NOVARTIS

Global Clinical Development - General Medicine

KAF156

Clinical Trial Protocol CKAF156A2202 / NCT03167242

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

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List of abbreviations

ACT	Artemisinin-based Combination Therapy
ACPR	Adequate Clinical and Parasitological Response
ACR	Albumin-Creatinine Ratio
AE	Adverse Event
Alb	Albumin
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
AUCinf	Area under 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 plasma concentration-time curve from zero to time t of the last measured concentration above the limit of quantification
BID	twice a day
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CFR	US Code of Federal Regulations
β-hCG	The β-subunit of human Chorionic Gonadotropin
CI	Confidence Interval
CQ	Chloroquine
Cmax	Maximum Peak Observed Concentration
CMO&PS	Chief Medical Office and Patient Safety
CPO	Country Pharma Organization
CRF	Case Report/Record Form (paper or electronic)
sCr	Serum Creatinine
CRO	Contract Research Organization
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome
DAR	Dose Administration Record
DHP/DMP	Data Handling Plan/Data Management Plan
DMC	Data Monitoring Committee
EC50	Half maximal effective concentration
ECG	Electrocardiogram
EDC	Electronic Data Capture
e.g.	For exemple (exempli gratia)
EMA	European Medicines Agency
EOT	End of Treatment
ETF	Early Treatment Failure
EU	European Union
FAS	Full Analysis Set

[redacted]

FBC	Full Blood Count
FCT	Fever Clearance Time
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Serum-γ-Glutamyl Transferase
GNF	Genomics Institute of the Novartis Research Foundation
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HTS	High Through-put Screening
IA	Interim Assessment
IB	Investigator Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
i.e.	That is (id est)
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio (blood clotting test)
IUD/IUS	Intrauterine Device/Intrauterine System
IRB	Institutional Review Board
IRT	Interactive Response Technology
LCF	Late Clinical Failure
LFT	Liver function test
LPF	Late Parasitological Failure
LTF	Late Treatment Failure
LUM-SDF	Lumefantrine Solid Dispersion Formulation
MedDRA	Medical dictionary for regulatory activities
MEF	Mefloquine
NITD	Novartis Institute for Tropical Diseases
NovDTD	Novartis Drug and Therapy Dictionary
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
OATP1B1	Organic Anion Transporting Polypeptide 1B1
P.	Plasmodium
PCT	Parasite Clearance Time
PCR	Polymerase Chain Reaction
PCV	Packed-Cell volume (hematocrit)
PD	Pharmacodynamic
PK	Pharmacokinetic
PPS	Per-Protocol Set
[redacted]	[redacted]
PSOC	Primary System Organ Class
PT	Prothrombin Time
PYR	Pyrimethamine
OC/RDC	Oracle Clinical/Remote Data Capture

[redacted]

PSW	Premature Study Withdrawal
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
QTcB	QT interval corrected by the Bazett's Correction Formula
QTcF	QT Interval Corrected by the Fridericia Correction Formula
RBC	Red Blood Cell Count
RSI	Reference Safety Information
eRT	eResearch Technology
SAE	Serious Adverse Event (paper or electronic)
SAP	Statistical Analysis Plan
SD	Standard Deviation
SFDX	Sulfadoxine
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SMQ	Standardized MedDRA query
SNP	Single-Nucleotide Polymorphism
SOP	Standard Operating Procedure
SS	Safety Set
SUSAR	Suspected Unexpected Serious Adverse Reactions
Tmax	Time after administration of a drug when the maximum plasma concentration is reached
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal range
uPCR	Urinary Protein-Creatinine Ratio
UNS	Unscheduled visit
US	United States
WBC	White Blood Cell
WHO	World Health Organization
WoC	Withdrawal of Consent
WOCBP	Women Of Child Bearing Potential
WWARN	World Wide Antimalarial Resistance Network

[redacted]

Glossary of terms

Cohort	A specific group of patients fulfilling certain criteria
Control drug	Drugs(s) used as a comparator to reduce assessment bias, assess internal study validity.
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)
Epoch	A portion of the study which serves a specific purpose. Typical epochs 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
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient ID	A unique number assigned to each patient upon signing the informed consent
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	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 is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

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Amendment 1

Amendment rationale

- In a recent preclinical in vivo study in dogs KAF156 (10 mg/kg) and LUM-SDF (15 mg/kg) were administered in combination and preliminary data suggest that exposure of both KAF156 and lumefantrine increased in presence of each other. There was around 2-3 fold increase in KAF156 exposure and around 1.5 fold increase in lumefantrine exposure.
- Given the above situation and the fact that the study has not yet started, a PK Run-in Part has been included in the amended study protocol. This first part of the study will explore the PK and safety of KAF156 given in combination with LUM-SDF to understand the impact of LUM-SDF on KAF156 exposure as victim drug. In the unlikely scenario of an increase in KAF156 exposure beyond the acceptable limit, doses in Part A of the study may be adjusted.

Changes to the protocol

- **Protocol summary**: The PK Run-in Part has been added in the table in the following sub-sections: Study Design, Population, Key inclusion criteria, Study treatment and Data analysis. In addition PK assessments has been added to the list of assessments.

- **Section 1**: The rationale for having a PK Run-in Part has been described in Section 1.1 and the design of the study has been changed (i.e., now a three-part sequential design including the PK run-in Part) in Section 1.2.

- **Section 2.1**: Primary objective for the PK Run-in Part has been added (i.e. Assessments of KAF156 exposure in the PK Run-in cohort to understand the impact of LUM-SDF on KAF156 exposure).

- **Section 3**: Text describing the PK-Run-in Part has been added to different sub-sections of Section 3. Modified sections are :
  - ***Section 3.1*** (study design of the PK-Run-in Part added, Table 3-1 added and Figure 3-1 modified accordingly)
  - ***Section 3.3*** (Rationale for dose/regimen in PK Run-in Part added)
  - ***Section 3.5*** (Purpose of interim assessments/data reviews for the PK Run-in Part added)
  - ***Section 3.6*** (Risks and benefits modified to include the PK Run-in Part)

- **Section 4**: PK Run-in Part has been added to population description.

- **Section 5.1**: Study treatment for the PK Run-in Part has been included in the text and Table 5-1. Also, as doses in Part A of the study may be adjusted, Table 5-2 has been

[redacted]

modified to indicate KAF156 dose levels for Part A based on the results of the PK Run-in Part.

- **Section 5.2**: Treatment arm for PK Run-in Part added.
- **Section 5.3**: Treatment assignment and randomization for the PK Run-in Part added.
- **Section 5.4**: Treatment blinding for PK Run-in Part added.
- **Section 5.5**: Transition from PK Run-in Part to Part A added.
- **Section 5.6.5**: Procedure for patients who vomit in the PK Run-in Part has been added.
- **Section 6**: Schedule of assessments to be used for the PK Run-in Part has been added (i.e., same visit schedule as for Cohorts 1 and 2).
- **Section 9**: Data analysis for the PK Run-in Part has been added to Section 9.4, Section 9.5.4, Section 9.7, and Section 9.8.
- **References**: Three references added.
- **Appendix 5**: Part A dosing scheme based on the results of the PK Run-in Part added.

Amendment 2

Amendment rationale

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

- To correct the typographical error regarding oral/tympanic/rectal temperature versus axillary temperature.
- To correct an inconsistency regarding the requirement for blinding the technician performing microscopy readings. Since this is an open label study, blinding of technicians is not required.
- 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.

[redacted]

- 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.
- Terms "Biochemistry" and "clinical chemistry" 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.
- For further clarification, time window for electrocardiogram (ECG) assessment has been added in the table of assessment as ECG and pharmacokinetic (PK) assessments should be aligned.
- Clarification on how some cardiac alerts should be reported. Resting heart rate < 50/min with > 25% decrease from pretreatment baseline verified by ECG should be reported to Sponsor as adverse event (AE).

Changes to the protocol

- **List of abbreviations**: has been updated based on the changes implemented in this amendment.

- **Protocol summary and Section 4.1**: Reference to the laboratory manual for technical details about microscopy has been added, and typographical error on oral/tympanic/rectal temperature as compared to axillary temperature has been corrected.

- **Section 3.2**: Blinding laboratory technicians who perform microscopy readings has been removed as it is not required for this open label study.

- **Sections 5.6.6, 6.5.4, 6.5.4.2**: Term "Biochemistry" or "clinical chemistry" replaced by "blood chemistry" to maintain consistency throughout the protocol.

- **Section 5.6.7**: The terms prior medication and concomitant medication have been defined for further clarity to make it consistent with existing information in Section 9.3.2. Clarification on how paracetamol or equivalent drug should be reported when given as an antipyretic up to 72 hours prior first dose has been added.

- **Section 5.7.2**: Information on rescue medication in case of treatment discontinuation has been added for clarification purposes.

- **Table 6-1**: To correct typographical errors, the following changes have been done:
- [redacted]

[redacted]

- Meals have to be recorded on dosing days only (Day 1 to3). Meal record at Day 4 has been deleted.
- Patients are discharged on Day 4, so time window at Day 5 cannot be +/- 1 day, but + 1 day.
- The sites are required to contact Interactive Response Technology (IRT) for the control drug (coartem) once per day only so they are not required to contact IRT at hour 8, 36 and 60.
- Addition of PCR sampling 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.
- PCR sampling are all shipped to central laboratory, but analyzed only in patients showing treatment failure. Footnote corrected.

