NOVARTIS

Global Clinical Development - General Medicine

KAE609

Clinical Trial Protocol 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

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[redacted]

List of abbreviations

ACPR	Adequate Clinical and Parasitological Response
ACR	Albumin-Creatinine Ratio
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical therapeutic Chemical
AUC	Area Under the Curve
AUCinf	Area under the plasma concentration-time curve from zero to infinity
AUClast	Area under the plasma concentration-time curve up to the last measurable concentration
AUC0-t	Area under the plasma concentration-time curve from zero to time t of the last measurable concentration above the limit of quantification
BID	twice a day
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CFR	US Code of Federal Regulations
CI	Confidence Interval
Cmax	Maximum Peak Observed Concentration
CMO&PS	Chief Medical Office and Patient Safety
CRF	Case Report/Record Form (paper or electronic)
eCRF	electronic Case Report/Record Form
CRO	Contract Research Organization
CTC	Common Toxicity Criteria
CTCAE	Common Toxicity Criteria for Adverse Events
CYP	Cytochrome
DAR	Dose Administration Record
ECG	Electrocardiogram
EDC	Electronic Data Capture
e.g.	For example (exempli gratia)
EMA	European Medicines Agency
ETF	Early Treatment Failure
EU	European Union
FAS	Full Analysis Set
FBC	Full Blood Count
FCT	Fever Clearance Time
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Serum-γ-Glutamyl Transferase
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure

[redacted]

ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International Normalized Ratio (blood clotting test)
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine System
LCF	Late Clinical Failure
LDH	Lactate dehydrogenase
LFT	Liver function test
LPF	Late Parasitological Failure
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
NovDTD	Novartis Drug and Therapy Dictionary
OC/RDC	Oracle Clinical/Remote Data Capture
OTC	Over-The-Counter
PoC	Proof of Concept
PCT	Parasite Clearance Time
PCR	Polymerase Chain Reaction
PCV	Packed-Cell volume (hematocrit)
PD	Pharmacodynamic
PK	Pharmacokinetic
PoC	Proof of Concept
PPS	Per-Protocol Set
[redacted]	[redacted]
PSOC	Primary System Organ Class
QD	Once daily (quaque die)
QM	Quality Management
QT	QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	heart rate-corrected QT
QTcF	QT Interval Corrected by the Fridericia Correction Formula
RBC	Red Blood Cell Count
SAE	Serious Adverse Event
eSAE	electronic Serious Adverse Event
SAF	Safety
SAP	Statistical Analysis Plan
SD	Single Dose
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum-Glutamat-Pyruvat-Transaminase
SOP	Standard Operating Procedure
SUSARs	Suspected Unexpected Serious Adverse Reactions

[redacted]

Tmax	Time after administration of a drug when the maximum plasma concentration is reached
T½	Half-life
ULN	Upper Limit of Normal range
UNS	Unscheduled Visit
WBC	White Blood Cell
WHO	World Health Organization
WoC	Withdrawal of Consent

[redacted]

Glossary of terms

Cohort	A specific group of patients/subjects fulfilling certain criteria
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Period	A portion of the study which serves a specific purpose. Typical periods are: Screening/Recruitment, Wash-out, Treatment, and Follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Medication pack number	A unique identifier on the label of each investigational drug package
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Study drug/treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug(s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

Amendment 3

Amendment rationale

As specified in Section 1.2 and Section 3.5 of the original protocol (version 1), KAE609A2202 could be amended to study additional cohorts with higher doses if the safety of KAE609 is acceptable up to 75 mg single dose. Doses up to 50 mg QD x 3 days and 75 mg single dose have been found to be safe and effective in the current KAE609A2202 study as confirmed by the Safety Review Committee. Hence, this amendment is being done to add two cohorts with higher doses of KAE609 (150 mg single dose and 225 mg/110 mg single dose) to achieve the predefined aim of the study i.e. to determine the maximum safe dose of the investigational drug KAE609 in malaria patients. In addition, this would provide scope for future studies to use higher single doses which may be necessary to achieve adequate cure rates as single dose and potentially prevent or slow the emergence of drug resistance. The pharmacokinetic exposure for proposed doses are expected to be covered by the previous human or animal safe and tolerable exposures (See Section 3.3 for details).

Changes to the protocol

- **Protocol summary:** Cohorts 5 and 6 with higher single dose of KAE609 (150 mg and 225 mg/110 mg respectively) and Coartem in standard dose as comparator are added. The planned number of patients is updated to 210 patients. [redacted]
- **Section 1.1:** Updated the background to clarify that doses up to 300 mg were already planned in patients in KAE609X2202 study, however the study was terminated after 75 mg dose.
- **Section 3.1:** Table 3-1 and Figure 3-1 are updated to add Cohorts 5 and 6. Updated that based on the review of safety data (and any other relevant data) by a safety review. committee during or after Cohort 5, the dose of KAE609 for Cohort 6 will be either 110 mg or 225 mg. 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.
- **Section 3.3:** Dosing rationale for Cohort 5 and Cohort 6 updated.
- **Section 3.6:** Updated the rationale for safety of 110 mg, 150 mg and 225 mg doses based on exposure data from previous human or animal studies.
- **Section 4:** The planned number of patients is updated to 210 patients.
- **Section 4.2**: Contraception methods for Women of child-bearing potential updated from basic to highly effective contraception methods. Also updated to clarify use of additional non-hormonal method of birth control by patients randomized to receive Coartem.
- **Section 5.1.1:** Table 5-1 updated to add the dosing scheme for Cohorts 5 and 6.
- **Section 5.2:** Radomization scheme for Cohorts 5 and 6 is updated.
- **Section 5.4:** Deleted the statement that “the randomization codes associated with patients from whom PK samples are taken will be disclosed to PK bioanalysts who will keep PK results confidential until the time of interim safety review or database lock” as this was not applicable to this study.

[redacted]

- **Section 5.5.8:** Clarification on the use of prohibited medications has been added.
- [redacted]
- **Section 7.1:** Investigational drug doses of 150 mg and 225 mg/110 mg is updated.
- **Section 7.2.2:** Typographical error with reference to erroneous double use of "Novartis" corrected.
- **Section 9.1:** Updated the definition of PK analysis set.
- **Section 9.4.2:** Reference to African patient population mentioned as strikethrough is removed.
- **Section 9.7:** Cohorts 5 and 6 added to interim safety review criteria.
- **Section 9.8:** Table 9-1 updated with additional rows of 50 and 60 patients treated with Coartem and the footnote to the table updated.

Amendment 2

Amendment rationale

This protocol is being amended to correct errors/inconsistencies, and provide clarifications. This includes:

- To remove hematology and blood chemistry assessment from randomization visit. Hematology and blood chemistry samples are analysed during screening visit and as the gap between screening visit and randomization visit is only up to 6 hours, there is no need to repeat the analysis of these samples.
- To correct the inconsistencies regarding requirement of meal records for Coartem
- To clarify & simplify the language regarding history of alcohol and drug abuse.

Changes to the protocol

- Table 6-1:
  - Removal of hematology and blood chemistry from randomization visit.
  - Footer no. 9 is amended to reflect the following: "Meals consumed within 30 min prior to dosing and 4 hours post dosing to be documented for Coartem cohort". Likewise, there is no need for superscript 10 and 11 for the Meal record row in Table 6-1 since this row is only for Coartem arm.
  - Replacing 'alcohol test and drug screen' in Table 6-1 with 'History of alcohol use and drug abuse' for clarification purpose. Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through colored font for deletions and colored underlined for insertions.

Amendment 1

Amendment rationale

This protocol is being amended to correct several errors/inconsistencies, and provide clarifications. This includes:

[redacted]

- To correct an inconsistency regarding the requirement for blinding the technician performing hematology, blood chemistry and microscopy readings. Since this is an open label study, blinding of technicians is not required.
- To make information regarding requirement to collect meal records for KAE patients consistent throughout the protocol.
- To remove serum phosphorus and uric acid assessment from the list of blood chemistry tests since these tests are normally not part of a routine laboratory assessment. There is no signal in the pre-clinical and clinical data collected so far to warrant measurement of these parameters.
- To remove albumin from the list of urinalysis assessment. As protein is already being assessed in urine samples, it is not required to have albumin in addition.
- To correct an inconsistency regarding the use of progesterone as an oral method of contraception. Progesterone is a prohibited medication in this protocol as an alteration in progesterone level may occur by concomitant administration with KAE609. However, exposure of synthetic progestins is not impacted by KAE609. Hence synthetic progestins are allowed as part of oral contraceptives. Therefore, clarification has been provided in the section for prohibited medication to allow use of synthetic progestins as part of hormonal contraceptives.
- Term "Biochemistry" replaced by "blood chemistry" to maintain consistency throughout the protocol.
- The terms prior medication and concomitant medication have been defined for further clarity to make it consistent with existing information in protocol.
- To clarify that in case of treatment discontinuation, patients may be given rescue medication at the discretion of the investigator.
- Allow potential inclusion of other endemic non-African sites and increase the total number of participating sites.
- Clarification on personal data and withdrawal of informed consent have been added to reflect changes implemented in the informed consent form.

Changes to the protocol

- **Glossary:** Definition of "Personal Data" and clarification of "Withdrawal of informed consent" definition has been added.
- **List of abbreviations**: has been updated based on the changes implemented in this amendment.
- **Protocol summary, Section 4 and 9.4.2**: Population is updated to include patients from approximately 15 sites in malaria endemic countries. Accordingly any reference to African patient population in the protocol (Section 9.4.2) is also removed. Reference to the laboratory manual for technical details about microscopy have been added to Protocol summary and Section 4.1.
- **Sections 3.2 and 5.4**: Blinding the technicians who perform hematology, blood chemistry parameters and microscopy readings has been removed as it is not required for this open label study.

[redacted]

- **Section 4.2**: Details on type of oral contraception have been removed since clarification about use of progestin has been provided in Section 5.5.8.
- **Section 5.5.4**: Correcting the inconsistency related to requirement for collection of meal records in KAE patients to make it consistent with the information already provided in Table 6-1.
- **Section 5.5.7**: Defining the terms prior medication and concomitant medication for further clarity to make it consistent with existing information in Section 9.3.2.
- **Section 5.5.8**: For clarification, it has been added that synthetic progestins are not prohibited.
- **Section 5.6.2**: Information on rescue medication in case of treatment discontinuation has been added for clarification purposes.
- **Section 5.6.4**: Clarification of withdrawal of informed consent has been added.
- **Table 6-1**:
  - Addition of Polymerase Chain Reaction (PCR) sampling point at unscheduled visit (UNS) to be consistent with protocol in order not to miss recrudescence/relapse cases and to ensure that patient receives rescue medication as soon as treatment failure criteria are met.
  - Deleted Interactive Response Technology (IRT) time points at 8 hours, 36 hours and 60 hours for Coartem cohort since IRT will be contacted only once per treatment day to register the visit in the system.
  - Correcting the typographical error in the footnote regarding explanation of term 'UNS' from 'Unscheduled treatment discontinuation visit' to 'Unscheduled visit'.
  - Description of how triplicate ECGs should be done, and time window for ECG assessment have been included in the footnote.
- **Section 6.2**: Body height included in the list of baseline demographic characteristics to make it consistent with the information in Table 6-1, Sections 6.5.1 and 6.5.3.
- **Section 6.4.1**: Reference to the laboratory manual for details has been added. Correction of typographical error in instructions for parasite counting to make it consistent with laboratory manual being implemented in the study: "if less than *100* parasites, counting will be extended to 500 leukocytes" instead of "less than *10* parasites, counting will be extended to 500 leukocytes" as mentioned in previous version.
- **Section 6.5.4.2**: Phosphorus, and uric acid removed from the blood chemistry testing as not required in this study.
- **Section 6.5.4.3**: Albumin was also removed from the urinalysis testing as not required because protein is assessed.
- **Section 6.5.5**: For clarification, a statement on local ECG readout has been added. Typographical error regarding QTcF increases corrected to be consistent with section 9.5.2.4: '> 60 ms from baseline' replaced by '≥ 60 ms from baseline'.
- **Section 6.5.6**: Definition for women of child bearing potential with reference to females aged 8 years and above is removed since this study includes adult patients only.
- **Section 6.5.8**: Deleted 'not able to breast feed' from the signs/symptoms indicative of severe/complicated malaria under danger signs as it is not applicable (only adult patients are included in the study).

