BF03	artesunate and amodiaquine	

	P01BF04	artesunate, sulphamethopyrazine and pyrimethamine	
	P01BF05	artenimol and piperaquine	
	P01BF06	artesunate and pyronaridine	
	P01BE01	artemisinin	
	P01BE03	artesunate	
	P01BE04	artemotil	
	P01BE05	artenimol	
Herbal medication			Do not have codes for this generic class
CYP3A4 metabolism thus potent and moderate CYP3A inhibitors (such as HIV antivirals: e.g. ritonavir miscellaneous: e.g. clarithromycin, itraconazole, ketoconazole, grapefruit juice, verapamil, cimetidine)	J05AR	Antivirals for treatment of HIV infections, combinations	do not have code for entire class of CYP inhibitors so provided codes for examples provided in the protocol
clarithromycin, itraconazole, ketoconazole, grapefruit juice, verapamil, cimetidine	J01FA09	clarithromycin	
	J02AC02	itraconazole	
	D01AC08	ketoconazole	
	G01AF11	ketoconazole	
	J02AB02	Ketoconazole	
	C08DA01	verapamil	
	A02BA01	cimetidine	grapefruit juice: code not available
barbiturates, carbamazepine, phenytoin, rifampin, st.John's wort	N03AA	Barbiturates and derivatives	
	N03AF01	carbamazepine	
	N03AB02	phenytoin	
	J04AB02	rifampicin	st.John's wort code not avaiable
Proton pump inhibitors: e.g. lansoprazole, omeprazole, anti-	A02BC	Proton pump inhibitors	
	N03	ANTIEPILEPTICS	
	N06AA09	amitriptyline	Indomethacin= Indometacin

epileptics: e.g. phenytoin, miscellaneous: e.g., amitriptyline, chloramphenicol, clomipramine, indomethacin, nelfinavir, progesterone, proguanil, propranolol, warfarin	D06AX02	chloramphenicol	
	D10AF03	chloramphenicol	
	G01AA05	chloramphenicol	
	J01BA01	chloramphenicol	
	S02AA01	chloramphenicol	
	S03AA08	chloramphenicol	
	N06AA04	clomipramine	
	C01EB03	indometacin	
	M01AB01	indometacin	
	M02AA23	indometacin	
	S01BC01	indometacin	
	J05AE04	nelfinavir	
	G03DA04	progesterone	
	P01BB01	proguanil	
	C07AA05	propranolol	
	B01AA03	warfarin	
Acetaminophen Alpha-methyldopa Ephedra Amoxicillin-clavulanic acid Amiodarone Senna Dantrolene Disulfiram Vitamin A Glyburide Halothane Anabolic steroids Heparin Cocaine HMG-Co A reductase inhibitors Isoniazid Phencyclidine (PCP) Ketoconazole Labetolol	N02BE01	paracetamol	Paracetamol=acetaminophen code not available for the following: Amoxicillin-clavulanic acid (co-amoxiclav) , Flucanozole, Glyburide, Ectasy (MDMA) , Phencyclidine, Labetolol, Hydrazine, Trazadone, Ephedra
	C02AB	Methyldopa	
	C01BD01	amiodarone	
	A06AB06	senna glycosides	
	M03CA01	dantrolene	
	N07BB01	disulfiram	
	P03AA04	disulfiram	
	A11CA	Vitamin A, plain	
	N01AB01	halothane	
	A14A	ANABOLIC STEROIDS	
	B01AB01	heparin	
	C05BA03	heparin	
	S01XA14	heparin	
	N01BC01	cocaine	
	R02AD03	cocaine	
	S01HA01	cocaine	
	S02DA02	cocaine	
	C10AA	HMG CoA reductase inhibitors	
	J04AC01	isoniazid	
	D01AC08	ketoconazole	

Carbon tetrachloride	G01AF11	ketoconazole	
Nicotinic Acid	J02AB02	ketoconazole	
Chloroform	C04AC01	nicotinic acid	
Nitrofurantoin	C10AD02	nicotinic acid	
NSAIDs	J01XE01	nitrofurantoin	
Hydrazine	M01A	NSAID	
Phenylbutazone	M01AA01	phenylbutazone	
Phenytoin	N03AB02	phenytoin	
Protease inhibitors	J05AE	Protease inhibitors	
Sulfonamides	A07AB	Sulfonamides	
Terbinafine	D06BA	Sulfonamides	
Trazadone	G01AE	Sulfonamides	
Troglitazone	S01AB	Sulfonamides	
(withdrawn)	D01AE15	terbinafine	
Valproic Acid	D01BA02	terbinafine	
Bosentan	A10BG01	troglitazone	
Propylthiouracil	N03AG01	valproic acid	
	C02KX01	bosentan	
	D05BB01	etretinate	
	H03BA02	propylthiouracil	
	N01AB02	chloroform	
	N01AB05	trichloroethylene	

The prohibited medications listed in Table 5-8 is not an exhausted list. Concomitant medications not listed above will be manually checked and will be categorized as Prohibited medication or non-prohibited medication.

The final list with all prohibited medications that were determined by medical review before database lock can be found in the excel file 'Copy of CKAE609A2202_possible_prohibited medications.xlsx'.

Copy of CKAE609A2202_poss

5.3 AEs coding/grading

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

5.4 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (specify version used in the RAP). The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.0 at the time of analysis will be used.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used.

5.5 Statistical models

5.5.1 Primary analysis

The primary analysis is detailed in Section 2.

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

5.5.2 Key secondary analysis

NA.

5.5.3 Other secondary/[redacted] analysis

Kaplan-Meier estimates

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

Median survival for each treatment group will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [Brookmeyer and Crowley 1982]. Kaplan-Meier estimates of the survival 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].

5.6 Rule of exclusion criteria of analysis sets

Table 5-9 Protocol deviations and non-PD criteria leading to exclusion from analysis sets

Analysis Set	PD (Description and ID) that causes Subjects to be excluded	Non-PD criteria that cause Subjects to be excluded
Randomized	• Informed Consent for study participation not obtained and subject entered trial (INCL06)	• 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 (EXCL01) • Baseline plasmodium falciparum parasite count <500/uL or >50000/uL at screening visit (INCL03) • No fever within the past 24 hours at baseline (INCL04) • Received non-study concomitant antimalarial drugs between Day 1 and Day 29 without experiencing treatment failure (COMD02) • Patients who received concomitant prohibited medication which found to change the exposure that impacts efficacy. (COMD01b)	• Not in FAS; • <80% of randomized study medication taken • 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. • 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;
SAF	NA	• Not in Randomized set; • No study drug taken
PK	Patients who received concomitant prohibited medication which found to change the exposure that impacts interaction in PK parameters (COMD01c)	• Not in SAF • No evaluable pharmacokinetic parameter data • <80% of randomized study medication taken

6 Reference

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Lin X, *et. al.* (2012) Validation of Multivariate Outlier Detection Analyses Used to Identify Potential Drug-Induced Liver Injury in Clinical Trial Populations. Drug Saf; 35 (10): 865-875.

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