- **Table 6-2**: Time window for ECG assessment has been added.

- **Section 6.2**: Body height included in the list of baseline demographic characteristics to make it consistent with the information in Table 6-1, Section 6.5.1.

- **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 6.4.3**: PCR sampling are all shipped to central laboratory, but analyzed only in patients showing treatment failure.

- **Sections 6.5.3, 9.5.1**: Typographical error on oral/tympanic/rectal temperature as compared to axillary temperature has been corrected.

- **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 has been corrected to be consistent with Section 9.5.2.4: “> 60 ms from baseline” replaced by “≥ 60 ms from baseline”.

- **Section 6.6**: Time points for biomarker assessment added for clarification purposes, and it has beenclarified that biomarker is assessed in Part A only.

[redacted]

- **Section 7.1, Section 7.3 and Table 16-1**: Deleted "Study treatment dosage increased/reduced" and/or "Study treatment interrupted" and/or "interruption" 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, 7.7**: DS&E replaced by CMO&PS to reflect the latest terminology for Novartis Safety.

- **Section 8.3**: "Dosage changes" deleted as not allowed as per protocol.

- **Table 15-1**: For clarification, how some cardiac alerts should be reported has been added.

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.

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 do not affect the Informed Consent.

[redacted]

Protocol summary

Protocol number	CKAF156A2202
Full Title	A Phase 2 interventional, multicenter, randomized open-label study to determine the effective and tolerable dose of KAF156 and lumefantrine Solid Dispersion Formulation in combination, given once daily for 1, 2 and 3-days to adults and children with uncomplicated *Plasmodium falciparum* malaria
Brief title	Efficacy and safety of KAF156 in combination with LUM-SDF in adults and children with uncomplicated *Plasmodium falciparum* malaria
Sponsor and Clinical Phase	Novartis Phase 2
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This study aims to determine the most effective and tolerable dose at the shortest dosing regimen of the investigational drug KAF156 in combination with a solid dispersion formulation of lumefantrine (LUM-SDF) in adult/adolescent and pediatric patients with uncomplicated *P. falciparum* malaria. There is unmet medical need for anti-malarial treatment with new mechanism of action to reduce probability of developing resistance, and for duration shorter than 3 days of treatment and/or reduced pill burden.
Primary Objective(s)	The primary objective of this study is to determine the effective doses of KAF156 combined with LUM-SDF given daily over 1, 2 or 3 days for treatment of uncomplicated malaria caused by *P. falciparum*. The primary efficacy endpoint is the polymerase chain reaction (PCR) corrected adequate clinical and parasitological response (ACPR) at Day 29.
Secondary Objectives	Objective 1: To evaluate the safety and tolerability of KAF156/LUM-SDF. Objective 2: To further assess the effect of treatment with KAF156/LUM-SDF by assessing uncorrected ACPR and corrected ACPR at additional time points, as well as fever- and parasite clearance times. Objective 3: To assess key pharmacokinetic (PK) parameters of KAF156 and lumefantrine.

[redacted]

Study design	This will be a multicenter and open-label study with a single cohort PK Run-in Part followed by 2 randomized, parallel-group parts in adults and children with confirmed and uncomplicated *P. falciparum* malaria.
Population	The study population will consist of male and female patients (PK Run-in Part and Part A: ≥ 12 years old and ≥ 35.0 kg; Part B: 2 to <12 years old and ≥ 10.0 kg) with confirmed and uncomplicated *P. falciparum* malaria. The plan is to enroll and treat 12 patients in PK Run-in Part and randomize approximately 500 patients in Parts A and B (325 in Part A and up to 175 in Part B) in approximately 15 sites in Africa and Asia.
Key Inclusion criteria	• PK Run-in Part and Part A: male and female patients ≥ 12 years and with a body weight ≥ 35.0 kg. Part B: after determining the effective/tolerated doses and regimens in adolescent and adult patients, male and female patients ≥ 2 and < 12 years and with a body weight ≥ 10.0 kg will be included. • Microscopic confirmation of *P. falciparum* by Giemsa-stained thick and thin films (refer to the laboratory manual for details). • *P. falciparum* parasitaemia of more than 1000 and less than 150 000 parasites/µL at the time of pre-screening (i.e., Study Visit 1). • Axillary temperature ≥ 37.5 ºC or oral/tympanic/rectal temperature ≥ 38.0C; or similar history of fever during the previous 24 hours (history of fever must be documented). • Written informed consent must be obtained before any assessment is performed. If the patient is unable to read and write, then a witnessed consent according to local ethical standards is permitted. Patients < 18 years old, who are capable of providing assent, must provide assent with parental/legal guardian consent or as per local ethical guidelines.
Key Exclusion criteria	• Mixed *Plasmodium* infections. • Signs and symptoms of severe malaria according to WHO (World Health Organization) 2015 criteria unless characterized by high parasitaemia only. • Patients with concurrent febrile illnesses (e.g., typhoid fever). • 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 watery stools per day. • Pregnant or nursing (lactating) women.

[redacted]

	• Clinically relevant abnormalities of electrolyte balance which require correction, e.g., hypokalemia, hypocalcemia or hypomagnesemia.
	• Anemia (Hemoglobin level < 8 g/dL).
	• Patients with prior antimalarial therapy or antibiotics with antimalarial activity within minimum of their five (5) plasma half-lives (or within 4 weeks of screening if half-life is unknown).
	• History or family history of long QT syndrome or sudden cardiac death, or any other clinical condition known to prolong the QTc (heart rate-corrected QT) interval, such as history of symptomatic cardiac arrhythmias, clinically relevant bradycardia or severe heart disease.
	• Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the patient in case of participation in the study. The investigator should make this determination in consideration of the patient's medical history and/or clinical or laboratory evidence of any of the following:
	  • AST/ALT > 2 x the upper limit of normal range (ULN), regardless of the level of total bilirubin
	  • AST/ALT > 1.5 and ≤ 2 x ULN and total bilirubin is > ULN
	  • Total bilirubin > 2 x ULN, regardless of the level of AST/ALT

Study treatment	**PK Run-in Part (≥ 12 years old, ≥ 35.0 kg):** • PK Run-in Cohort: KAF156 200 mg and LUM-SDF 960 mg - QD for 1 day **Part A (≥ 12 years old, ≥ 35.0 kg):** • Cohort 1: KAF156 400 mg and LUM-SDF 960 mg once daily (QD) for 1 day • Cohort 2: KAF156 800 mg and LUM-SDF 960 mg QD for 1 day • Cohort 3: KAF156 400 mg and LUM-SDF 960 mg QD for 2 days • Cohort 4: KAF156 200 mg and LUM-SDF 480 mg QD for 3 days • Cohort 5: KAF156 400 mg and LUM-SDF 480 mg QD for 3 days • Cohort 6: KAF156 400 mg and LUM-SDF 960 mg QD for 3 days • Cohort 7: Coartem® twice a day (BID) for 3 days

	The above dosages may be adjusted based on the results of PK Run-in Part. **Part B (2 to < 12 years, ≥ 10.0 kg):** • KAF156 and LUM-SDF (up to 3 cohorts selected depending on the outcome of Part A) • Coartem® BID for 3 days
Efficacy assessments	• Parasitaemia • Blood sample for molecular diagnostic purposes
PK assessments	• PK parameters of study drugs (measured by AUC0-24h, AUClast, AUCinf, Cmax, Tmax, T½)
Key safety assessments	• Physical examination and malaria signs and symptoms • Vital signs • Body temperature • Monitoring of laboratory parameters in blood and urine • Electrocardiogram • Adverse event (AE) monitoring
Other assessments	• Additional back-up blood samples for certain specific safety biomarkers (e.g., miR122) will be collected and analyzed if required
Data analysis	For the PK Run-in Part, the primary objective is to investigate the pharmacokinetic interaction potential between KAF156 and lumefantrine-SDF. 2-sided 90% confidence intervals for PK parameters of KAF156 and lumefantrine will be calculated. Subsequent statistical analyses for Part A and Part B will be performed separately and similarly. For ACPRs (PCR corrected and uncorrected ACPR at Days 15, 29, and 43), 2-sided 95% confidence intervals for each treatment group will be constructed using the exact (Pearson-Clopper) method. For parasite clearance time and fever clearance time, descriptive statistics (mean, standard error, median, quartiles) for each treatment group will be presented using the Kaplan-Meier method.
Key words	Plasmodium falciparum malaria, KAF156, LUM-SDF, adults, children

[redacted]

1 Introduction

1.1 Background

Malaria is one of the most important infectious diseases which threatens about 3.2 billion people, almost half of the world's population. Despite increasing international efforts for malaria control, in 2015, there were 214 million cases worldwide of malaria and 438 000 deaths according to the latest World Health Organization estimates (WHO 2015). Sub-Saharan Africa carries a disproportionately high share of the global malaria burden. In 2015, the region was home to 88% of malaria cases and 90% of malaria deaths. Also, in areas with high transmission of malaria, children under 5 are particularly susceptible to infection, illness and death; more than two thirds (70%) of all malaria deaths occur in this age group (306 000 estimates deaths in 2015; see WHO 2015).

Malaria is caused by *Plasmodium* parasites. There are five parasite species that cause malaria in humans, and two of these species – *P. falciparum* and *P. vivax* – pose the greatest threat. *P. falciparum* is the most prevalent malaria parasite on the African continent. It is responsible for most malaria-related deaths globally. *P. vivax* is the dominant malaria parasite in most countries outside of sub-Saharan Africa (WHO 2015).