[redacted]

- **Sections 7.1 and 7.3, and Appendix 2 and 3**: Deleted 'Study treatment dosage increased/reduced' and 'Study treatment interrupted' from the standard text under the management of adverse events since change in dose or temporary interruption of treatment is not allowed as per the protocol. Interruption was replaced by discontinuation.
- **Sections 7.2.2 and 7.6**: DS&E replaced by CMO & PS to reflect the latest terminology for Novartis Safety.
- **Section 8.3**: Typographical error with reference to tracking dosage changes in IRT is corrected since no dosage changes are allowed as per the study design.
- **Section 12**: One reference 'Hamed and Grueninger 2012' quoted in section 3.4 was missing in the reference list, hence reference list was updated.
- Term 'clinical chemistry' and 'biochemistry' replaced by 'blood chemistry' to maintain consistency throughout the protocol.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Global Model Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Protocol summary

Protocol number	CKAE609A2202
Full Title	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.
Brief title	Safety of KAE609 in adults with uncomplicated *Plasmodium falciparum* malaria.
Sponsor and Clinical Phase	Novartis Phase IIa
Investigation type	Drug
Study type	Interventional
Purpose and rationale	KAE609 will be evaluated primarily for hepatic safety of single and multiple doses in sequential cohorts with increasing doses. This study aims to determine the maximum safe dose of the investigational drug KAE609 in malaria patients.
Primary Objective(s)	The primary objective of this study is to characterize hepatic safety aspects of single- and multiple ascending doses of KAE609 in adult malaria patients.
Secondary Objectives	To evaluate overall safety and tolerability of KAE609. To assess key pharmacokinetic (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.
Study design	This will be a multicenter, open label, randomized, dose escalation study in adult patients with uncomplicated malaria caused by *Plasmodium (P.) falciparum*.
Population	The study population will consist of male and female patients (≥ 18 years old and ≥ 45 kg) with uncomplicated *P. falciparum* malaria. The plan is to randomize approximately 210 patients in approximately 15 sites in malaria endemic countries.
Key Inclusion criteria	• Male and female patients ≥ 18 years with a body weight ≥ 45 kg.

[redacted]

	• Microscopic confirmation of acute uncomplicated *P. falciparum* using by Giemsa-stained thick film (refer to the laboratory manual for details). • *P. falciparum* parasitaemia of 500 to 50 000 parasites/µL. • Axillary temperature ≥ 37.5ºC or oral/tympanic/rectal temperature ≥ 38.0ºC; or history of fever during the previous 24 hours. • Written informed consent must be obtained before any study assessment is performed. If the patient is unable to write, then a witnessed consent according to local ethical standards is permitted.

Key Exclusion criteria	• Mixed *Plasmodiun* infections.
	• Signs and symptoms of severe malaria according to World Health Organization (WHO) 2016 criteria (WHO 2016).
	• Known liver abnormalities, liver cirrhosis (compensated or decompensated), known active or history of hepatitis B or C (testing not required), known gallbladder or bile duct disease, acute or chronic pancreatitis.
	• Clinical or laboratory evidence of any of the following:
	  • AST/ALT > 1.5 x the upper limit of normal range (ULN), regardless of the level of total bilirubin
	  • AST/ALT > 1.0 and ≤ 1.5 x ULN and total bilirubin is > ULN
	  • Total bilirubin > 2 x ULN, regardless of the level of AST/ALT
	• History of photodermatitis/increased sensitivity to sun.
	• Pregnant or nursing (lactating) women.
	• Known disturbances of electrolyte balance, e.g. hypokalemia, hypocalcemia or hypomagnesemia.
	• Moderate to severe anemia (Hemoglobin level <8 g/dL).

Study treatment	**COHORT 1** • Treatment arm 1: KAE609 10 mg once daily (QD) for 1 day • Treatment arm 2: Coartem® 80/480 mg twice a day (BID) for 3 days **COHORT 2** • Treatment arm 3: KAE609 25 mg QD for 1 day • Treatment arm 4: KAE609 10 mg QD for 3 days • Treatment arm 5: Coartem 80/480 mg twice a day (BID) for 3 days **COHORT 3**

[redacted]

	• Treatment arm 6: KAE609 50 mg QD for 1 day • Treatment arm 7: KAE609 25 mg QD for 3 days • Treatment arm 8: Coartem 80/480 mg twice a day (BID) for 3 days **COHORT 4** • Treatment arm 9: KAE609 75 mg QD for 1 day • Treatment arm 10: KAE609 50 mg QD for 3 days • Treatment arm 11: Coartem 80/480 mg twice a day (BID) for 3 days **COHORT 5** • Treatment arm 12: KAE609 150 mg QD for 1 day • Treatment arm 13: Coartem 80/480 mg twice a day (BID) for 3 days **COHORT 6** • Treatment arm 14: KAE609 225 mg QD or KAE609 110 mg QD for 1 day • Treatment arm 15: Coartem 80/480 mg twice a day (BID) for 3 days
Key safety assessments	• Monitoring of laboratory parameters in blood and urine • Adverse event (AE including Serious Adverse Event (SAE)) monitoring • Body temperature • Physical examination and malaria signs and symptoms • Vital signs • Electrocardiogram
PK assessments	• PK parameters of study drugs (measured by AUC0-24h, AUClast, AUCinf, Cmax, Tmax, T½)
Efficacy assessments	• Parasitaemia
[redacted]	
Data analysis	Data will be summarized by cohort and treatment arm. Data from all cohorts pooled will be also summarized for Coartem. For the primary variable of at least 2 Common Toxicity Criteria for Adverse Events (CTCAE) grades increase from baseline in ALT or AST, and Adequate Clinical and Parasitological Response (ACPR; PCR corrected and uncorrected ACPR at Days 15 and 29), 2-sided 95% confidence intervals (CI) will be constructed using the exact (Pearson-Clopper) method. For parasite clearance time and fever

[redacted]

	clearance time, descriptive statistics (mean, standard error, median, quartiles) will be presented using the Kaplan-Meier method.
Key words	Plasmodium falciparum malaria, KAE609, adults

[redacted]

1 Introduction

1.1 Background

KAE609 is a novel spiroindolone class drug with potent and fast-acting schizonticidal activity, which acts by disrupting the malaria parasite Na^+ homeostasis by inhibition of the ATPase PfATP4. KAE609 has been evaluated in healthy volunteers in single doses up to 300 mg and repeated doses up to 150 mg (3-day Once daily (QD)) without any significant safety and tolerability issue. In the initial patient study, a 3-day QD treatment of 30 mg was well tolerated. A subsequent patient study (KAE609X2202) was designed to evaluate efficacy and safety of doses from 75 mg single dose to 300 mg single dose in patients in Asia infected with *Plasmodium falciparum*. In KAE609X2202, at a single dose of 75 mg, transient Grade 2-3 LFT elevations were however observed in 5/11 patients and the study was terminated (See KAE609 Investigator Brochure (IB) for further details). In a malaria challenge study with healthy volunteers in Australia, transient Grade 3-4 LFT elevations were observed in 3/8 subjects following a single dose of 10 mg of KAE609. Following evaluation of these events, it was concluded that hepatic toxicity of KAE609 cannot be excluded, and that an additional safety dose escalation study should be performed before exploring safety and efficacy in a fixed-dose combination of KAE609 with a long acting anti-malarial.

1.2 Purpose

This Phase 2 study aims to determine the maximum safe dose of the investigational drug KAE609 in malaria patients.

The study population consists of adult malaria patients (≥ 18 years, ≥ 45 kg body weight) with uncomplicated symptomatic malaria caused by *Plasmodium (P.) falciparum*.

KAE609 will be evaluated primarily for hepatic safety following administration of single and multiple doses (once a day for 3 days) in sequential cohorts with escalating doses.

In case that safety is acceptable for all consecutive cohorts, a protocol amendment could be considered to study additional higher dose(s).

2 Study objectives and endpoints

2.1 Objectives and related endpoints

Table 2-1 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)	**Endpoint(s) for secondary objective(s)**

Objective(s)	Endpoint(s)
• To evaluate overall safety and tolerability of KAE609.	• Standard safety/tolerability assessments (AE incidence and severity, vital signs, ECG, laboratory abnormalities)
• To assess key PK parameters following treatment with KAE609.	• PK parameters such as AUC, Cmax, Tmax, T½ etc.
• To assess the efficacy of KAE609 in patients with uncomplicated *falciparum* malaria.	• 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
• To assess recrudescence after single and multiple doses of KAE609	• Incidence rate of recrudescence at Day 29
[redacted]	

3 Investigational plan

3.1 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 x3 days) according to schedule below (Figure 3-1).

Based on the safety pattern observed in previous studies with KAE609, 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 3-1):

[redacted]

Table 3-1 Decision criteria for dose escalation based on LFT results with KAE609

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 cohort have been followed for at least 28 days post treatment (**Study Day 29**)
	> 1 to ≤ 1.5 ULN	≥ 2 to < 3 times baseline (from **Day 1 to Day 15**)	
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, 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.

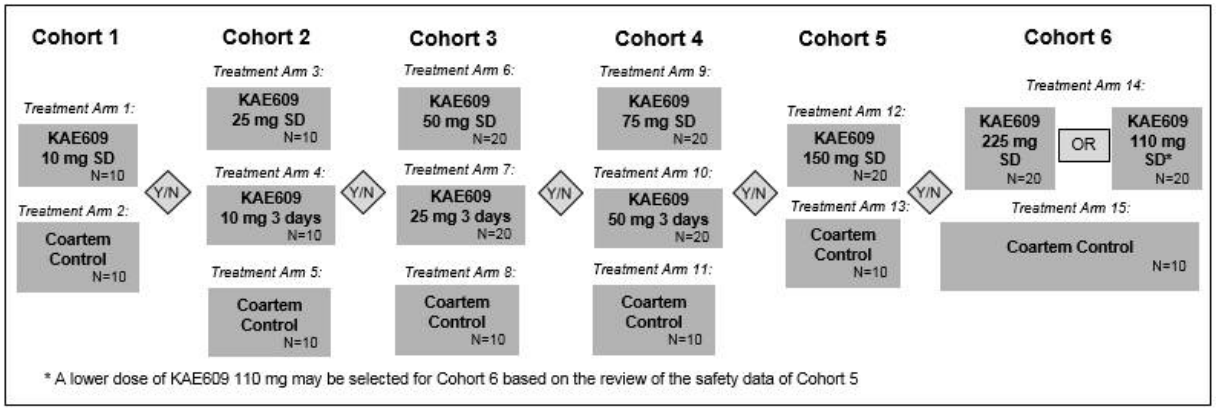
In consultation with the safety review committee, Novartis can suspend recruitment and trigger safety review any time based on safety signals including any potential Hy's law case.

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.

[redacted]

Figure 3-1 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 remain in the hospital under close supervision until they are discharged by the investigator or designee on Study Day 4. To be discharged, patients should present 2 consecutive study assessments with negative blood smear for *P. falciparum* parasites and clearance of fever. At the discretion of the investigator, patients may remain in hospital for additional days if needed.

Coartem® (Artemether-Lumefantrine) will be used as rescue medication in KAE609 patients meeting the treatment failure criteria (see Section 5.5.6). Any patient on KAE609 who does not need rescue medication up to Study Day 28 will be given Coartem at the end of the study (Study Day 29) and will be followed as per standard medical care.

Visits to assess safety and efficacy will be scheduled during the follow-up period as described in the assessment schedule table (Table 6-1). If malaria symptoms re-emerge outside the scheduled study visits, patients will be instructed to contact the investigator as soon as possible. For severe malaria, rescue medication according to local guidance will be used.

Frequent blood samples (see Table 6-1) for monitoring blood chemistry parameters including ALP, ALT, AST, total bilirubin (direct and indirect), creatinine phosphokinase levels, LDH, and haptoglobin. Additional samples will be collected for safety analyses at baseline and at predefined time in case of observed LFT elevations (e.g., viral hepatitis). Additional sera will be saved for possible further analyses to assess the mechanism of hepatic toxicity, if needed (e.g., miR122).

The safety of the entire study will be overseen by a primarily internal Novartis safety review committee with inclusion of at least one external hepatologist (Section 8.4).

[redacted]

3.2 Rationale for study design

This will be a multicenter, open-label, randomized, sequential, dose escalation study in adults with uncomplicated *P. falciparum* malaria.

The objective of this dose escalation study design is to characterize hepatic safety aspects of single- and multiple ascending doses of KAE609 and determine the maximum tolerated dose of the investigational drug KAE609 in malaria patients.

Dose escalation sequential design of the study is the standard design for evaluating safety and tolerability of a new chemical entity in the early phase (Phase I and II) of clinical development. Single doses up to 75 mg and repeated dosing up to 30 mg (3 day QD) have been evaluated in patients without any significant hepatic tolerability issue with the exception of LFT elevations observed in human challenge study at 10 mg single dose and 75 mg single dose in proof of concept (PoC) extension study. Single as well as repeated doses will be evaluated in this study since knowledge about safety profile of both schedules is important to inform further development of the dosing strategy with the best benefit risk profile. Single dosing is a necessary step prior to repeat dosing and allows the detection and management of adverse events (AE) which may be more severe with repeated dosing. Hence, to characterize the safety profile of the entire dose range of KAE609, patients will be first dosed with a single dose of lowest strength i.e., 10 mg and be escalated in a stepwise manner.

Coartem will be used as reference group to help distinguish if the hepatic events and other adverse events observed in the study are exclusive to KAE609 or resulting from the disease (*P. falciparum* malaria) itself.

Coartem will be dosed in the fed state. Furthermore, KAE609 will be dosed (irrespective of fed state) as single dose or QD for 3 days whereas Coartem will be dosed as twice a day (BID) for 3 days. Considering the differences in food requirement and differential frequency of administration for both the drugs, achieving blinding for patients and investigators is not feasible. The risk of bias arising out of the open-label design is minimized due to the fact that objective endpoints have been chosen for the study.

The patient population will be described in more detail in the Section 4 below

3.3 Rationale for dose/regimen, route of administration and duration of treatment

As mentioned in Section 1.1 and Section 3.2, KAE609 has been evaluated in single dose up to 75 mg and repeated dose up to 30 mg (3 day-QD) in malaria patients. It has also been evaluated in healthy volunteers in single dose up to 300 mg and repeated doses up to 150 mg (3 day-QD).

Considering the LFT elevations observed at 10 mg single dose (3 out of 8 patients in the Human Challenge Study) and at 75 mg single dose (5 out of 11 patients in the PoC extension study), and because causal relationship could not be established there is a need to further characterize the safety profile of the entire range of doses expected to be used as single doses or repeated dose in uncomplicated *P. falciparum* malaria.

As expected in a dose escalation sequential study, patients will be dosed initially at the lowest dose and be escalated in a stepwise manner. Single dosing is a necessary step to repeat dosing

[redacted]

and allows the detection and management of adverse events which may emerge or be more severe with repeated dosing.

The doses proposed in the newly added Cohort 5 and Cohort 6 are expected to be comparable or lower than the exposures which are considered to have acceptable safety and tolerability based on human and animal data (Table 3-2). In addition, the unbound exposure in patients (unbound fraction 0.08%) are expected to be much lower compared to healthy subjects (unbound fraction 0.15%) and dogs (unbound fraction 0.21%) (See KAE609 IB for further details).

Table 3-2 Estimated mean PK parameters in malaria patients for Cohort 5 and Cohort 6 in comparison with measured exposures in malaria patients and healthy subjects and preclinical toxicity studies

PK Parameter	50 mg single dose exposure in current study (Observed preliminary values)	110 mg** dose in patients (Estimated values)	150 mg dose in patients (Estimated values)	225 mg dose in patients (Estimated values)	Observed 300 mg dose in healthy subjects (Observed values)	IV 5 mg/kg/day for 14 days in dogs (Observed values)*	Oral 15 mg/kg/day for 3 days in dogs (Observed values)*
Cmax (ng/mL)	810	1925	2625	3937	2090	33600	6200
AUC0-24h (µg·h/mL)	12.4	37.4	50.9	76.5	36.0	55.9	119

The estimated exposures are calculated with reasonable assumption of linear pharmacokinetics of KAE609

*LOAEL (Lowest observed adverse effect level): Minimal to slight reversible adrenal findings

** A lower dose of KAE609 i.e. 110 mg may be selected for Cohort 6 based on the review of the liver safety data of Cohort 5 by a safety review committee.

Dose regimen for Coartem is in accordance with the product label.

3.4 Rationale for choice of comparator

The control treatment used in this study is Coartem, the artemisinin-based combination therapy artemether-lumefantrine. Coartem is widely used for *P. falciparum* malaria and has a well-characterized hepatic safety and efficacy profile (Hamed and Grueninger 2012). For these reasons, Coartem is considered the appropriate comparator treatment for this study.

3.5 Purpose and timing of interim safety review

Safety data will be reviewed by a safety review committee at predefined time points to decide about progression to the next cohort with the escalated doses (see Section 3.1).

In case safety data review is inconclusive for a particular cohort, number of patients in that cohort could be increased by up to 100% patients per treatment arm.

[redacted]

3.6 Risks and benefits

Based on the preclinical and clinical evaluation to date as presented in the IB for KAE609, it has been generally safe and well tolerated in patients up to single doses of 75 mg and repeated dose of 30 mg (3 day-QD) with the exception of reversible and asymptomatic LFT elevations observed with 10 mg single dose in human challenge study and 75 mg single dose in PoC extension study. Increase in LFT levels in earlier studies could have been influenced by the disease condition itself and/or the specific human challenge model. Hence, this study is being performed to characterize the hepatic safety profile of the expected dose range of KAE609 to be used in further development.

For newly added Cohort 5 and Cohort 6, single doses of 150 mg and 225 mg are proposed, respectively. PK exposure (AUC) of single dose 150 mg should be comparable to three doses of 50 mg once daily, already administered in this study and found to be safe and well tolerated during interim reviews (data not provided). Estimated AUC0-24h for 225 mg dose would be >2 fold lower than the exposure which are considered safe based on oral dog toxicology study (15 mg/kg for 3 days) or comparable with 2 weeks IV toxicity study. The Cmax is also expected to be around 1.7 fold lower than Cmax observed in oral dog toxicology study (Table 3-2). Following ongoing review of the data of 150 mg dose if the safety events are found to be related to PK exposure, then dose of 110 mg may be studied to establish the exposure thresholds.

The risk to patients in this trial will be minimized by compliance with the eligibility criteria and study procedures, sequential dose escalation starting from the lowest strength of dose (10 mg), close clinical monitoring and minimal treatment duration (single dose evaluated before repeated dosing), and by the fact that dose-escalation will be carried out after the known peak time of LFT increases (i.e., 14 days) for KAE609. Patients will be hospitalized under close supervision until they are discharged by the investigator or designee on Study Day 4. To be discharged, patients should present 2 consecutive study assessments with negative blood smear and clearance of fever. At the discretion of the investigator, patients may remain in hospital for additional days if needed. Patients are advised to use commonly recommended precautions when in the sun (e.g. sunscreen, hat, protective clothing).

In the current study, KAE609 will be given to patients with uncomplicated symptomatic *P. falciparum* malaria. KAE609 is expected to reduce the number of circulating malaria parasites in the blood of patients and consequently improve their clinical symptoms within the first 24 hours. There is also the possibility of complete cure of their illness.

The risk of developing resistant strains of parasite is possible but low in this small study.

KAE609 has been earlier evaluated in adult patients with acute, uncomplicated malaria due to *P. falciparum* mono-infection at doses of 75 mg in a PoC extension study and 30, 20 mg, 15 mg and 10 mg in a Minimum Inhibitory Concentration (MIC) study (Hien et al 2017). In the MIC study, treatment failure due to recrudescence was reported in 4 (36%) patients and one patient had late treatment failure due to new malaria infection in the PoC extension study at 75 mg dose. There were no patients with early treatment failure (ETF) in the 30 mg and 15 mg dose groups while three patients from the 10 mg dose group (42%) and one patient from the 20 mg dose group (25%) were ETFs.

[redacted]

The risk of any treatment failure (see Section 6.5.8), recrudescence or new infection in this study will be managed with rescue medication in the form of standard-of-care pharmacotherapy (Coartem). This may minimize the likelihood of resistance emergence or spread of infection.

The current study will include only adult patients (≥18 years) suffering from uncomplicated symptomatic *P. falciparum* malaria. Given the expected sub-therapeutic efficacy of the doses of KAE609 in the first 2 cohorts, only a small number (N=10) of patients to assess safety events will be included (10 mg SD, 25 mg SD and 10 mg 3 Days). Following acceptable safety results in these cohorts, higher doses (25 mg 3 days and 50 mg SD or higher) with an increased number of patients (20 patients) will be enrolled in the study. Thereafter, the dose of KAE609 may be increased sequentially up to 225 mg based on continuous monitoring of safety.

This is the first time that KAE609 will be tested in African patients. All previous studies involved Asian and Caucasian participants only.

4 Population

The study population will consist of male and female patients (≥ 18 years old and ≥ 45 kg) with confirmed and uncomplicated symptomatic *P. falciparum* malaria.

Only patients with malaria symptoms and documented *P. falciparum* counts of 500 to 50 000 parasites/µl (assessed within 6 hours of screen visit) will be further screened for eligibility in the study. Routine microscopy data may be used as baseline parasite count for the protocol if the assessment was done within 6 hours and is compliant with protocol requirements.

The plan is to randomize approximately 210 patients in approximately 15 sites in malaria endemic countries.

A patient who enters screening but is determined not to be eligible to enter the treatment period will be considered a screen failure.

Rescreening of a patient who had failed screening assessments earlier in the study is allowed as per investigator discretion and/or after consultation with the sponsor.

4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria:

Demography

1. Male and female patients ≥ 18 years with a body weight ≥ 45 kg

Disease specific

2. Microscopic confirmation of acute uncomplicated *Plasmodium falciparum* using by Giemsa-stained thick film (refer to the laboratory manual for details)
3. *Plasmodium falciparum* parasitaemia of 500 to 50 000 parasites/µL

Health status

4. Axillary temperature ≥ 37.5ºC or oral/tympanic/rectal temperature ≥ 38.0ºC; or history of fever during the previous 24 hours
5. Negative pregnancy test for patients of childbearing potential

[redacted]

Regulations

6. Written informed consent must be obtained before any study assessment is performed. If the patient is unable to write, then a witnessed consent according to local ethical standards is permitted
7. The subject is able to understand and comply with protocol requirements, instructions and protocol-stated restrictions and is likely to complete the study as planned
8. Living within reachable distance to the trial site to enable attendance for follow-up visits

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

Medical history and clinical status

1. Mixed *Plasmodiun* infections
2. Signs and symptoms of severe malaria according to World Health Organization (WHO) 2016 criteria (WHO 2016)
3. Active tuberculosis, or history of taking anti-tuberculosis medications within 12 months prior to screening
4. History of, or current alcohol misuse/abuse defined as five or more drinks on the same occasion on each of 5 or more days in the past 30 days
5. Known liver abnormalities, liver cirrhosis (compensated or decompensated), known active or history of hepatitis B or C (testing not required), known gallbladder or bile duct disease, acute or chronic pancreatitis
6. Clinical or laboratory evidence of any of the following:
   - AST/ALT > 1.5 x the upper limit of normal range (ULN), regardless of the level of total bilirubin
   - AST/ALT > 1.0 and ≤ 1.5 x ULN and total bilirubin is > ULN
   - Total bilirubin > 2 x ULN, regardless of the level of AST/ALT
7. History of photodermatitis/increased sensitivity to sun
8. Known disturbances of electrolyte balance, e.g. hypokalemia, hypocalcemia or hypomagnesemia
9. Moderate to severe anemia (Hemoglobin level < 8 g/dL)
10. Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection
11. Severe malnutrition (Body Mass Index (BMI) < 16.0)
12. Severe vomiting, defined as more than 3 times in the 24 hours prior to inclusion in the study or severe diarrhea defined as more than 3 times watery stools per day
13. Pregnant or nursing (lactating) women
14. Sexually active patients not willing to practice effective contraception
15. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during

[redacted]

dosing and for 30 days after administration of KAE609. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject).
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception. Coartem/Riamet may reduce the effectiveness of hormonal contraceptives. Therefore, patients randomized to Coartem using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control.
- In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.
- Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

16. Sexually active males must use a condom during intercourse while taking drug and for at least 30 days after stopping the study medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid
17. Patients with a family history of congenital prolongation of the QTc interval or sudden death or with any other clinical condition known to prolong the QTc interval such as patients with a history of symptomatic cardiac arrhythmias, with clinically relevant bradycardia or with severe cardiac disease
18. Patients taking drugs that are known to prolong the QTc interval
19. Resting QTcF > 450 ms (males), QTcF > 460 ms (females) at screening
20. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject in case of participation in the study. The investigator should make this determination in consideration of the patient's medical history, clinical and/or laboratory results.