Standard antimalarial drugs such as chloroquine (CQ), pyrimethamine (PYR), sulfadoxine (SFDX) and mefloquine (MEF) have become largely ineffective in many malaria endemic regions. The only exceptions are the artemisinin-based combination therapies (ACTs) such as Novartis' Coartem®/Riamet® and Eurartesim®, current standard-of-care for *P. falciparum* malaria. Unfortunately, some recent reports (Ashley et al 2014; Menard et al 2016) suggest that decades of continuous use of artemisinin and bisquinoline derivatives as monotherapies may have fostered the emergence of drug resistance in *Plasmodium* species in Southeast Asia. Reduced *in vitro* susceptibility of *P. falciparum* to artemisinin in this region has been documented (Dondorp 2009). Recent studies showed that artemisinin resistance extends over more of Southeast Asia than had previously been known, and is now present close to the border with India (Menard et al 2016). If widespread artemisinin drug resistance was to occur, malaria pharmacotherapy would be severely impaired. This finding signifies that spread of resistance is inevitable, thus there is urgent need for new antimalarials with new mechanism of actions (Tun et al 2015).

In addition, current *falciparum* malaria treatments require at least a 3-day dosing regimen which may contribute to therapeutic non-compliance in some patients. Indeed, patients often have resolution of clinical symptoms within 1 to 2 days and may neglect taking final doses. This may contribute to the development of drug resistance.

There is therefore a strong medical need for new chemical entities with a new mode of action as additional treatment options for this very common disease with substantial morbidity and mortality. Simplifying regimens by developing treatments that can be used in a once daily dose for less than 3-day administration can improve treatment success and reduce probability of developing resistance via improved adherence and thus accelerate malaria eradication.

The purpose of this study is to determine the effective and tolerable dose of KAF156, a new antimalarial molecule that can be administered in combination with a Solid Dispersion Formulation of lumefantrine (LUM-SDF) for the shortest treatment duration possible.

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KAF156 is the first drug from a different and novel class of drugs called imidazolepiperazines and was developed by the Novartis Institute for Tropical Diseases (NITD) following a high through-put screening (HTS) of the Novartis compound library by the Genomics Institute of the Novartis Research Foundation (GNF). KAF156 is structurally distinct from currently marketed antimalarial drugs and other experimental antimalarial compound classes currently in development. The mechanism of action of KAF156 is still being characterized, but may be related to a previously uncharacterized gene (*Plasmodium falciparum* cyclic amine resistance locus, Pfcarl). KAF156 kills/inhibits the erythrocytic replication life cycle stages (blood stages) of the two main causative agents of human malaria, *P. falciparum* and *P. vivax*, both at low nanomolar EC50s (*in vitro*). In addition, KAF156 has shown activity in liver stage models of *Plasmodium* infection, conferring causal prophylactic protection in animal infection models. Limited evidence of gametocyticidal activity may confer transmission blocking activity. KAF156 has not demonstrated activity against liver hypnozoites and therefore has a low probability to be used for a radical cure for *P. vivax*. Also, KAF156 is equally potent against drug-sensitive and a broad panel of drug resistant malaria strains (Kuhen et al 2014).

KAF156, when combined in a fixed-dose formulation with an anti-malarial partner drug, could offer a much needed new treatment for malaria, including in areas where resistance to ACTs is emerging. A fixed-dose formulation with a single-dose regimen to ensure patient adherence to the full treatment would be an ideal option. However, the development of such single-dose regimens are more challenging in terms of maintaining adequate blood levels during 6-7 days (3 parasite replication cycles). Considering the impending risk of resistance to existing antimalarials and higher risk of therapeutic failure with a single- or two day regimen, a three day regimen will also be evaluated with the simultaneous exploration of one and two day treatment regimen in order to reduce the overall development risk and address the critical unmet medical need due to emerging resistance to standard therapy.

Lumefantrine-Solid Dispersion Formulation (SDF) will be used as partner drug in this study. In contrast to the conventional lumefantrine formulation, lumefantrine-SDF has an improved absorption profile and less food effect, leading to exposure which allows for a once-daily regimen. LUM-SDF is expected to have a similar safety profile to conventional LUM used as partner drug in Coartem®.

KAF156 and lumefantrine will be administered as combination for the first time in this study. Based on their metabolism, no clinically relevant interaction is expected between KAF156 and lumefantrine. However, in a recent preclinical in vivo study in dogs KAF156 (10 mg/kg) and LUM-SDF (15 mg/kg) were administered in combination and preliminary data suggest that exposure of both KAF156 and lumefantrine increased in presence of each other. There was around 2-3 fold increase in KAF156 exposure and around 1.5 fold increase in lumefantrine exposure.

A slightly increased lumefantrine exposure is not considered of clinical significance as it was anticipated, based on potential metabolic interaction. KAF156 is a weak CYP3A4 inhibitor based on an interaction study with piperaquine and can potentially increase lumefantrine exposure slightly. However, in clinical interaction studies of lumefantrine with strong CYP3A4 inhibitors such as ketoconazole (Lefevre et al 2002) and lopinavir/ritonavir-based antiretroviral (Kredo et al 2016) despite up to 5 fold increase in lumefantrine exposure it was concluded that

[redacted]

this interaction did not result in lumefantrine exposures above seen in patients following a standard dose of Coartem (Lefevre et al 2001).

On the other hand, increased KAF156 exposure was unanticipated and there is no sufficient data to cover for exposure for the highest doses of KAF156 in this study, should KAF156 exposure increase by 2 fold. The dog data suggest that increased KAF156 exposure potentially occurs because of interaction of LUM-SDF with KAF156 at absorption-level which in turn suggest that interaction may not lead to more than 2 fold increase in KAF156 exposure in human given its estimated bioavailability of at least 50% in humans. There is no experience of KAF156 exposure beyond that of 1200 mg single dose or 600 mg daily for 3 days. Given the above situation, the first part of the study will explore the PK and safety of KAF156 given in combination with LUM-SDF to understand the impact of LUM-SDF on KAF156 exposure as victim drug. In the unlikely scenario of an increase in KAF156 exposure beyond the acceptable limit, doses in Part A of the study may be adjusted (as described in Section 3.3).

1.2 Purpose

This Phase 2 study aims to determine the most effective and tolerable dose at the shortest dosing regimen of the investigational drug KAF156 and a Solid Dispersion Formulation of lumefantrine (LUM-SDF) in combination in adult/adolescent and pediatric patients with uncomplicated *P. falciparum* malaria. Different dose combinations and dosing regimens (i.e., 3-, 2-, and 1-day regimens) of KAF156 and LUM-SDF in combination and a reference product Coartem® will be assessed.

This study is set up in a three-part sequential design. Following the PK Run-in Part, Part A of the study will determine in adults and adolescents (greater than or equal to 12 years of age and with a body weight ≥ 35.0 kg) the most effective and tolerated dose regimens to be carried forward into Part B which will be conducted in pediatric (2 to < 12 years old and with a body weight ≥ 10.0 kg) population. Combined data obtained from Parts A and B will then form the basis for identifying the dose regimen(s) that should be further investigated in Phase 3 development in adults and children down to 2 years of age.

Coartem® will be used as a control for trial sensitivity in Parts A and B so as to evaluate if any significant safety issues or low efficacy results observed in the experimental treatment groups for both adults/adolescents and children are due to treatment or population. It will also provide preliminary relative efficacy for experimental treatment groups compared to the control although it's not statistically powered to show non-inferiority or superiority.

2 Study objectives and endpoints

2.1 Objectives and related endpoints

Table 2-1 Objectives and related endpoints (PK Run-in Part, Part A and Part B)

Objective(s)	Endpoint (s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To determine the effective doses of KAF156 combined with LUM-SDF given	• PCR-corrected adequate clinical and parasitological response (ACPR) at Day

[redacted]

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

[redacted]

[redacted]

3 Investigational plan

3.1 Study design

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

Screening of patients for inclusion in the study consists of two parts: a Pre-Screening Part and a Screening Part.

- **Pre-Screening Part (Study Visit 1)**: Pre-screening is a key element to successfully identify the correct patients to be screened for this clinical study. Study Visit 1 should be used to obtain a *P. falciparum* parasite count (see Section 6.4.1), which is to be conducted locally.
  Patients should have a *P. falciparum* parasitaemia of more than 1000 and less than 150 000 parasites/µL at the time of Study Visit 1 to be further screened.
- **Screening Part (Study Visit 99)**: Further screening assessments will take place as soon as the pre-screening *P. falciparum* parasitaemia outcome is available and only if outcome is in the pre-defined range (more than 1000 and less than 150 000 parasites/µL).
  Pre-screening parasite count should be used as baseline count. In case parasite count has been done > 6 hours before Visit 99, then it should be repeated and the outcome of the repeated test should be considered as baseline parasite count.

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

PK Run-in Part;

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

The drug-exposure results of the PK Run-in Part will be evaluated by the sponsor and trigger the start of Part A with KAF156 dosing as planned, or lead to a dose adaptation in Part A in case an interaction is shown between LUM-SDF and KAF156. Following this evaluation of drug-exposure, all investigators will be informed of the results and IRT/dosing will be implemented as specified in Table 3-1 and Appendix 5.