[redacted]

21. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in situ* cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
22. Known chronic underlying disease such as sickle cell disease, and severe cardiac impairment.
23. Patients with serum creatinine ≥ 2 X ULN in the absence of dehydration. In case of dehydration, patients with serum creatinine ≥2 X ULN after oral or parenteral rehydration.
24. Inability to tolerate oral medication, to drink.
25. Patients taking any drug which is metabolized by the cytochrome (CYP) 2D6 enzyme (e.g., flecainide, metoprolol, imipramine, amitriptyline, clomipramine).
26. Patients taking drugs that are strong inducers of CYP3A4 such as rifampicin, carbamazepine, phenytoin, St. John's wort (*Hypericum perforatum*)
27. Known hypersensitivity to any of the agents used in the study

Interfering substances

28. Patients with prior antimalarial therapy or antibiotics with antimalarial activity within less than five (5) plasma half-lives (or within 4 weeks of screening if half-life is unknown)
29. Patients with prior herbal medication within one week of screening
30. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days or until the expected pharmacodynamic (PD) effect has returned to baseline, whichever is longer
31. Patients taking medications prohibited by the protocol (see Section 5.5.8, Appendix 4)
32. Previous participation in any malaria vaccine study or received malaria vaccine in any other circumstance

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Table 5-1 Dosing scheme

Cohorts	Treatment Arm	KAE609 dose (mg)	Coartem dose (mg)	Dosing regimen	Available strengths to achieve recommended dose
1	1	10		QD 1 day	1 x 10 mg
	2		80/480	BID 3 days	80/480 mg or 4 x 20/120 mg
2	3	25		QD 1 day	1 x 25 mg
	4	10		QD 3 days	1 x 10 mg

[redacted]

	5		80/480	BID 3 days	80/480 mg or 4 x 20/120 mg
3	6	50		QD 1 day	1 x 50 mg
	7	25		QD 3 days	1 x 25 mg
	8		80/480	BID 3 days	80/480 mg or 4 x 20/120 mg
4	9	75		QD 1 day	1 x 25 mg 1 x 50 mg
	10	50		QD 3 days	1 x 50 mg
	11		80/480	BID 3 days	80/480 mg or 4 x 20/120 mg
5	12	150		QD 1 day	1 x 50 mg 1 x 50 mg 1 x 50 mg
	13		80/480	BID 3 days	80/480 mg
6	14	225		QD 1 day	1 x 50 mg 1 x 50 mg 1 x 50 mg 1 x 50 mg 1 x 25 mg
		110 (if required)		QD 1 day	1 x 50 mg 1 x 50 mg 1 x 10 mg
	15		80/480	BID 3 days	80/480 mg

5.1.2 Additional treatment

Antipyretic will be allowed for symptomatic management of fever (see Section 5.5.7). No other additional treatment beyond investigational drug and control drug are included in this trial. The control drug, Coartem, will be also provided as rescue medication (Section 5.5.6).

5.2 Treatment arms

Patients will be randomized in a 1:1 ratio between KAE609 single dose and Coartem in Cohort 1. Patients will be randomized in a 1:1:1 ratio between KAE609 single and repeated doses and Coartem in Cohort 2. Patients will be randomized in a 2:2:1 ratio between KAE609 single dose and repeated dose and Coartem in Cohort 3 and Cohort 4. Patients will be randomized in a 2:1 ratio between KAE609 single dose and Coartem in Cohort 5 and Cohort 6.

[redacted]

5.3 Treatment assignment and randomization

Randomization to treatment groups will be performed sequentially, cohort by cohort with a pause between cohorts to allow safety review (see Section 3.1 and Section 8.4). Randomization may be put on hold within a cohort if there are patients experiencing safety events (see Table 3-1).

Once a cohort is active for enrollment, clinical sites will be informed and Interactive Response Technology (IRT) will be activated to accept patients. At Visit 101, all eligible patients will be randomized via the IRT to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller. The randomization per cohort may be extended after consultation with the sponsor to cover for some early study/treatment discontinuation, for e.g., patient who was randomized but not treated by study medication etc.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

No stratified randomization will be used in all the cohorts for this study.

The randomization scheme for patients/subjects will be reviewed and approved by a member of the Randomization Group.

5.4 Treatment blinding

Treatment will not be blinded to patients, investigator staff, and persons performing the clinical assessments since KAE609 is dosed once daily for one day or 3 days while Coartem is dosed twice daily for 3 days. Since the primary and secondary objectives of the trial are mainly based on objective laboratory assessments, this should not bias the safety endpoint and the efficacy assessments. To reduce the selection bias to treatment groups, IRT will be used to randomize patients to treatment groups and randomization data are kept strictly confidential until formal interim safety review or final analysis. At the time of interim safety review or final analysis, the randomization data will be loaded into the statistical programming system for access to programmers, trial statisticians, and pharmacokineticists.

At the time of formal interim safety review, if needed, summaries of results by cohort and treatment arm, if necessary, will be prepared only for Novartis internal/external experts to make decision for progress to the next cohort. These reports will be performed by the study biostatistics team (or deputy Contract Research Organization (CRO)) and pharmacokineticist if necessary (see Section 9.7).

[redacted]

Since this is open-label study, unblinding is not needed in the case of patient emergencies (see Section 5.6).

5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

5.5.1 Patient numbering

Investigators will screen patients only when a cohort is active for enrollment. Each patient is uniquely identified by a Subject Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a patient, the Subject Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number by the investigator. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site must select the case report/record form (CRF) book with a matching Subject Number from the Electronic Data Capture (EDC) system to enter data. In case that a patient signs the informed consent form during the pause of study, the IRT will inform the investigator that the patient cannot be enrolled.

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the Screening period Study Disposition CRF.

5.5.2 Dispensing the study drug

Each study site will be supplied with study drugs in individual packaging for each patient.

The study drug packaging has a 2-part label for KAE609. A unique medication number is printed on each part of this label which corresponds to one of the treatment arms and dose. Coartem will not have 2-part label, the medication number will be printed on the main panel. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

If a patient vomits study drugs, KAE609 within 30 min or Coartem within 1 hour of intake, a replacement dose will be given to the patient and the investigator or designee will notify IRT (see Section 5.5.4).

Medication number and quantity of treatment drug taken by patients have to be collected by the investigator or designee.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees

[redacted]

have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient except for the medication pack number.

The investigator must maintain an accurate record of the dispensing of study treatment in a drug accountability log. The study treatment will be administered to patients under hospital supervision. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of additional treatment

The following non-study treatment will be provided by the Sponsor and has to be monitored specifically:

- Coartem as rescue medication

Details are described in the CRF completion guidelines.

5.5.4 Instructions for prescribing and taking study treatment

KAE609

KAE609 can be administered irrespective of the timing of food intake.

Study medication will be administered by the study center personnel with approximately 180-240 ml of water. Each subject's mouth must be checked to ensure that the medication was swallowed. In the case that the patient vomits within 30 minutes of intake a replacement dose will be given to the patient and the investigator or designee will notify IRT. If the second dose is vomited the patient has to be given Coartem as rescue medication.

Coartem

Patients will be dosed BID for 3 days (at the following time points: 0, 8, 24, 36, 48, and 60 hours) and must receive a standard meal within 30 min prior to dosing, as per label. In the case that the patient vomits within 1 hour of intake a replacement dose will be given to the patient and the investigator or designee will notify IRT. If the second dose is vomited the patient has to be given non-lumefantrine standard of care.

Conventional 80/480 mg tablets or 20/120 mg tablets are to be taken orally with a glass of water. The dispersible tablet is to be dissolved in 10 mL of water in a small cup, and subsequently administered orally under hospital supervision; thereafter the cup will be rinsed with an additional 10 mL of water and the content is to be swallowed again.

[redacted]

Coartem medication should be followed whenever possible by food/drink (broth, sweetened condensed milk, etc.) as appropriate.

All dosages prescribed and dispensed to the subject during the study must be recorded on the Dosage Administration Record (DAR) CRF.

All kits of study treatment assigned by the IRT will be recorded in the IRT.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Additional doses can be given in case of vomiting (see Section 5.5.4). These changes must be recorded on the Dosage Administration Record (DAR) CRF.

Otherwise, investigational or other treatment dose adjustments and/or interruptions are not permitted.

5.5.6 Rescue medication

The following circumstances warrant discontinuation of study treatment and the implementation of rescue medication (see Section 6.5.8):

Early treatment failure (ETF)

ETF is defined within this protocol as:

1. Clinical decline or lack of improvement (per Investigator) at 24 hours after first dose of treatment.
2. Development of any clinical complications (described in the WHO definition of complicated/severe malaria (WHO Guidelines 2010)) in the presence of parasitaemia within 72 hours of the first dose of treatment
3. Parasitaemia > 75 000/µL at or after 12 hours post-dose
4. Parasitaemia ≥ baseline with or without fever at 36 hours after first dose of treatment
5. Any parasitaemia based on microscopy with fever, 48 hours post-dose
6. Parasitaemia > 100/ µL based on microscopy with or without fever, 72 hours post-dose

Late Clinical Failure (LCF)

Development of danger signs or severe malaria on any day between Study Day 5 and Day 29 in the presence of parasitaemia without previously meeting any of the criteria of ETF.

Presence of parasitaemia and axillary temperature ≥ 37.5ºC on any day between Study Day 5 and Day 29 without previously meeting any of the criteria of ETF.

Late Parasitological Failure (LPF)

Presence of parasitaemia on any day between Study Day 5 and Day 29 and axillary temperature < 37.5ºC without previously meeting any of the criteria of ETF or LCF.

Commencement of rescue medication with Coartem may occur after start of trial medications and up to Study Day 28 as deemed necessary by the investigator. Any patient on KAE609 who

[redacted]

did not need rescue medication up to Study Day 28, will be given Coartem at end of the study at Study Day 29. Rescue medication according to local guidance will be used for severe malaria.

Patients randomized to Coartem and meeting treatment failure definition will be further treated by rescue medication as per local treatment guidance.

The patients receiving rescue medication will not be replaced and will not discontinue the study (i.e., all the examinations as per the assessment schedule and all CRF pages for this patient will need to be completed).

Safety blood tests (Full Blood Count (FBC) and blood chemistry) will be collected on the initial day of rescue medication dosing. Blood films and blood sampling for parasite count and genotyping must be taken before giving the rescue treatment.

Patients treated with at least one dose of trial medications will continue to be followed-up until Study Day 29 according to schedule.

Use of rescue medication (including exact rescue regimen and route of administration) must be recorded on the electronic case report form (eCRF).

5.5.7 Prior and concomitant medication

Prior medications are defined as drugs taken and stopped prior to first dose of study medication.

Concomitant medication is defined as any medication, other than the Investigational Medicinal Product (IMP), which is given at least once between the day of first dose of randomized study medication and the last day of study visit (including those which were started pre-baseline and continued into the treatment period), including prescription and over-the-counter medicines, and any traditional or herbal remedies.

Paracetamol as an antipyretic, and metopimazine for repeated vomiting (or if not available, any other antiemetic which is not known to prolong QT and/or cause torsade de pointes) will be allowed. If paracetamol or equivalent drug is given as an antipyretic up to 72 hours prior first dose, it has to be reported as prior medication

Metoclopramide is contraindicated from the period prior to first dose to Day 5 post-dose (120 hours).

Beta-lactam antibiotics can be given in case of a bacterial infection appearing after enrolment. All other antibiotics, new-quinolones included, should be avoided where possible.

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including herbal therapy, physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the concomitant medications eCRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started.

[redacted]

5.5.8 Prohibited medication

Use of the following treatments is NOT allowed as per below recommendation in **KAE609 Cohorts**:

- Antimalarials other than the study drug and rescue medication (Coartem) are not permitted during the entire study period.
- Herbal medication should not have been taken within 1 week before the study treatment is given and should be avoided until the last study visit.
- Any other investigational treatment for the whole study duration.
- KAE609 undergoes 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) and inducers (such as HIV antivirals: e.g., efavirenz miscellaneous: e.g., barbiturates, carbamazepine, phenytoin, rifampin, St. John's wort) are not allowed up to 14 days before enrolment in the study or minimum 5 half-lives of the perpetuator drug (whichever is longer) administration and up to 7 days post administration.
- KAE609 is a potent inhibitor of CYP2C19 and can potentially increase the exposure of drugs which are a substrate of CYP2C19 by many folds (such as Proton pump inhibitors: e.g., lansoprazole, omeprazole, anti-epileptics: e.g., phenytoin, miscellaneous: e.g., amitriptyline, chloramphenicol, clomipramine, indomethacin, nelfinavir, progesterone (synthetic progestins used in hormonal contraceptives are not prohibited since they are metabolized by CYP3A4), proguanil, propranolol, warfarin). Therefore, these are prohibited for the treatment duration and 7 days after last dose.
- Drug known to cause QTc prolongation or known to be potentially hepatotoxic (see Appendix 4) are prohibited for the treatment duration and 7 days after last dose.

Apart from the above mentioned possible interactions in vitro data suggest KAE609 is inhibitor of CYP2B6, CYP2C9, CYP2A6, CYP1A2, CYP2D6, CYP2C8, and CYP3A4, however, assessment including SimCYP simulation suggests that potential change in the exposure of drug substrate of any of these would be less than two fold and unlikely to be of clinical significance. Nonetheless caution should be exercised such as staggering the dose of victim drug by ~12 hours from last dose of KAE609.

Use of the following treatments is NOT allowed as per below recommendation in **Coartem/Riamet Cohorts**:

Coartem/Riamet prescribing information should be followed in general. Use of any prescription drugs (with particular attention to use of CYP3A4 inhibitors, e.g., erythromycin, ketoconazole, itraconazole, cimetidine or CYP3A4 inducers e.g., rifampin, phenobarbital etc. Also drugs metabolized by CYP2D6 like flecainide, metoprolol, imipramine, amitriptyline, clomipramine, neuroleptics and those that increase QTc interval like terfenadine, astemizole, cisapride) is prohibited during study and within four (4) weeks prior to dosing. Herbal supplements are also prohibited during study and within one week prior to dosing. Medication which may be required to treat adverse events can be administered considering the potential interaction. Administration of paracetamol (daily total dose not to exceed 3g) / acetaminophen is acceptable, but dose and time of administration must be documented in the Concomitant medications / significant non-drug therapies section of the eCRF.

[redacted]

5.5.9 Emergency breaking of assigned treatment code

Emergency breaking of assigned treatment code is not needed since this is an open-label trial.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

Each patient will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the investigator.

Patients who discontinue study drug and/or are put on rescue medication at any time during the study will be followed for the entire study duration (i.e., until Study Day 29).

The investigator and/or referring physician must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care. This care may include:

- Treatment of their malaria and complications
- Treatment of secondary infections
- Treatment of associated diseases

A safety review committee will review patient safety at several time points (see Section 8.4) and may recommend stopping a treatment arm or the study early for safety reasons.

5.6.2 Discontinuation of study treatment

Patients will be treated under hospital supervision during the treatment period. Discontinuation of study treatment for a patient occurs when study drug is stopped earlier than the protocol planned duration, and discontinuation can be initiated by either the patient or the investigator. For patients assigned to 1-day treatment arm, they will not be considered as treatment discontinuation if those discontinuation events occur after they have completed the treatment as assigned.

The investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation would negatively impact the participation of the patient in the trial.

Study treatment must be discontinued under the following circumstances:

- Patient request
- Pregnancy (see Section 6.5.6 and Section 7.6)
- Use of prohibited treatment as per recommendations in Section 5.5.8
- Any situation in which study participation might result in a safety risk to the patient and/or any adverse events that in the judgment of the investigator, taking into account the patient's overall status, prevent the patient from continuing participation in the study
- Unsatisfactory therapeutic effect (see Section 6.5.8)

[redacted]

- Emergence of the following adverse events: severe nausea/vomiting, severe pruritus, increases in QTcF to >500 ms (based on repeat Electrocardiograms (ECGs), development of ventricular arrhythmia or clinically significant (symptomatic) bradycardia (see Appendix 3)
- Any laboratory abnormalities (e.g., LFT increase) that in the judgment of the investigator, taking into consideration the patient's overall status, prevent the patient from continuing taking the study medication (see Appendix 2)
- Deviation from the planned dose regimen for the study drug

Patients who discontinue study drug for any of the above reasons may be given rescue medication at the discretion of the investigator and will be followed for the whole study duration until Study Day 29.

If discontinuation of study treatment occurs, the patient should NOT be considered withdrawn from the study and should undergo the scheduled study visits. The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the Treatment Completion eCRF. If the patient completes all the scheduled visits in the treatment period, the patient is considered to have completed the treatment period. If a patient does not complete the scheduled visits in the treatment period, premature treatment discontinuation visit assessments detailed in the assessment schedule table should be completed and recorded in the eCRF. The only reason a patient would not complete all these visits is because he/she withdrew study consent/ died/ lost to follow up or the sponsor terminated the study early.

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient, to collect key safety data. This telephone contact should preferably be done according to the study visits schedule.

The investigator must also contact the IRT to register the patient's discontinuation from study treatment (this patient will not be replaced).

5.6.3 Premature Study Withdrawal

Patients are considered to be withdrawn prematurely from the study if they do not complete the follow-up visits until Study Day 29.

A patient may voluntarily discontinue participation in this study at any time. The investigator may also, at their discretion, discontinue the patient from participating in this study at any time. Patients may be prematurely discontinued from the study for any of the following reasons:

- Adverse event
- Protocol deviation
- Study closed/terminated
- Loss to follow-up
- Consent withdrawal
- Study or investigator non-compliance
- At the request of the investigator

[redacted]

- Pregnancy

Patients are not obligated to state the reason for withdrawal from this study. However, the reasons for withdrawal, or failure to provide a reason, must be documented by the investigator on the Completion/Withdrawal section of the eCRF.

If a patient is withdrawn from the study for any reason, the investigator must make every effort to perform the study evaluations for Withdrawal visit as specified in the Table 6-1. Withdrawn patients will not be replaced.

5.6.4 Withdrawal of informed consent

Patients/subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent (WoC) from the study occurs only when a subject:

- Does not want to participate in the study anymore

and

- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a patient's samples until their time of withdrawal) according to applicable law.

All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

5.6.5 Loss to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

5.6.6 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient

[redacted]

must be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Patients must be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the eCRF.

[redacted]

Table 6-1 Assessment schedule

Period	Screen	Treatment															Follow-up							UNS
Visit Numbers[1]	1	101							102		199 EOT Period / premature discontinuation						201	202	203	204	205	206	299 End of Follow up / PSW	
Study Day		1							2		3						4	5	8	11	15	22	29	
Window		±0 day							±0 day		±0 day						±0 day	±0 day	±1 day	±1 day	±1 day	±1 day	±2 day	
Time (post first dose) in hours	-6 to < 0	0	1	2	4	6	8	12	24	36	48	50	52	56	60	68	72	96	168	240	336	504	672	
Obtain informed consent[2]	x																							
Demography	x																							
Inclusion/Exclusion criteria	x																							
History of alcohol use and Drug abuse	S																							
Initial Medical and Treatment history	x																							
Signs and symptoms of Severe Malaria	x	x		x	x		x	x	x	x	x				x		x	x	x	x	x	x	x	x
Malaria Blood Film for parasite count	x			x	x		x	x	x	x	x				x		x	x	x	x	x	x	x	x
Blood sampling for PCR genotyping	x																		x	x	x	x	x	x
Vital Signs (blood pressure, pulse)	x	x							x		x						x	x	x	x	x	x	x	x
Body temperature	x	x		x	x		x	x	x	x	x				x		x	x	x	x	x	x	x	x
Drug Administration Record		x					x[10]		x[11]	x[10]	x[11]				x[10]									
Rescue Medication (Coartem)[3]																							x	
Physical Exam and malaria signs and symptoms[4]	S	S			S		S	S	S	S	S				S		S	S	S	S	S	S	S	S
Prior and concomitant medications	x	x							x		x						x	x	x	x	x	x	x	x
Blood chemistry[5]	x								x		x						x	x	x	x	x	x	x	x
hematology[5]	x								x		x						x	x	x	x	x	x	x	x
PK KAE609 Single Dose Cohort (rich PK)[6]			x	x	x	x	x	x	x								x		x					
PK KAE609 Three Dose Cohort (rich PK)[6]			x	x	x	x			x		x	x	x	x	x		x		x					
PK Coartem Cohort[6]						x			x		x					x			x					
Triplicate ECG KAE609 Single Dose Cohort[7]	x				x			x	x														x	
Triplicate ECG KAE609 Three Dose Cohort[7]	x				x								x		x		x						x	
Triplicate ECG Coartem Cohort	x					x										x							x	
Urinalysis (Dipstick)	x								x									x			x		x	x
Pregnancy test[8]	x																						x	
Adverse events	←																							→
Meal records[9]		x					x		x	x	x				x									
Contact IRT	x	x							x[11]		x[11]												x	
Screening period disposition page	x																							
Treatment completion		x					x[10]		x[11]	x[10]	x[11]				x[10]									
Treatment period disposition page																x								
Follow-up period disposition page																							x	

[redacted]

EOT = End of treatment; UNS = Unscheduled visit; PSW = Premature study withdrawal
X = assessment to be recorded on clinical data base
S = assessment to be recorded on source documentation only
β-hCG = The β-subunit of human Chorionic Gonadotropin

[1] Visit structure given for internal programming purpose only.

[2] Prior to start of any study procedure.

[3] Commencement of rescue medication with Coartem may occur after start of trial medications and up to Study Day 28 as deemed necessary by the investigator. Any patient on KAE609 who have not been rescued till Study Day 28, will be given Coartem at end of the study at Study Day 29.

[4] A complete physical examination will be performed by the investigational staff *at screening* and include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen including splenomegaly, back, lymph nodes, extremities, vascular and neurological. Body height and body weight will also be measured at screening and data recorded on clinical data base.

An abbreviated physical examination will be performed at all other visits starting from Study Day 1. An abbreviated physical exam will include the examination of general appearance, vital signs (blood pressure and pulse) and body temperature. Fever monitoring will be done until resolution of fever, defined as being afebrile for 48 hours.

Body weight will also be measured at Study End (Study Day 29 or earlier in case of premature patient discontinuation) and data recorded on clinical data base.

[5] Laboratory tests should also be taken at any time of withdrawal/discontinuation.

[6] Missed PK sampling time should be taken as soon as possible and actual time should be recorded. **For Scheduled time ≤ 2 h ± 10 min; 2 - ≤ 24 h ± 30 min; > 24 - ≤ 72 ± 2 h, > 72 h ± 24 h.**

[7] Will be repeated in case of abnormalities.

[8] The patient´s menstrual and contraceptive history will be taken and a serum/plasma β-hCG pregnancy test will be performed at screening to exclude pregnancy. A urine β-hCG test will be performed at end of study. Results must confirm negative ***before*** dosing.

[9] Meals consumed within 30 min prior to dosing and 4 hours post dosing to be documented for Coartem cohort.

[10] Comparator only (Coartem).

[11] Not applicable to 1-day treatment regimen.

[12] ECG's should be taken in triplicate within 5 min after resting for at least 10 min in the supine position to ensure a stable heart rate according to the ECG investigator manual. Also, ECG's should be taken before any other procedure taken at the same nominal time point is performed. **For Scheduled time ≤ 2 h ± 10 min; 2 - ≤ 24 h ± 30 min; > 24 - ≤ 72 ± 2 h, > 72 h ± 24 h.**

6.1 Information to be collected on screening failures

All patients/subjects who have signed informed consent but not entered into the next period will have the study completion page for the screening period, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include:

- Age
- Gender
- Body weight
- Body height
- Body temperature
- Severe malaria
- Vital signs
- Prior and concomitant medications
- Blood chemistry and hematology
- Urinalysis
- Pregnancy test
- Malaria blood film for parasite
- Blood sampling for Polymerase Chain Reaction (PCR) genotyping
- Medical history
- Triplicate 12-lead ECG

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

6.3 Treatment exposure and compliance

All study treatment taken must be recorded in the Drug Administration Record (DAR) CRF, along with any comments about whether the patients swallowed all or part of the medication, whether and when vomiting occurred, and whether replacement medication had to be initiated.