Patients in the PK Run-in cohort in whom the drug exposure cannot be established due to vomiting or drop-out, will be replaced by additional patients in order to achieve a total of 12 patients with evaluable exposure results in the PK Run-in Part.

Part A:

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

At screening, eligible patients will be randomized into one of the seven cohorts, i.e., six KAF156 and LUM-SDF dose combinations and a control arm (see Figure 3-1), in 2:2:2:2:2:2:1 ratios. The standard doses of KAF156 as shown below may be corrected according to Table 3-1 in case of increased exposure in the PK Run-in Part (see Appendix 5).

[redacted]

- Cohort 1: KAF156 400 mg and LUM-SDF 960 mg once daily (QD) for 1 day
- Cohort 2: KAF156 800 mg and LUM-SDF 960 mg QD for 1 day
- Cohort 3: KAF156 400 mg and LUM-SDF 960 mg QD for 2 days
- Cohort 4: KAF156 200 mg and LUM-SDF 480 mg QD for 3 days
- Cohort 5: KAF156 400 mg and LUM-SDF 480 mg QD for 3 days
- Cohort 6: KAF156 400 mg and LUM-SDF 960 mg QD for 3 days
- Cohort 7: Coartem® twice a day (BID) for 3 days (dosing as per product label)

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

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

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

Part B:

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

Eligible patients will be enrolled into one out of the up to four dosing cohorts i.e., up to three investigational drug dosing arms and a control arm (see Figure 3-1). Dosing will be adjusted based on children's body weight similar to the adjustment of Coartem®.

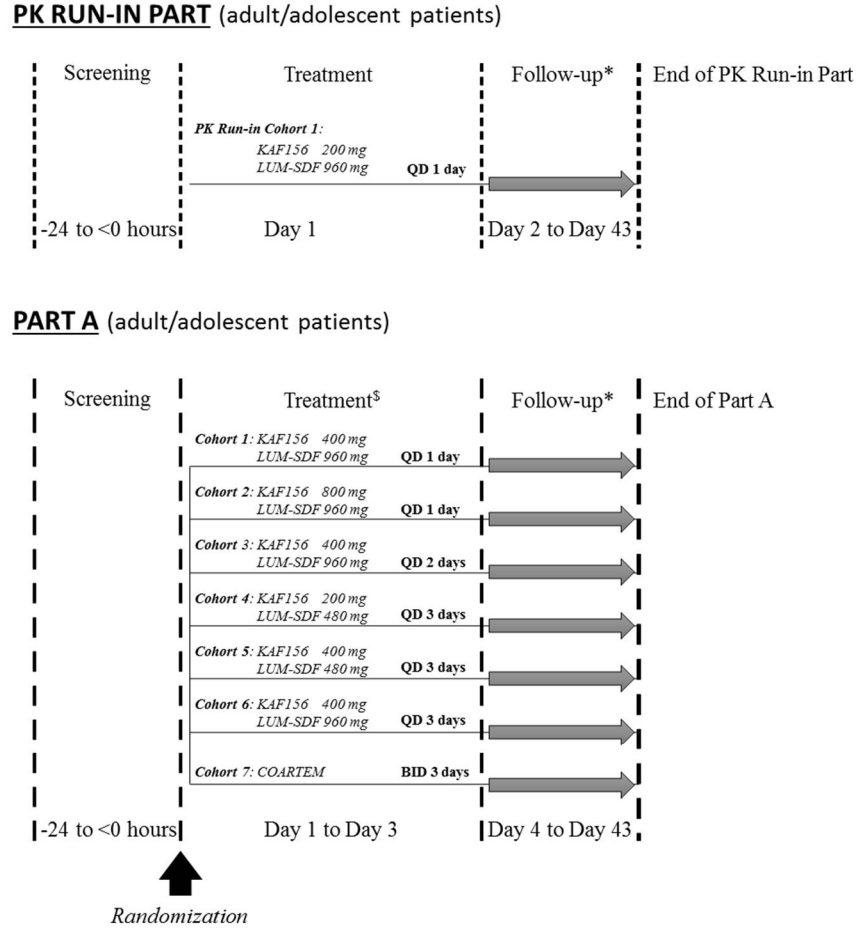
- KAF156 and LUM-SDF: up to 3 cohorts selected depending on the outcome of Part A
- Coartem® BID for 3 days

Initially, 4-6 children in the age range of 6 to < 12 years will be included in Part B to confirm that KAF156 and LUM-SDF PK/drug exposure is consistent with Part A and that the assumption in dosing is correct in these cohorts. Following confirmation of drug exposure in these children, the additional patients will be included in Part B of the study.

[redacted]

Study design, procedures and assessments are the same in Part A and Part B (see above). The safety of entire study will be monitored by an Independent Data Monitoring Committee (DMC).

Figure 3-1 Study design



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

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

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

QD: once daily; BID: twice a day

3.2 Rationale for study design

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

The use of a combination regimen with two drugs is well established for evaluation of anti-malaria therapy and is recommended by WHO guidelines (WHO 2015). As specified in Section 1, there is unmet medical need for anti-malarial treatment with new mechanism of action to reduce probability of developing resistance, and for shorter duration of treatment and/or reduced pill burden.

The objective of this dose finding (Phase 2) study design is to identify the most effective and tolerated dose regimen of KAF156 and LUM-SDF in combination with the shortest duration in adults/adolescents (Part A) and in children (Part B) with uncomplicated *P. falciparum* malaria.

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 chosen study design is the most efficient one to achieve the study goals (i.e., determine optimal dose, combination and duration in adults, adolescents and pediatrics down to age of 2).

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

Rationale for dose/regimen in PK Run-in Part:

The objective of the PK Run-in cohort is to assess the maximum potential increase in KAF156 exposure as victim due to LUM-SDF with sufficient safety margins. Therefore, the lowest dose of KAF156 (200 mg) will be administered with the highest dose of LUM-SDF (960 mg) to understand the worst case scenario.

The highest single dose and multiple dose planned in Part A of this study are 800 mg and 400 mg, respectively which is 2/3 of the highest previously tested dose of 1200 mg as single dose and the 600 mg as highest multiple dose (with acceptable safety profiles).

Therefore, an increase in KAF156 exposure of <1.4 fold observed in the PK Run-in Part is not considered to be of clinical concern. For higher increases in exposure the doses of KAF156 in Part A will be adjusted as detailed in Table 3-1 below. The subsequent doses in Part B will be as planned in Table 5-4.

In the PK Run-in cohort $AUC_{0\text{-}24h}$ will be used as main parameter for the comparison with historical data as it covers the full absorption profile and is a more stable parameter than Cmax. Cmax and AUC are expected to be proportional. Given the straightforward interpretation of this PK analysis, the sponsor will subsequently make the decision on dose adaptation in Part A according to Table 3-1 below.

[redacted]

Table 3-1 Dose adjustment for Part A

Standard Dose KAF156 in Part A		200 mg	400 mg	800 mg
KAF156 relative exposure factor in PK Run-in vs. the reference mean AUC_{0-24h} (4930 ng*h/mL)*	Correction Factor	Adapted Doses (mg)		
<1.4	1.0	200	400	800
≥1.4 to <1.8	0.75	150	300	600
≥1.8 to <2.5	0.50	100	200	400
≥2.5 to 4	0.25	50	100	200

*The reference value of AUC_{0-24h} for 200 mg is extrapolated from the mean value (9860 ng*h/mL) after the first dose of 400mg in *P. falciparum* patients

No clinically significant interaction is anticipated for the lumefantrine exposure. Although the safety margin of lumefantrine is high, in the PK Run-in cohort lumefantrine levels will nevertheless be analyzed for confirmation.

Rationale for dose/regimen in Part A:

A range of doses and regimens of KAF156 combined with LUM-SDF was selected based on expected exposure, efficacy and safety outcomes, and supported by clinical as well as pre-clinical data (Kuhen et al 2014; Leong et al 2014).

As a general principle, the drug combination should provide adequate parasiticidal serum levels over a period of at least 6-7 days (3 parasite life-cycles approximately) in order to achieve cure in a patient. It is known that lumefantrine Day 7 serum concentrations above 200 ng/mL correlate strongly with treatment success (WWARN 2015). From initial experience with KAF156, Day 6 concentrations above 58 ng/mL (2 times EC99) correlate with treatment success (Kuhen et al 2014; Leong et al 2014).

The highest tolerated doses identified in healthy volunteer and proof of concept studies were: KAF156 400 mg for multiple days, KAF156 800 mg for single dosing, LUM-SDF 960 mg for single dosing. Total exposure and Cmax for LUM-SDF 960 mg QD for 3 days is expected not to exceed total exposure and Cmax following dosing with the conventional lumefantrine formulation.

Preliminary pharmacokinetic/pharmacodynamic (PK/PD) modeling was performed to assess the percentage of patients in whom threshold concentration of lumefantrine (above 200 ng/mL) and KAF156 (above 58 ng/mL) will be maintained over 6-7 days. Simulations from these models suggest that under fasting conditions, the 3-day doses and the 2-day doses of KAF156 and LUM-SDF combinations have a relatively high likelihood to be effective; the 1-day doses have a lower likelihood of being effective. Testing the proposed dose/regimens allows for a more complete characterization of the dose-response relationship.