Records of study medication used and exact dosages administration will be kept during the study. Drug accountability will be noted by the field monitor during site visits and at the completion of the study.

All medication (other than study drug) and significant non-drug therapies administered after the patient starts treatment with study drug will be documented on the concomitant medications/Significant non-drug therapies (surgical and medical procedures CRF and non-surgical procedures CRF) CRF after start of study drug.

[redacted]

6.4 Efficacy

Efficacy assessments will be based on the PCR-corrected Adequate Clinical and Parasitological Response (ACPR) and PCR-Uncorrected ACPR at Study Days 15 and 29 (see Section 6.5.8).

6.4.1 Parasitaemia assessment

Blood sampling for parasitology can be done by means of finger prick except when the timing for parasitology assessments coincide with time for clinical laboratory tests, in which case, blood sample can be taken from the venous blood collected for clinical laboratory analyses.

Parasite counts:

- Giemsa stained thick (and thin) films will be examined. Thin films will be examined only if identification of species is needed after malaria (*Plasmodium*) parasite is detected in a thick film
- Examination with binocular microscope and with oil immersion lens
- Screening examination (prior to patient inclusion into the trial), thick film:
  - at least 200 thick film fields are examined. If there is no malaria parasite, the slide is declared negative, and the patient is not suitable for inclusion.
  - if asexual forms of Plasmodia are found, a total of 200 thick film fields are to be screened for *Plasmodium* species other than *P. falciparum*.
  - when it has been ascertained that *P. falciparum* is present, a count is made of the asexual forms against leukocytes, using a tally counter. Counting needs to be done based on at least 200 leukocytes according to the WHO standards. If less than 100 parasites, counting will be extended to 500 leukocytes. The parasite density will be calculated according to the formula:

$$\text{Parasite density per } \mu l = \frac{\text{Number of } \textit{Plasmodium} \text{ parasites x actual leukocytes (White Blood Cell, WBC)}}{\text{Number of leukocytes (WBC) counted (200)}}$$

- Blood examination during the 29 day trial period:
  - a total of 200 thick films fields are examined (tally counter) before a slide can be pronounced negative
  - if asexual forms of *P. falciparum* are present, a parasite count is required
  - if *Plasmodium* species other than *P. falciparum* are found, note species

The **count should be made for <u>each species</u>** (White et al 2014). Blood film may be potentially confirmed by PCR. Thick (and thin blood) films will be taken as specified in the assessment schedule table and evaluated by standard techniques (Giemsa stain). This will be the definitive test for a positive *P. falciparum* infection. The parasite counts can also be quantified in ‰ (per 1000) of red cells in the thin film.

Further technical details are provided in the laboratory manual.

[redacted]

6.4.2 Appropriateness of efficacy assessments

The microscopy examination methods to quantify the malaria parasite in blood are validated methods (Sinden et al 2012; White et al 2014). For full details refer to the Study Laboratory Procedures Manual.

6.5 Safety

Clinical adverse events will be monitored throughout the study to assess the general safety and tolerability of the treatment groups.

6.5.1 Physical examination and malaria signs and symptoms

A ***complete*** physical examination will be performed by the investigational staff *at screening* and include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen including splenomegaly, back, lymph nodes, extremities, vascular and neurological.

An ***abbreviated*** physical examination will be performed at all other visits starting from Study Day 1 including the examination of general appearance and vital signs. Fever monitoring will be done until resolution of fever, defined as being afebrile for 48 hours.

A full assessment of ***malaria signs and symptoms*** will be made alongside the physical examinations at timepoints described in the assessment schedule for all patients (Table 6-1).

Information for all physical examinations must be included in the source documentation at the study site. Body height and body weight must be recorded in the clinical database. Clinically relevant findings that are present prior to signing informed consent must be included in the Medical History part of the eCRF. Significant findings made after first administration of investigational drug which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the eCRF.

6.5.2 Vital signs

Vital signs (blood pressure, body pulse) will be monitored as part of the physical exam as indicated in the study assessment schedule table and recorded on the clinical database.

After the patient has been in supine position for five minutes, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g., OMRON, with an appropriately sized cuff. The repeat measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. The same arm must be used throughout the study. A sphygmomanometer with an appropriately sized cuff should be used.

6.5.3 Height and weight

In addition, body height in centimeters (cm) will be measured at screening and body weight to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes will be measured at screening and at study end (Study Day 29 or earlier in case of premature patient withdrawal from study participation).

[redacted]

6.5.4 Laboratory evaluations

A local laboratory will be preferably used for analysis of all specimens collected except for PCR (parasite identification), ECG and PK measurements where central laboratory will be used. Details on the collections, shipment of samples and reporting of results by the central laboratories are provided to investigators in the laboratory manuals where applicable. Assessments will be done as indicated in the study assessment schedule table.

Clinically notable laboratory findings are defined in Appendix 1.

Hematology, *Blood chemistry* and *Urinalysis* assessments will be done as described in the assessment schedule table (Table 6-1).

6.5.4.1 Hematology

Hemoglobin, hematocrit (packed-cell volume (PCV)), platelets, white blood cell (WBC) count with differential (as much as possible, neutrophil, lymphocyte and eosinophils counts will be performed while basophils and monocytes can be aggregated as 'other') counts will be measured. Red blood cell count (RBC), reticulocytes count will be performed in case of significant hemoglobin drop > 2 g/dL or hemoglobin levels ≤ 5 g/dL (will be optional depending on site equipment). Assessments will be done as indicated in the study assessment schedule table (Table 6-1).

6.5.4.2 Blood chemistry

Routine blood chemistry testing will be performed according to the visit schedule in order to monitor the general medical condition of the patient.

This includes: Glucose, creatinine (serum), transaminases (ALT/SGPT and AST/SGOT), serum-γ-glutamyl transferase (GGT), Total and conjugated bilirubin, haptoglobin, LDH, ALP, BUN, INR, sodium, potassium, magnesium, calcium, chloride, total protein and, albumin, .

6.5.4.3 Urinalysis

Dipstick measurements for specific gravity, protein, glucose and blood will be performed as indicated in the study assessment schedule table. Microscopy will be performed and urine sediment will be assessed in case of an abnormal dipstick test.

6.5.5 Electrocardiogram (ECG)

ECGs should be taken in triplicate within 5 minutes (after 10 minutes rest in the supine position to ensure a stable heart rate according to the ECG investigator manual). The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling.

The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Triplicate 12 lead ECGs are to be collected with ECG machines supplied by the central laboratory. Initial manual readout will be done locally in order to detect significant safety findings and allow for immediate response if needed. Local readout will be used for inclusion/exclusion purposes as central readout is not available within 24 hours.

[redacted]

In the event that a clinically significant ECG abnormality is identified at the site (e.g., severe arrhythmia, conduction abnormality of QTcF > 500 ms) the SAE must be reported according to the procedure described in Section 7.2. If the patient is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

If QTcF is > 500 ms or QTcF increases ≥ 60 ms from baseline occur at any time, the patient should be assessed at the site and appropriate safety procedures (e.g., electrolyte correction) initiated without delay, if required. In addition two additional ECGs should be collected at 2-min intervals and provided to the central ECG laboratory for confirmation.

Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE eCRF page as appropriate.

For 3 day regimens, any post-dose average QTc ≥ 500 ms will result in patient discontinuation from the treatment if there is a planned subsequent treatment.

Assessments will be done as indicated in the study assessment schedule table. All ECGs will be assessed centrally by an independent and blinded (with age of patient identified) cardiologist.

6.5.6 Pregnancy and assessments of fertility

A serum or plasma pregnancy test will be performed at the screening visit and urine pregnancy test will be performed at study completion. All female patients in this study must undergo obligatory pregnancy testing as per schedule of assessment (Table 6-1).

6.5.7 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

6.5.8 Definition of Treatment Failure

Early treatment failure (ETF)

ETF is defined within this protocol as:

1. Clinical decline or lack of improvement (per Investigator) at 24 hours after first dose of treatment.
2. Development of any clinical complications (described in the WHO definition of complicated/severe malaria (WHO Guidelines 2010)) in the presence of parasitaemia within 72 hours of the first dose of treatment
3. Parasitaemia > 75 000/µL at or after 12 hours post-dose
4. Parasitaemia ≥ baseline with or without fever at 36 hours after first dose of treatment
5. Any parasitaemia based on microscopy with fever, 48 hours post-dose
6. Parasitaemia > 100/ µL based on microscopy with or without fever, 72 hours post-dose

Late Clinical Failure (LCF)

Development of danger signs or severe malaria on any day between Study Day 5 and Day 29 in the presence of parasitaemia without previously meeting any of the criteria of ETF

[redacted]

Presence of parasitaemia and axillary temperature ≥ 37.5ºC on any day between Study Day 5 and Day 29 without previously meeting any of the criteria of ETF

Late Parasitological Failure (LPF)

Presence of parasitaemia on any day between Study Day 5 and Day 29 and axillary temperature < 37.5ºC without previously meeting any of the criteria of ETF or LCF

Adequate Clinical and Parasitological Response (ACPR):

Absence of parasitaemia on Study Day 29 irrespective of axillary temperature, without previously meeting any of the criteria of ETF or Late Treatment Failure or LPF.

Note: The first day of treatment with study medication is defined as Study Day 1 while the day prior to the first day of treatment is defined as Day -1. Compared to WHO (2016) which defined Day 0 as the first day of treatment with study medication, days after treatment referred to in this protocol are 1 day greater. For example, Study Day 29 in this protocol corresponds to Day 28 by WHO (2016).

Signs/symptoms indicative of severe/complicated malaria

Danger signs:

1. not able to drink
2. vomiting > twice within preceding 24 hours
3. one convulsion within preceding 24 hours
4. unconscious state
5. unable to sit or stand

Signs of severe malaria:

Severe falciparum malaria is defined as one or more of the following, occurring in the absence of an identified alternative cause and in the presence of *P. falciparum* asexual parasitaemia:

- Impaired consciousness (Glasgow coma score < 11 in adults)
- Prostration (generalized weakness i.e., unable to sit, stand or walk without assistance)
- Multiple convulsions (more than two episodes within 24 hours)
- Acidosis (a base deficit of > 8 mEq/L or if not available a plasma bicarbonate level of < 15 mmol/L or venous plasma lactate ≥ 5 mmol/L. severe acidosis manifests clinically as respiratory distress i.e., rapid, deep, laboured breathing)
- Hypoglycemia (blood or plasma glucose < 2.2 mmol/L; < 40 mg/dL)
- Severe malarial anemia (haemoglobin concentration < 7 g/dL or haematocrit of < 20% in adults with a parasite count > 10 000/µL)
- Renal impairment (plasma or serum creatinine > 265 µmol/L (3 mg/dL) or blood urea > 20 mmol/L)
- Jaundice (plasma or serum bilirubin > 50 µmol/L (3 mg/dL) with a parasite count > 100 000/µL)
- Pulmonary edema (radiologically confirmed or oxygen saturation < 92% on room air with a respiration rate > 30/min, often with chest indrawing and crepitations on auscultation)

[redacted]

- Significant bleeding (including recurrent or prolonged bleeding from the nose, gums or venipuncture sites, haematemesis or melaena)
- Shock (compensated shock i.e., capillary refill ≥ 3s or temperature gradient on leg but no hypotension; decompensated shock i.e., systolic blood pressure < 80 mm Hg in adults with evidence of impaired perfusion)
- Hyperparasitaemia (*P. falciparum* parasitaemia > 10%)

[redacted]

6.6.1 Pharmacokinetics

Details on sample collection, numbering, processing and shipment can be found in the Laboratory Manual.

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

The occurrence of adverse events must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

[redacted]

Study drug/treatment includes investigational drug KAE609 (10 mg, 25 mg, 50 mg, 75 mg, 150 mg, 225 mg, or 110 mg) as well as Coartem.