[redacted]

Rationale for dose/regimen in Part B:

Upon completion of Part A, all dose cohorts will be evaluated according to the following success/failure criteria:

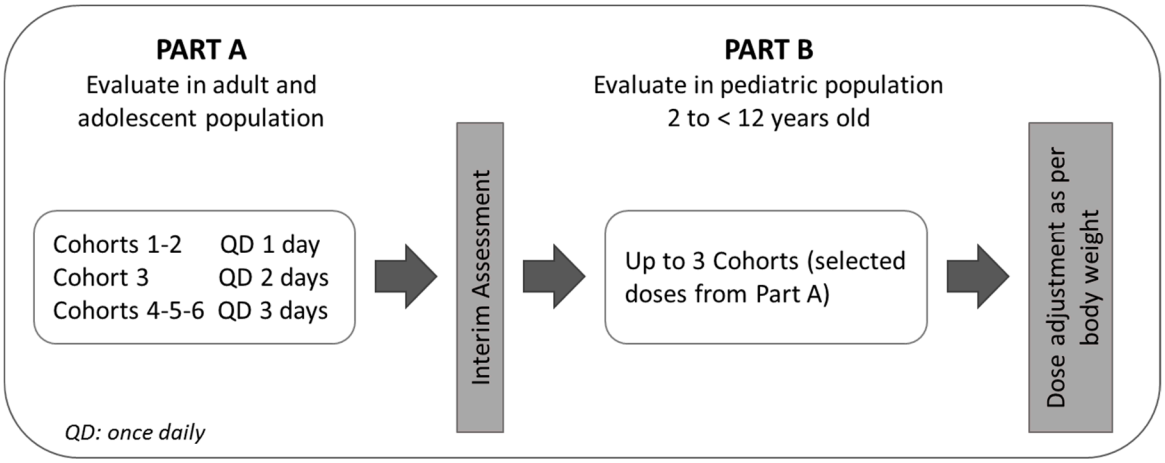
Table 3-2 Cohort Success Criteria

Efficacy	The lower limit of 2-sided 95% exact confidence interval for PCR corrected ACPR at Day 29 is greater than 80%
Safety	A comprehensive assessment of AEs, SAEs, lab data and ECG for investigational and reference product (Coartem®) by DMC/Novartis will determine the tolerability success criteria for the cohorts

If needed, secondary efficacy parameters can also be evaluated to discriminate between cohorts in Part A.

Selected cohorts that pass the efficacy/safety hurdles will be further evaluated in Part B.

Figure 3-2 Dose selection for Part B



The number of cohorts to be assessed in pediatric population (Part B) will depend on the outcome of the interim assessment. Up to 4 cohorts will be assessed in Part B (i.e., up to 3 cohorts with KAF156/LUM-SDF and 1 cohort with Coartem®). The selected adult doses from Part A will be adjusted to the pediatric population in Part B using the proven body weight bands for Coartem® (see Table 5-4). Initially, 4-6 children in the age range of 6 to < 12 years will be included in Part B to confirm that KAF156 and LUM-SDF PK/drug exposure is consistent with Part A and that the assumption in dosing is correct in these cohorts. Following confirmation of drug exposure in these children, the additional patients will be included in Part B of the study.

Due to the fact that their metabolizing cytochrome (CYP) enzymes are not yet fully matured, children < 2 years will not be included in this study.

Patients must be fasted 3 hours before and for 4 hours after KAF156/LUM-SDF administration.

Coartem® will be administered with food and doses will be based on patient's body weight as per product label.

[redacted]

Rationale for duration of treatment:

With LUM-SDF as partner drug for KAF156, the goal is to provide at least the same efficacy as current standard treatment, but with lower dosing frequency and pill burden compared to Coartem®: from a 3-day twice a day treatment regimen (for ≥ 35.0 kg patient 4 tablets per dose for total of 6 doses i.e. 24 tablets) to a 3, 2 or 1-day single daily dose treatment regimen.

3.4 Rationale for choice of control

The control treatment used in Parts A and B of this study is Coartem®, the artemisinin-based combination therapy artemether-lumefantrine. Coartem® is widely used for *P. falciparum* malaria and has a well-characterized safety and efficacy profile (Hamed and Grueninger 2012). In addition, Coartem® tablets contain the same partner drug as in the current study (lumefantrine). For these reasons, Coartem® is considered the appropriate comparator treatment for this study.

3.5 Purpose and timing of interim assessments/data reviews

For the PK Run-in Part the first 24 hours of PK samples will be analyzed for KAF156 and lumefantrine blood levels in order to confirm doses of KAF156 for Part A. In case of unexpected increase in exposure of KAF156 doses in Part A will be adjusted according to Table 3-1.

An interim assessment (IA) will be conducted after completion of Part A. The purpose of this assessment is to assess key parameters of efficacy and tolerability of KAF156 and LUM-SDF dose combinations for each dosing regimen (3 days vs. 2 days vs. 1 day) in adolescent/adult patients (see Section 3.3). Upon determining the preferred dose combinations, children 2 to < 12 years will be treated with these dose combinations adjusted for their body weight (Part B). In addition, the pharmacokinetic data will be reviewed as available, to ensure that exposures of KAF156 and lumefantrine are not considerably different than expected, however pharmacokinetic data alone will not lead to any change in conduct of the study. Before fully enrolling patients in Part B, 4-6 children in the age range of 6 to < 12 years will be included to confirm that KAF156 and LUM-SDF PK/drug exposure is consistent with Part A and that the assumption in dosing is correct. Following confirmation of drug exposure in these children, the additional patients will be included in Part B of the study.

Additional interim safety review of study data will be conducted by the independent Data Monitoring Committee (DMC, see Section 8.4). These reviews may also be conducted to support decision making concerning the current clinical study, or in case of any safety concerns.

3.6 Risks and benefits

Based on the preclinical and clinical evaluation to date as presented in the respective Investigator Brochures (IB) for KAF156 and LUM-SDF, the combination of KAF156 and LUM-SDF is expected to be generally safe and well tolerated. The risk to patients in this trial will be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring and minimal treatment duration. Patients will be hospitalized under close supervision until they are discharged by the investigator or designee on Day 4. At the discretion of the investigator, patients may stay additional days if needed.

[redacted]

In the current study, KAF156 will be given to patients with uncomplicated *P. falciparum* malaria. KAF156 is expected to reduce the number of circulating malaria parasites in the blood of patients and consequently improve their clinical symptoms over the first 48 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 group. Any early treatment failure (ETF) (see Section 6.5.8), recrudescence or new infection will be managed with standard-of-care pharmacotherapy. This may minimize the likelihood of resistance emergence or spread. Any recrudescing parasites will be analyzed for standard markers of resistance.

Following confirmation of drug exposure in the PK Run-in Part, the current study will initially include adolescents from 12 to < 18 years and adults (Part A), followed by children 2-11 years (Part B) after an effective/safe dose has been established for adults and adolescents. PK/drug exposure will be also confirmed first in 4-6 children in the age range of 6 to < 12 years before the additional patients will be included in Part B of the study.

This is the first time that KAF156 and lumefantrine-SDF will be tested in patients as a combination treatment. All previous studies involved KAF156 alone. Whereas lumefantrine in the conventional formulation has been fully characterized and widely used as partner drug in Coartem®, lumefantrine-SDF has been produced in pilot-scale only. LUM-SDF is expected to have an improved bioavailability and similar safety profile to conventional LUM used as the partner drug in Coartem®.

4 Population

The study population will consist of male and female patients (PK Run-in Part and Part A: ≥ 12 years old and ≥ 35.0 kg; Part B: 2 to < 12 years old and ≥ 10.0 kg) with confirmed and uncomplicated *P. falciparum* malaria.

Only patients with malaria symptoms and *P. falciparum* counts more than 1000 and less than 150 000 parasites/µL will be included in the study.

The plan is to enroll and treat 12 patients in PK Run-in Part and to randomize approximately 500 patients (325 in Part A and up to 175 in Part B) in approximately 15 sites in Africa and Asia. Expected recruitment in Africa is approximately 85% for both Parts A and B with the rest of the patients expected to be recruited in Asia. The expected drop-out rate is 16% (Held et al 2015).

4.1 Inclusion criteria

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

Demography

1. PK Run-in Part and Part A: male and female patients ≥ 12 years and with a body weight ≥ 35.0 kg

   Part B: after determining the effective/tolerated doses and regimens in adolescent and adult patients, male and female patients ≥ 2 and < 12 years and with a body weight ≥ 10.0 kg will be included

[redacted]

Health status

2. Microscopic confirmation of *P. falciparum* by Giemsa-stained thick and thin films (refer to the laboratory manual for details)
3. *P. falciparum* parasitaemia of more than 1000 and less than 150 000 parasites/μL at the time of pre-screening (i.e., Study Visit 1)
4. Axillary temperature ≥ 37.5 ºC or oral/tympanic/rectal temperature ≥ 38.0ºC; or similar history of fever during the previous 24 hours (history of fever must be documented)
5. Negative pregnancy test for women of child bearing potential (WOCBP)

Regulations

6. Written informed consent must be obtained before any assessment is performed. If the patient is unable to read and write, then a witnessed consent according to local ethical standards is permitted. Patients < 18 years old, who are capable of providing assent, must provide assent with parental/legal guardian consent or as per local ethical guidelines
7. The patient or his/her parent/legal guardian (in case of pediatric patients) is able to understand and comply with protocol requirements, instructions and protocol-stated restrictions and is likely to complete the study as planned

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 *Plasmodium* infections
2. Signs and symptoms of severe malaria according to WHO 2015 criteria unless characterized by high parasitaemia only
3. Active infections including tuberculosis
4. Patients with concurrent febrile illnesses (e.g., typhoid fever)
5. 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
6. Known relevant liver disease e.g. chronic hepatitis, cirrhosis, compensated or decompensated, history of hepatitis B or C, hepatitis B or A vaccination in last 3 months, known gallbladder or bile duct disease, acute or chronic pancreatitis
7. Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection
8. Severe malnutrition (body mass index (BMI) < 16.0 for patients ≥ 12 years, and less than 70% of median normalized WHO reference weight for children < 12 years)
9. 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 watery stools per day
10. Pregnant or nursing (lactating) women
11. Sexually active patients not willing to practice effective contraception

[redacted]

12. Women of child bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for the duration of the study. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - 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 patients on the study, the vasectomized male partner should be the sole partner for that patient
    - Use of oral, (estrogen and progesterone), 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

    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
13. Sexually active males must use a condom during intercourse while taking drug and for the duration of the study 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
14. Active duodenal ulcer, ulcerative colitis, Crohn's disease, chronic (i.e., > 2 weeks) use of non-steroidal anti-inflammatory drugs (NSAIDs)
15. Clinically relevant abnormalities of electrolyte balance which require correction, e.g., hypokalemia, hypocalcemia or hypomagnesemia.
16. Anemia (Hemoglobin level < 8 g/dL)
17. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the patient in case of participation in the study. The investigator should make this determination in consideration of the patient's medical history and/or clinical or laboratory evidence of any of the following:
    - AST/ALT > 2 x the upper limit of normal range (ULN), regardless of the level of total bilirubin
    - AST/ALT > 1.5 and ≤ 2 x ULN and total bilirubin is > ULN

[redacted]

- Total bilirubin > 2 x ULN, regardless of the level of AST/ALT

18. Resting QTcF > 450 ms (males), QTcF > 460 ms (females) at screening
19. Creatinine > 2 x ULN in the absence of dehydration. In the case of dehydration, the creatinine should be < 2 x ULN after oral/parenteral rehydration
20. 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
21. Known chronic underlying disease such as sickle cell disease, and severe cardiac, renal, or hepatic impairment
22. Known active or uncontrolled thyroid disease
23. Inability to tolerate oral medication (in tablet and/or liquid form)

Interfering substances

24. Patients with prior antimalarial therapy or antibiotics with antimalarial activity within minimum of their five (5) plasma half-lives (or within 4 weeks of screening if half-life is unknown)
25. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days or until the expected pharmacodynamic effect has returned to baseline, whichever is longer
26. Patients taking medications prohibited by the protocol (see Section 5.6.8, Table 5-5)
27. Previous participation in any malaria vaccine study or received malaria vaccine in any other circumstance

Specific to the study

28. History or family history of long QT syndrome or sudden cardiac death, or any other clinical condition known to prolong the QTc interval, such as history of symptomatic cardiac arrhythmias, clinically relevant bradycardia or severe heart disease
29. Use of agents known to prolong the QT interval unless it can be permanently discontinued for the duration of study
30. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Novartis will supply the following investigational products as open label patient specific supplies (see Table 5-1, Table 5-3, Table 5-4 and Appendix 5).

- For PK Run-in Part:
  - KAF156 50 mg and/or 100 mg and/or 200 mg (Tablets in bottles)
  - Lumefantrine 480 mg (SDF in sachets)

[redacted]

- For Part A:
  - KAF156 100 mg and/or 200 mg (Tablets in bottles)
  - Lumefantrine 480 mg (SDF in sachets)
  - Coartem® 20/120 mg and 80/480 mg (tablets in blister pack)
- For Part B:
  - KAF156 (Tablets in bottles). Dose strengths based on Table 5-4 to be confirmed
  - Lumefantrine (SDF in sachets). Dose strengths based on Table 5-4 to be confirmed
  - Coartem® 20/120 mg (dispersible tablets in blister pack)

Table 5-1 PK Run-in Part: KAF156 and LUM-SDF dosing scheme

Cohort	Treatment	Dose (mg)	Dosing regimen	Daily dosing based on available strengths
PK Run-in	KAF156 LUM-SDF	200 960	QD 1 day	1 x 200 mg or 2 x 100 mg 2 sachets

Table 5-2 Part A: KAF156 and LUM-SDF dosing scheme*

Cohort	Treatment	Dosing regimen
1	KAF156 LUM-SDF	QD 1 day
2	KAF156 LUM-SDF	QD 1 day
3	KAF156 LUM-SDF	QD 2 days
4	KAF156 LUM-SDF	QD 3 days
5	KAF156 LUM-SDF	QD 3 days
6	KAF156 LUM-SDF	QD 3 days

**KAF156 dose levels are based on the results of the PK Run-in Part and will be adjusted according to Table 3-1 (see also Appendix 5 for dosing details).*

Table 5-3 Parts A and B: Coartem® dosing per weight

	Artemether/Lumefrantine
≥ 12 years and ≥ 35.0 kg	80/480 mg BID during 3 days
25.0 to < 35.0 kg	60/360 mg BID during 3 days
15.0 to < 25.0 kg	40/240 mg BID during 3 days
10.0 to < 15.0 kg	20/120 mg BID during 3 days

[redacted]

Table 5-4 Part B: Children KAF156 and LUM-SDF dosing per weight

	KAF156 and LUM-SDF
25.0 to < 35.0 kg	0.75 of the adult dose
15.0 to < 25.0 kg	0.50 of the adult dose
10.0 to < 15.0 kg	0.25 of the adult dose

The selected adult doses from Part A will be adjusted to the pediatric population in Part B using the proven body weight bands for Coartem®. Specific details on medication will be communicated to relevant internal and external stakeholders before the start of Part B.

5.1.2 Additional treatment

No additional treatment beyond investigational drug and control drug are included in this trial. Rescue medication will be provided by the investigator according to local practices (Section 5.6.6).

5.2 Treatment arms

Following confirmation of exposure in the PK Run-in Part, patients will be randomized in 2:2:2:2:2:2:1 ratios between six KAF156 and LUM-SDF dose combinations and the Coartem® cohort in Part A. In Part B, patients will be randomized in 2:1 ratios (2 for each KAF156 and LUM-SDF dose combination and 1 for Coartem) to one of up to three KAF156 and LUM-SDF dose combinations and the Coartem® cohort depending on the outcome of Part A interim assessment.

PK Run-in Part (≥ 12 years old, ≥ 35.0 kg):

- PK Run-in Cohort: KAF156 200 mg and LUM-SDF 960 mg - QD for 1 day

Part A (≥ 12 years old, ≥ 35.0 kg)*:

- Cohort 1: KAF156 400 mg and LUM-SDF 960 mg - QD for 1 day
- Cohort 2: KAF156 800 mg and LUM-SDF 960 mg - QD for 1 day
- Cohort 3: KAF156 400 mg and LUM-SDF 960 mg - QD for 2 days
- Cohort 4: KAF156 200 mg and LUM-SDF 480 mg - QD for 3 days
- Cohort 5: KAF156 400 mg and LUM-SDF 480 mg - QD for 3 days
- Cohort 6: KAF156 400 mg and LUM-SDF 960 mg - QD for 3 days
- Cohort 7: Coartem® BID for 3 days

*KAF156 dose levels are based on the assumption of non-significant drug-drug interaction in the PK Run-in Part and will be adjusted according Table 3-1 in case of increased exposure to KAF156 in the PK Run-in cohort.

Part B (2 to < 12 years, ≥ 10.0 kg):

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

[redacted]

5.3 Treatment assignment and randomization

PK Run-in Part

At Visit 101, the investigator or his/her delegate will contact the IRT after confirming that a patient fulfills all the inclusion/exclusion criteria. If the enrollment for this part is still open, the eligible patient will be assigned to receive KAF156 200 mg and LUM-SDF 960 mg QD 1 day via Interactive Response Technology (IRT). The IRT will specify medication number(s) and amount (e.g., number of tablets, etc.) to the patient. The medication number(s) and the appropriate amount for each medication number will be communicated to the caller so that the corresponding investigational drug(s) can be dispensed to the patient.

Parts A and B

Following completion of the PK Run-in Part, at Visit 101, all eligible patients will be randomized via Interactive Response Technology (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 (cohort) and will specify medication number(s) and amount (e.g., number of tablets, etc.). The medication number(s) and the appropriate amount for each medication number will be communicated to the caller so that the corresponding investigational drug(s) can be dispensed to the patient. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from Novartis Clinical Trial Team. 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.

The randomization scheme for patients will be reviewed and approved by a member of the Randomization Group. Randomization will be stratified by country in Part A and by country and age category at screening in Part B (2 to < 6, 6 to < 12 years).

5.4 Treatment blinding

5.4.1 PK Run-in Part

Treatment blinding in the PK Run-in Part is not applicable since the part is a single cohort.