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the Common Toxicity Criteria (CTC) AE grade

If Common Toxicity Criteria for Adverse Events (CTCAE) grading does not exist for an adverse event, use

1= mild

2= moderate

3= severe

4= life-threatening (see Section 7.2 for definition of SAE)

CTCAE Grade 5 (death) is not used, but is collected as a seriousness criteria and also collected in other CRFs (Study Completion, Death/Survival).

There may be cases where a CTCAE with a grade of 4 (life-threatening) may not necessarily be an SAE (e.g., certain laboratory abnormalities in the absence of meeting other seriousness criteria).

- its relationship to the study treatment and the reference product Coartem (Yes/No)
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- whether it constitutes a SAE (see Section 7.2 for definition of SAE) and which seriousness criteria have been met.
- action taken regarding (investigational) treatment

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g., further observation only)
- study treatment withdrawn
- concomitant medication or non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving; recovered/resolved with sequelae; fatal; or unknown)

The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the patient informed consent and should

[redacted]

be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate. New information might require an update to the informed consent and has then to be discussed with the patient.

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing)) undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g., defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood

[redacted]

dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

Any suspected transmission of an infectious agent via a medicinal product is also considered a serious adverse reaction.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and following the last administration of study treatment must be reported to Novartis safety within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis safety if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs (either initial or follow up information) is collected and recorded in English in the electronic Serious Adverse Event (eSAE) Form within the Oracle Clinical/Remote Data Capture (OC/RDC) system (wherever available and/or feasible) or on the paper SAE Report Form that should be used as back-up, especially in case where there is no feasibility of the use of eSAE Form. The investigator must assess the relationship of each SAE to the study treatment (KAE609 or Coartem).

SAEs (initial and follow-up) that are recorded electronically in the OC/RDC system should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing SAE. These data will automatically be submitted to Novartis Chief Medical Office and Patient Safety (CMO&PS) immediately after investigator signature or 24 hours after entry, whichever occurs first.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the IB for KAE609 or Package Insert for Coartem (new occurrence) and is thought to be related to the study treatment a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with European Union (EU) Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

[redacted]

7.3 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as (S)AE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which are considered as medically significant events, i.e., SAEs and which consist of marked elevations of LFTs and / or pre-specified adverse events. These events will require close observation, follow-up monitoring and completion of the standard base liver CRF pages.

Any liver event which meets the criteria for a **"medically significant"** event should follow the **standard procedures for SAE reporting** as described in Section 7.2.

Please refer to Table 14-1 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 14-1 of Appendix 2 should be followed up by the investigator or a designated medically qualified person at the trial site as summarized below. Detailed information is outlined in Table 14-2 in Appendix 2.

For the liver laboratory trigger:

- Repeating the LFT within 24 hours to confirm elevation.

These LFT repeats can be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event should be reported on the liver CRF pages.

Repeat laboratory tests must be entered on the appropriate unscheduled local laboratory CRF page.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment discontinuation if deemed appropriate.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed must be recorded on appropriate CRF pages, including the liver event overview CRF pages.

[redacted]

7.4 Renal safety monitoring

The following two categories of abnormal renal laboratory values have to be considered during the course of the study:

- Serum event:
  - confirmed (after ≥ 24h) increase in serum creatinine of ≥ 25% compared to baseline during normal hydration status
- Urine event
  - new onset (≥ 1+) proteinuria; confirmed by doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable)
  - new onset (≥ 1+), hematuria or glycosuria

Every renal laboratory trigger or renal event as defined in Table 15-1 in Appendix 3 should be followed up by the investigator or designated personnel at the trial site as summarized in Appendix 3.

7.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (European Medicines Agency (EMA) definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration Record (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

7.6 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of

[redacted]

the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local/regional Novartis CMO & PS Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on an eSAE form/paper SAE form (as applicable).

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice (GCP), the progress of enrollment, and to ensure that study drugs are being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents (archival and storage) for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments as per ICH-GCP standards. All information on eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients/subjects will be disclosed.

[redacted]

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the eCRFs using fully validated software that conforms to 21 US Code of Federal Regulations (CFR) Part 11 requirements and into the OC/RDC. Designated investigator site staff will not be given access to the system until they have been trained. Automatic validation programs check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the eCRFs are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

All data captured for this study will have an external originating source (either written or electronic), the eCRF is not considered as source.

8.3 Database management and quality control

Novartis staff (or CRO working on behalf of Novartis) review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

For those laboratory samples that will be processed centrally the results will be sent electronically to Novartis (or a designated CRO). ECG readings will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drug(s) dispensed to the patient will be tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

8.4 Safety review committee

A safety review committee will be established for this study to review patient safety at several time points. The safety review committee can recommend stopping the study or a specific treatment arm in case of serious safety observations especially related to hepatic safety profile. The safety review committee will include at least one external hepatologist. Regular interim review for patient safety will be performed during the study as specified in the safety review committee charter.

[redacted]

Additional ad-hoc safety review may be requested by the safety review committee or the Study Team if needed.

Details of safety analyses will be specified in the analysis plan for the safety review committee. The safety review committee will make recommendations to the Study Team on any safety issues that are deemed relevant and any changes in the conduct of the study.

Further details of the safety review committee's composition, organization and responsibilities will be described in the safety review committee charter.

8.5 Adjudication Committee

Not required.

9 Data analysis

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.

9.1 Analysis sets

Randomized set

All patients who are randomized.

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. Full details will be described in the statistical analysis plan (SAP).

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

[redacted]

- 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 6.5.8), (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 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 took at least 80% of assigned study medication.

9.2 Patient demographics and other baseline characteristics

Demographic data and baseline disease characteristics will be descriptively presented and tabulated (n, mean, standard deviation, median, minimum, and maximum for continuous variables; n and percent for categorical variables) per cohort and treatment arm, as well as overall, using the Randomized set.

9.3 Treatments

All analyses in this section will be performed using the safety set.

9.3.1 Study treatment

Number and percentage of doses taken will be presented by cohort and treatment arm. The percentage will be calculated based on the planned number of doses per treatment arm. Percentage of patients with study drug vomiting and dose replacement will be presented by treatment arm. Average daily dosage and total dosage (in mg or tablet) of each drug (KAE609, Coartem) will be summarized by cohort and treatment arm.

9.3.2 Prior and concomitant medication

Medications will be identified using the Novartis drug and therapy dictionary (NovDTD) including ATC code.

Prior and concomitant medications will be summarized by cohort and treatment group in separate tables. Concomitant rescue and other anti-malarial medications will also be summarized by cohort and treatment group. Medications will be presented by ATC class and preferred term. Tables will also show the overall number and percentage of subjects receiving at least one drug of a particular ATC class.

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 randomized 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.

[redacted]

9.4 Analysis of the primary variable(s)

The primary variable is a safety related endpoint. Therefore, it will be analyzed primarily using the SAF set. Efficacy variables are related to secondary [redacted] and the related analyses will be presented in Section 9.5 and Section 9.6.

9.4.1 Primary Variable(s)

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.

9.4.2 Statistical model, hypothesis, and method of analysis

The study is a Phase II safety study 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 regiment is safe for further development.

9.4.3 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 imputation will be done in this study.

9.4.4 Sensitivity analyses

In the past KAE609 studies, peak LFT occurred during the first 2 weeks. For patients who discontinued the study during the first 2 weeks, their peak LFT may not be observed. Analyses in Section 9.4.2 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.

9.5 Analysis of secondary variables

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.

9.5.1 Efficacy variables

Secondary efficacy variables include:

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

[redacted]

- Proportion of patients with parasitaemia at 12, 24, and 48 hours after treatment;
- 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.

9.5.1.1 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.

Data will be handled as follows:

- Treatment failures after 7 days (i.e., Study Day 8) due to reinfection based on PCR genotyping are not considered as failure for PCR-corrected analyses.
- For parasitological uncorrected ACPR, patients will be treated as failure on and after the visit when a new infection (i.e., reinfection) with P. falciparum or other species is detected.
- Patients who received rescue medication for the treatment of *P. falciparum* malaria (except for the treatment of a new infection) will be considered treatment failures. Patients who received other concomitant medication having an effect on malaria for reasons other than rescue therapy e.g., for the treatment of *P. vivax* (e.g., primaquine, certain antibiotics (sulfonamides, tetracycline, etc.)) will be considered in the analysis as if they had not taken the drug.
- Patients will be counted as failure at a visit (e.g., Study Day 15, etc.) if (a) they did not have a parasite count i.e., missing parasite count at that visit unless these patients could be classified as cured based on absence of parasitaemia (parasite count = 0) at a later time (e.g., Study Day 29), or (b) they did not have valid PCR evaluations at baseline and the visit if parasitaemia was present at that time (e.g., Study Day 15).

In addition, PCR-corrected ACPR rate will be calculated and plotted using the Kaplan-Meier method (Stepniewska and White 2006; WHO 2016) for each treatment group by cohort in the FAS. Treatment failure is the event for analysis and patients without Study Day 29 data and treatment failure is considered as censored instead of treatment failure. The PCR-corrected ACPR rate at Study Day 29 is estimated by the survival function at Study Day 29. Patients who had a new infection (i.e., reinfection) with *P. falciparum* or other species without *P. falciparum* recrudescence on or after Study Day 8 will be censored at the time of the first PCR that indicate the infection; patients who took antimalarial medications for reinfection or reasons other than

[redacted]

rescue medication given for *P. falciparum* related treatment failure will be censored at the first time of such antimalarial medications; other patients without treatment failure will be censored at the time of last parasitaemia assessment.

9.5.1.2 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.

In addition, patients whose outcome status cannot be determined due to incomplete/missing data will be excluded from analysis.

9.5.1.3 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. 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. 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.

9.5.1.4 Recrudescence

Reinfection is defined as appearance of asexual parasites after clearance of initial infection with a genotype different from those parasites present at baseline.

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 by Study Day 7. Time to recrudescence will be calculated from the time of first study medication to the date of first event if a patient experience the event and be censored at the time of last parasite assessment if a patient does not experience the event.

9.5.2 Safety variables

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

[redacted]

9.5.2.1 Adverse event

The number and percentage of patients who report adverse events will be provided according to primary system organ class (PSOC), preferred term, and severity. If a patient reports more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a patient reports more than one adverse event within the same PSOC, the patient will be counted only once with the greatest severity.

Cause of death, SAEs, adverse event causing study drug discontinuation, adverse events by severity and causality will be presented. Listings of these events will be provided.

9.5.2.2 Laboratory evaluations

Summary of laboratory evaluations will be presented with respect to three groups of laboratory tests (hematology, blood chemistry, and urinalysis).

Descriptive summary statistics (mean, median, standard deviation, minimum and maximum) for the baseline, each study visit, and change from baseline to each study visit will be presented. These descriptive summaries will be presented by laboratory test group.

In addition, shift tables will be provided in order to compare a patient's baseline laboratory evaluation relative to each study visit and at the maximum value. For the shift tables, the normal laboratory values will be used to evaluate whether a particular laboratory test value is normal, low, or high for each visit value relative to whether or not the baseline value is normal, low, or high. For liver enzymes (ALT, AST, etc.), the shift table of CTCAE grades relative baseline and number and percent of patients with $\geq$ 2 x ULN (if baseline is normal) or 2 x baseline (if baseline is > ULN) will be provided. These summaries will be presented by laboratory test group.

9.5.2.3 Vital signs

Descriptive summary statistics for the baseline, each study visit, and change from baseline to each study visit will be presented for each vital sign parameter (pulse rate, systolic/diastolic blood pressures).

Number and percentage of patients who have vital sign values that meet the criteria for being clinically notable after the first dose of study medication will be presented.

9.5.2.4 ECGs

Descriptive summary statistics for the baseline, each study visit, and change from baseline to each study visit will be presented for heart rate, PR interval, QRS interval, RR interval, QT interval and QTcF (QT interval corrected for heart rate according to Fridericia). Number and percentage of patients with abnormal values (such as QTc > 480 ms and > 500 ms or HR < 50 /min) and changes from baseline (such as increases in QTc for $\geq$ 30 ms and $\geq$ 60 ms) will be tabulated at each time point and at the maximum value by treatment group in the form of a categorical analysis.

[redacted]

9.5.3 Resource utilization

Data relating to resource utilization will be used for the purpose of economic evaluation which will be carried out and reported as a separate activity.

9.5.4 Pharmacokinetics

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 mean, geometric mean, standard deviation, median, minimum and maximum, etc. Parameters such as AUCinf, AUClast, AUC0-t, Cmax and Tmax will be reported using non-compartmental method of analysis (using Phoenix 6.4 or higher).