5.4.2 Parts A and B

Treatment will not be blinded to patients and investigators since dose frequency and dosages for KAF156 and LUM-SDF may change from cohort to cohort and double-blinding will require triple dummies for 3 different drugs (KAF156, LUM-SDF, and Coartem®). Double-blinding is further complicated by the food requirement where patients assigned to KAF156 and LUM-SDF combinations are required to be fasted while patients assigned to Coartem® are

required to be fed. KAF156, LUM-SDF, and Coartem® will be provided to investigators who will dispense the correct dosage to patients based on IRT's instruction. However, since the primary and secondary objectives of the trial are mainly based on objective, laboratory assessments, this should not bias the efficacy and the safety endpoint assessments. Moreover, the lab technician performing these efficacy assessments will not have knowledge of the treatment arms to which the patients are assigned.

In order to minimize the potential impact of treatment knowledge, treatment allocation, dose information, electrocardiogram (ECG), and PK assessment schedule and concentration data, as well as other data that may result in systematic unblinding will not be uploaded into any Novartis analysis or data review system that is available to the Clinical Trial Team (particularly clinicians, statisticians, programmers) until the database is locked for each part. Further details on data handling are documented in the appropriate data handling plan (DHP)/data management plan (DMP). The pharmacokineticist will be unblinded for PK/drug exposure data only for the whole duration of the study (i.e., Part A and Part B).

During the conduct of Part A and during Part B, summaries of results by treatment arm will be prepared only for Data Monitoring Committee (DMC) assessments. The DMC reports will be performed by an independent team (see Section 9.7).

The bioanalyst will request a copy of the randomization to facilitate analysis of the samples. The bioanalyst will provide the sample data to the team under blinded conditions. The bioanalyst will keep this information confidential until the final clinical database lock for each part.

5.5 Transition from PK Run-in Part to Part A and from Part A to Part B

Following the PK results from the PK Run-in cohort, the sponsor will set up IRT/dosing of KAF156 for Part A as specified in Table 3-1 and Appendix 5. All investigators will be informed accordingly.

After completion of Part A, the database will be cleaned and locked for Part A. Interim assessment of selected efficacy and safety endpoints will be performed to determine the most effective and safe dose of KAF156 and LUM-SDF combination for each tested dosing regimen and assess the dosage to be used in children in Part B for the selected dosing regimen. The results from Part A and the doses to be used for Part B will be communicated to relevant internal and external stakeholders.

5.6 Treating the patient

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

5.6.1 Patient numbering

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.

[redacted]

Upon signing the pre-screening 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.

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 epoch Study Disposition CRF.

5.6.2 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. A unique medication number is printed on each part of this label which corresponds to one of the treatment drugs and dose. 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 within 1 hour of intake a replacement dose will be given to the patient and the investigator or designee will notify IRT.

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

5.6.3 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 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. Technical complaints are to be reported to the respective Novartis country pharma organization (CPO) Quality Assurance.

Medication labels will be in the locally accepted 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 Study monitor or to the Novartis address provided in the investigator folder at each site.

[redacted]

5.6.4 Instructions for prescribing and taking study treatment

KAF156 and LUM-SDF

Patients must be fasted 3 hours before and 4 hours after KAF156/LUM-SDF administration. Water can be provided ad-libitum. In Part B, pediatric patients may be given non-fatty liquids such as orange juices prior to 1 hour of dosing and 1 hour after dosing and recorded. Patients may receive some food at the time they arrive at the hospital and then be fasted for 3 hours minimum before they receive KAF156/LUM-SDF.

Administration of LUM-SDF and KAF156 must be under staff supervision. Patients will take the KAF156 and LUM-SDF according to the assigned dose level and dosing regimen (once daily for either 1, 2 or 3 days) of the KAF156 and LUM-SDF combination.

The content of LUM-SDF sachet(s) should be emptied in mouth directly and then patients should drink some water. This will ensure that the complete dose is administered without any loss. A pair of scissors is needed to open the LUM-SDF sachets. Subsequently (preferably in 2 min, but in any case < 15 min), KAF156 will be administered orally. Tablet(s) to be swallowed with water.

For the pediatric population in Part B specific strength of the KAF156 tablet and LUM-SDF sachet will be available. These children will be given LUM-SDF as dispersible powder in mouth directly and then patients should drink some water. Subsequently (preferably in 2 min, but in any case < 15 min), KAF156 will be given as film-coated tablets that could be dissolved in pre-specified amount of liquid. Administration of LUM-SDF and KAF156 must be under study staff supervision.

Each patient's mouth must be checked to ensure that the medications were swallowed. 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.

Food intake information will be collected only on dosing day, i.e., time of last food intake before dosing, time of first food intake after dosing, amount of meal consumed (%) and type of food based on the following 6 categories:

1. none (=no meal)
2. liquid only (zero fat)
3. minimal meal (estimate of < 200 calories, ~ 1 g of fat)
4. light meal (estimate of 200-300 calories, 5-10 g of fat)
5. Standard meal (estimate of 400-500 calories, 20-30 g of fat)
6. high fat meal (estimate of 800-1000 calories, > 50 g of fat)

In Part B, a low fat vehicle may be used for drug administration in children < 6 years old if they are unable to take the medication normally with water, depending on the outcome of Part A.

Coartem®

With respect to 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 less than 30 min prior to dosing, as per label. Dosages will be administered according to weight group as described in Table 5-3.

[redacted]

Conventional 20/120 mg and 80/480 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. This procedure will be repeated as necessary in order to administer the amount of doses indicated.

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

All kits of study treatment assigned by the IRT will be recorded in the IRT and IMP accountability log.

Food intake information will be collected on each dosing day, i.e., time of last food intake before dosing, time of first food intake after dosing, amount of meal consumed (%) and type of food based on the following 6 categories:

1. none (=no meal)
2. liquid only (zero fat)
3. minimal meal (estimate of < 200 calories, ~ 1 g of fat)
4. light meal (estimate of 200-300 calories, 5-10 g of fat)
5. Standard meal (estimate of 400-500 calories, 20-30 g of fat)
6. high fat meal (estimate of 800-1000 calories, > 50 g of fat)

5.6.5 Permitted dose adjustments and interruptions of study treatment

No dose adjustments other than according to body weight group as described above (see Section 5.1.1) are permitted.

Additional doses can be given in case of vomiting (see Section 5.6.4).

The changes must be recorded on the electronic Dosage Administration Record (eCRF).

For both Parts A and B, patients who vomit within 1 hour of trial drug administration will be given a replacement dose, and IRT must be notified.

For the PK Run-in Part, patients who vomit within 1 hour of trial drug administration will not be assessed in the PK analysis. In such case, additional patients will be dosed to compensate for the missing PK data and to achieve the total number of 12 patients with evaluable PK data in the PK Run-in Part.

5.6.6 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)

- Development of danger signs or severe malaria on Day 2, Day 3, Day 4 in the presence of parasitaemia.
- Parasitaemia on Day 3 higher than Day 1 count irrespective of axillary temperature
- Parasitaemia on Day 4 with axillary temperature ≥ 37.5°C

[redacted]

- Parasitaemia on Day 4 equals to or more than 25% of count on Day 1

Late Clinical Failure (LCF)

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

Late Parasitological Failure (LPF)

- Presence of parasitaemia on any day from Day 8 to Day 43 and axillary temperature < 37.5ºC without previously meeting any of the criteria of Early Treatment Failure or Late Clinical Failure

Commencement of rescue medication with a combination antimalarial product (local standard at the discretion of the investigator or a medically qualified person) may occur after start of trial medications and up to 43 days after the last dose of KAF156/LUM-SDF as deemed necessary by the investigator. Lumefantrine-based treatment must be avoided in case of early treatment failure (ETF). Patients will be monitored, either in clinic, by telephone, or via home visits for three days to ensure adherence to the rescue medication therapy. These patients 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 established anti-malarial treatment.

Patients treated with at least one dose of trial medications will continue to be followed-up until Day 43 according to schedule.

Use of rescue medication (including exact rescue regimen and route of administration) must be recorded on the Concomitant medications/Significant non-drug therapies after start of study drug.

5.6.7 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.

[redacted]

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 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.

5.6.8 Prohibited medication

5.6.8.1 Drug with potential impact on efficacy & safety

Drugs with antimalarial effect: Drugs/supplements which are known to have antimalarial effects are NOT allowed within minimum of their five (5) plasma half-lives (or minimum of 4 weeks if half-life is unknown) prior to enrollment and during the entire study period. They may be used in the course of managing a patient which has developed early or late treatment failure (ETF or LTF) or failed to respond to standard-of-care.

Lumefantrine-based treatments should not be used even in the case of treatment failure, at least up to Day 28 post last dose.

Drug with QTc Potential: Drugs/supplements which have potential to increase QTc interval such as but not limited to antiarrhythmic drugs, neuroleptics and antidepressant agents, metoclopramide, macrolides and fluoroquinolones antibiotics, imidazole and triazole antifungal agents, certain non-sedating antihistamines (terfenadine, astemizole), and cisapride, should be avoided during the study and within minimum of their five (5) plasma half-lives of last dose (or minimum of 14 days if unknown) prior to dosing. Furthermore, drugs that slow the heart rate (HR), like digitalis and beta blockers should be avoided.

Drugs with potential liver safety concerns: Drugs which are known to have potential hepatotoxicity should not be used during study and within minimum of their five (5) plasma half-lives of last dose (or minimum of 14 days if half-life is unknown) prior to dosing. This includes NSAIDs (also over-the-counter medicines) and herbal medicines. Paracetamol < 4g/day (or equivalent pediatric dosage; 10 to 15 mg/kg orally every 4 to 6 hours) may be used however, exact doses and time should be recorded appropriately.