[redacted]

[redacted]

[redacted]

9.7 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 is no significant LFT elevations observed in a cohort at Day 15 (see Table 3-1), 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 3-1), 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 regiment 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.

9.8 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.

9.8.1 Single arm approach

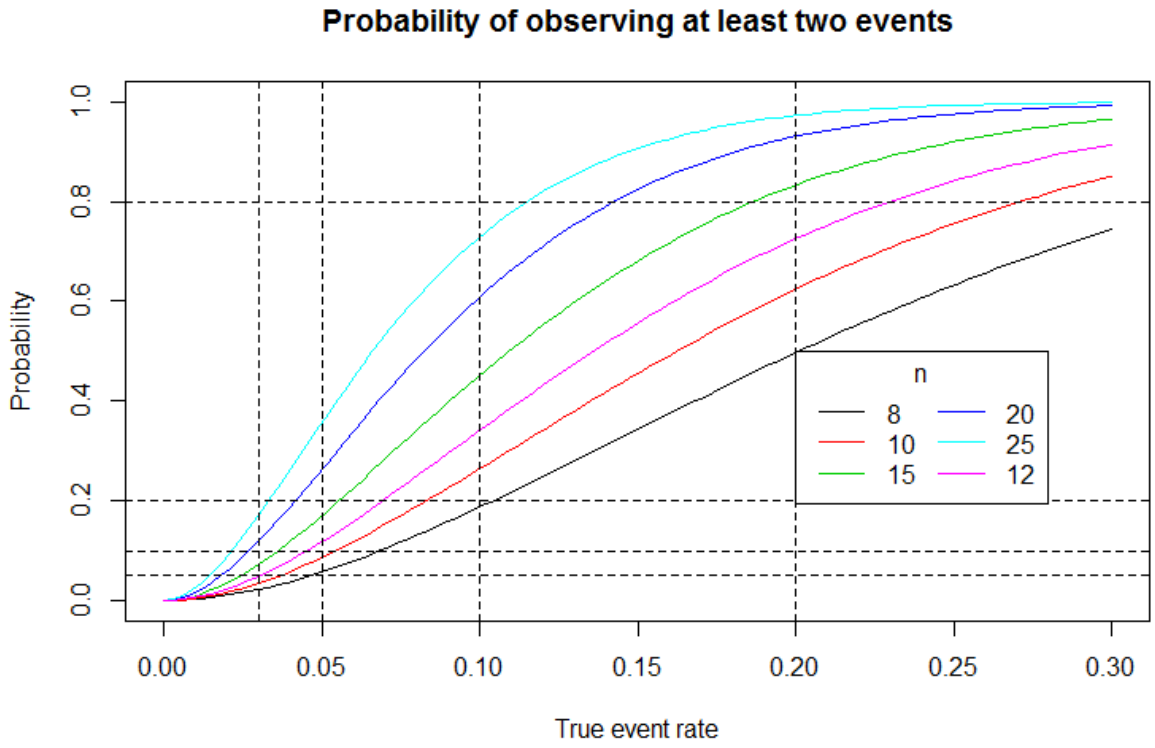
Figure 9-1 and 9-2 present the probability of observing at least 2 and 3 safety events, respectively, in a treatment group by various sample sizes and true event rates to assess the operational characteristics for the proposed sample sizes.

[redacted]

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:

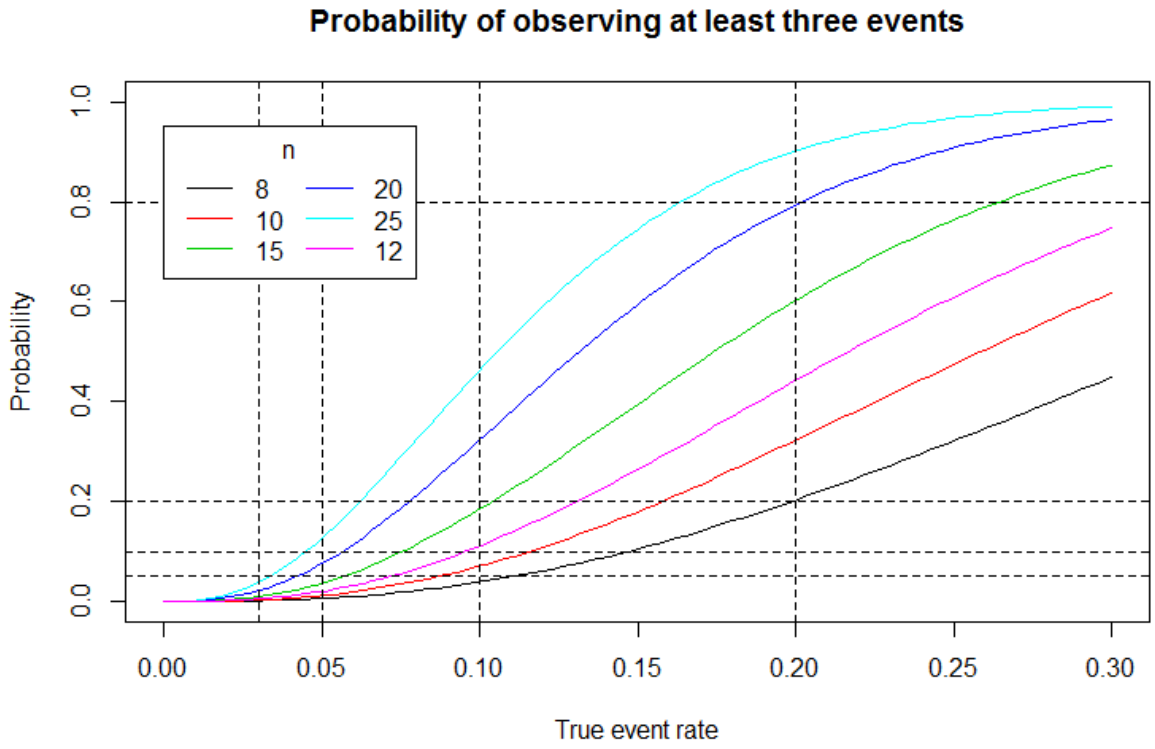
- For a sample size of 10 patients per treatment group, the probability of observing ≥ 2 safety events is greater than 80% if the true event rate is ≥ 30% and less than 5% if the true event rate is ≤ 3% (Figure 9-1).
- For a sample size of 20 patients per treatment group, the probability of observing ≥ 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 9-2).

Figure 9-1 Probability of observing at least 2 safety events by sample size and true event rate



[redacted]

Figure 9-2 Probability of observing at least 3 safety events by sample size and true event rate



9.8.2 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.

[redacted]

Table 9-1 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%

[redacted]

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 proceeds 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.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if applicable after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the

investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients/subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance, a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach. Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal standard operating procedures (SOPs), and are performed according to written Novartis processes.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances is an

investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients/subjects may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

12 References

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Hien T, White N, Thuy-Nhien N et al (2017) Estimation of the in vivo MIC of Cipargamin in uncomplicated Plasmodium falciparum malaria, Antimicrobial Agents Chemother;61:e01940-16.

Sinden RE, Blagborough AM, Churcher T, et al (2012) The design and interpretation of laboratory assays measuring mosquito transmission of Plasmodium. Trends Parasitol;28(11):457-65.

Stepniewska K and White NJ (2006) Some considerations in the design and interpretation of antimalarial drug trials in uncomplicated falciparum malaria. Malaria Journal; 5:127.

White NJ, Ashley EA, Recht J, et al (2014) Assessment of therapeutic responses to gametocytocidal drugs in Plasmodium falciparum malaria. Malar J;13:483.

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World Health Organization (2016) World Malaria Report (http://apps.who.int/iris/bitstream/10665/252038/1/9789241511711-eng.pdf?ua=1).

[redacted]

13 Appendix 1: Clinically notable laboratory values and vital signs

Certain adverse events should be considered medically significant and should be submitted to Novartis as SAEs within 24 hours.

1. Hepatic
   - ALT or AST > 5 × ULN
     ALP > 2 × ULN (in the absence of known bone pathology)
     TBL > 2 × baseline value
   - ALT or AST > 3 × ULN and INR > 1.5
   - Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)
   - Any clinical event of jaundice (or equivalent term)
   - ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
   - Any adverse event potentially indicative of a liver toxicity, like hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions; non-infectious hepatitis, liver neoplasms
2. Cardiac
   - Absolute QTcF > 500 ms (confirmed by repeat ECGs)

[redacted]

14 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 14-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS (Medically significant events to be reported as SAEs)	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

Table 14-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Repeat LFTs within 24hHospitalize, if clinically appropriate • Establish causality • Complete liver CRF • **Report to Novartis as an SAE**	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency twice a week until resolution, stabilize or return to within baseline values)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Repeat LFTs within 24h • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF • **Report to Novartis as an SAE**	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency twice a week until resolution, stabilize or return to within baseline values)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Repeat LFTs within 24h • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF • **Report to Novartis as an SAE**	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency twice a week until resolution, stabilize or return to within baseline values)

Criteria	Actions required	Follow-up monitoring
> 5 to ≤ 8 × ULN	• Repeat LFT within 24 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete liver CRF • **Report to Novartis as an SAE**	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency twice a week until resolution, stabilize or return to within baseline values)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Repeat LFT within 24 hours • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF • **Report to Novartis as an SAE**	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency twice a week until resolution, stabilize or return to within baseline values)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within 48 hours • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 24 hours • If elevation persists, establish causality • Complete liver CRF • **Report to Novartis as an SAE**	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 24 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF • **Report to Novartis as an SAE**	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency twice a week until resolution, stabilize or return to within baseline values) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Preferred terms		
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality • Complete liver CRF • **Report to Novartis as an SAE**	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency twice a week until resolution, stabilize or return to within baseline values)
Any AE potentially indicative of a liver toxicity* - severe events only SMQ AE	• Consider study treatment discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF • **Report to Novartis as an SAE**	Investigator discretion

[redacted]

Criteria	Actions required	Follow-up monitoring
*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms [a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN [b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia [c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death. Alb: albumin; PT: prothrombin time.		

15 Appendix 3: Specific Renal Alert Criteria and Actions

Table 15-1 Specific Renal Alert Criteria and Actions

Serum Event	
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ≥ 50% compared to baseline	Follow up within 24-48h if possible Consider study treatment discontinuation Consider patient hospitalization /specialized treatment
Urine Event	
New dipstick proteinuria ≥ 1+ Albumin- or Protein-creatinine ratio increase ≥ 2-fold Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol; Protein-creatinine ratio (PCR) ≥ 150 mg/g or > 15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider study treatment discontinuation
New dipstick glycosuria ≥ 1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine
New dipstick hematuria ≥ 1+ not due to trauma	Urine sediment microscopy Perform serum creatinine
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor patient regularly (frequency at investigator's discretion) until either: Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or Event stabilization: sCr level with ± 10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ± 50% variability over last 6 months. sCr: serum creatinine.	

16 Appendix 4: Medications, herbs and toxins as cause of ALT/AST elevations

Table 16-1 Medications, herbs and toxins as cause of ALT/AST elevations

Medications and drugs

Alpha-methyldopa
Amoxicillin-clavulanic acid
Amiodarone
Bosentan
Carbamazepine
Dantrolene
Disulfiram
Etretinate
Fluconazole
Glyburide
Halothane
Heparin
HMG-Co A reductase inhibitors
Isoniazid
Ketoconazole
Labetalol
Nicotinic Acid
Nitrofurantoin
NSAIDs
Phenylbutazone
Phenytoin
Propylthiouracil
Protease inhibitors
Sulfonamides
Terbinafine
Trazadone
Troglitazone (withdrawn)
Valproic Acid

Herbs and alternative medications

Chaparral leaf
Ephedra
Gentian
Germander
Ji Bu Huan
Senna
Kava kava
Scutellaria (skullcap)
Shark cartilage
Vitamin A

Illicit drugs

Anabolic steroids
Cocaine
Ecstasy (MDMA)
Phencyclidine (PCP)

Toxins

Carbon tetrachloride
Chloroform
Dimethylformamide
Hydrazine
Hydrochlorofluorocarbons
2-Nitropropane
Trichloroethylene
Toluene

[redacted]