5.6.8.2 Drug with potential for pharmacokinetic interaction:

Drugs/supplements impacting KAF156 and lumefantrine exposure: drugs or supplements which are known CYP3A inhibitors (e.g., erythromycin, ketoconazole, itraconazole, cimetidine) or CYP3A inducers (e.g. rifampin, phenobarbital) etc. should not be used during study and within 14 days prior to dosing.

[redacted]

Drugs/Supplements which can be impacted by KAF156 and lumefantrine: KAF156 and lumefantrine both have strong potential for inhibition of CYP2D6 enzyme and KAF156 also has strong potential for inhibition of CYP3A enzyme. It has relatively lower inhibition potential for CYP2C8, CYP2C9 and CYP2B6 enzyme and OATP1B1 transporter. The following table (Table 5-5) lists drugs which have either been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor or whose exposure-response relationship indicated that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns. These drugs should not be used within 14 days or at least within their 5 half-lives of last dose prior to dosing. These drugs should also not be used during the study period or at least up to Day 29 post last dose even in the course of treating an adverse event. If this cannot be avoided, extreme caution is advised and dosing and monitoring should be adjusted to account for the possible CYP enzyme inhibition. Drugs outside of this list may be used to treat adverse events unless they are recognized as falling into either of the two categories listed in the table.

Table 5-5 Prohibited medications

CYP Enzymes/transporter	Sensitive substrates[a]	Substrates with narrow therapeutic range[b]
CYP2D6	Atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine	Thioridazine, neuroleptics, flecainide, metoprolol, and tricyclic antidepressants such as imipramine, amitriptyline, clomipramine
CYP3A	Alfentanil, aprepitant, budesonide, buspirone,conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil	Alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine
CYP2B6[c]	Bupropion, efavirenz	
CYP2C8	Repaglinide[d]	Paclitaxel
CYP2C9	Celecoxib	Warfarin, phenytoin
OATP1B1	Bosentan, pravastatin	

[a] Sensitive CYP substrates refers to drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor.

[redacted]

[b] CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

[c] The AUC of these substrates were not increased by 5-fold or more with a CYP2B6 inhibitor, but they represent the most sensitive substrates studied with available inhibitors evaluated to date.

[d] Repaglinide is also a substrate for OATP1B1, and KAF156 potentially inhibits therapeutic OATP1B1 as well.

Except for medication which may be required to treat adverse events, no new medication other than study drugs will be allowed from the first dosing until up to completion of Day 7 evaluations.

Should a patient have an *incidental and limited* need for a medication to be taken within the restricted pre-dose timeframe (e.g., antibiotic prophylaxis prior to dental surgery, etc.), the sponsor should be advised, as administration of any concomitant medication *may* require the patient to be withdrawn from the study. Decisions regarding withdrawal from study participation will be discussed with the sponsor on a case-by-case basis. Administration of paracetamol < 4 g/day (or equivalent pediatric dosage; 10 to 15 mg/kg orally every 4 to 6 hours) as an antipyretic is acceptable. If within 36 hours of study drug administration, infections other than malaria require the administration of drugs with antimalarial activity (such as co-trimoxazole, tetracycline, doxycycline, etc.), with the exception of the use of topical antibiotics, the patient will be followed up until the end of the study.

5.7 Study completion and discontinuation

5.7.1 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 are put on rescue medication will be followed for the entire study duration (i.e., until Day 43).

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

An independent Data Monitoring Committee (DMC) will review patient safety at several time points (see Section 8.4) and may recommend stopping a cohort or the study early for safety reasons.

5.7.2 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

[redacted]

planned duration, and discontinuation can be initiated by either the patient or the investigator. For patients assigned to 1-day and 2-day cohorts, 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 patient's risk of trial participation.

Study treatment must be discontinued under the following circumstances:

- Patient request
- Pregnancy (see Section 6.5.6 and Section 7.7)
- Use of prohibited treatment as per recommendations in Table 5-5
- 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)
- Emergence of the following adverse events: severe nausea/vomiting, severe pruritus, increases in QTcF to > 500 ms (based on repeat ECGs), development of ventricular arrhythmia or clinically significant (symptomatic) bradycardia (see Appendix 3)
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the patient's overall status, prevent the patient from continuing participation in the study (e.g., increase in liver enzymes > 3 times the upper limit of normal (see Appendix 2)
- Deviation from the planned dose regimen for the study drug (e.g., vomiting of the replacement dose within 2 hours of intake)

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 Day 43.

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 Epoch, the patient is considered to have completed the treatment Epoch. If a patient does not complete the scheduled visits in the treatment Epoch, premature treatment discontinuation visit assessments detailed in the table of assessment should be completed and recorded in the eCRF.

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).

[redacted]

5.7.3 Premature Study Withdrawal

Patients are considered to be withdrawn prematurely from the study if they do not complete the follow-up visits until Day 43.

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 patient, investigator, or sponsor
- 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.

5.7.4 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent (WoC) from the study is defined as when a patient:

- Does not want to participate in the study anymore

and/or

- Does not want any further visits or assessments

and/or

- Does not want any further study related contacts

and/or

- Does not allow analysis of already obtained biologic material

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine 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.

[redacted]

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 below.

5.7.5 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.

5.7.6 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 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 in the Epoch will be performed. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications recorded on the eCRF. An overview of the specific CRF pages are listed on Table 6-5 (for database development purposes). The PK Run-in Part will follow the same visit schedule as for Cohorts 1 and 2 which have QD dosing for 1 day.

[redacted]

Table 6-1 Assessment schedule (except PK sampling and ECG measurements) for all patients (PK Run-in Part, Part A and Part B)

Epoch	Screen[15]		Treatment[1]															Follow-up						UNS
Visit Numbers[2]	1	99	101							102				199 EOT Epoch / premature discontinuation				201	202	203	204	205	299 End of Follow up / PSW	
Study Day			1							2				3				4	5	8	15	29	43	
Window			±0 day							±0 day				±0 day				±0 day	+1 day	±1 day	±2 day	±4 days	±4 days	
Time (post-dose) in hours	-24 to < 0		0	1	3	6	8	12	18	24	27	30	36	48	51	54	60	68	72	96	168	336	672	1008	
Obtain pre-screening informed consent	x																							
Obtain informed consent		x																						
Demography	x																							
Inclusion/Exclusion criteria		x																						
Initial Medical and Treatment history		x																						
Signs and symptoms of Severe Malaria		x				x				x				x				x	x	x	x	x	x	x
Vital Signs (blood pressure, pulse)		x	x							x				x				x	x	x	x	x	x	x
Body temperature[3]		x	x			x		x	x	x		x	x	x				x	x	x	x	x	x	x
Drug Administration Record			x				x[4]			x[5]			x[4]	x[6]			x[4]							
Physical Exam and malaria signs and symptoms[7]		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	x	x	x	x
Blood chemistry, hematology and [redacted]		x								x				x					x	x	x	x	x	x
Thyroid function		x																			x		x	
Urinalysis (Dipstick)		x								x				x					x	x	x	x	x	x
Pregnancy test[9]		x																					x	
Malaria Blood Film for parasite and gametocyte count	x[10]	x[10]				x		x		x			x	x					x	x	x	x	x	x
Blood sampling for PCR Genotyping and resistance markers[11]		x																		x	x	x	x	x
[redacted]																								
Adverse events	x	x	x		x	x	x			x		x	x	x	x	x	x	x	x	x	x	x	x	x
Meal records[13]			x				x[4]			x[5]			x[4]	x[6]			x[4]							
Contact IRT[14]	x		x							x[5]				x[6]									x	

[redacted]

UNS = Unscheduled visit
EOT = End of Treatment
PSW = Premature Study Withdrawal
X = assessment to be recorded on clinical database
S = assessment to be recorded on source documentation only

[1] Patients will be admitted to the hospital on Day 1 and will remain in the hospital under close supervision until they are discharged by the investigator or designee on Day 4.

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

[3] Fever monitoring will be done every 6 hours until resolution of fever, defined as being afebrile for 24 hours.

[4] Comparator only (Coartem®). Coartem® will be given at 0, 8, 24, 36, 48 and 60 hours. For all drug administrations actual time should be recorded.

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

[6] Not applicable to 1 and 2-day treatment regimens.

[7] 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. Malaria signs and symptoms, body height and body weight will also be recorded at screening as part of the complete physical examination. An *abbreviated* physical examination will be performed at all other visits starting from Day 1. An abbreviated physical exam will include the examination of general appearance and malaria signs and symptoms. Body weight will also be measured at End of Study Visit (Day 43 or earlier in case of premature patient discontinuation).

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

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

[10] Pre-screening parasite count should be used as baseline count. In case parasite count has been done > 6 hours before Study Visit 99 then it should be repeated at Study Visit 99 and the outcome of the repeated test should be considered as baseline parasite count

[11] PCR will be used for genotyping to establish malaria recrudescence/reinfection. PCR blood samples will be used for reviewing resistance markers. At screening, blood sample will be collected in all patients fulfilling eligibility criteria for inclusion in the study. A second blood sample collected as per Table above will be analyzed only in patients showing treatment failure before standard-of-care is administered.

[redacted]

[13] Meals within 3 hours prior to dosing and within 4 hours post-dosing to be documented.

[14] IRT has to be notified at Study Visit 1, at each study drug dispensing and at the completion or discontinuation of study treatment, upon completion of study or premature withdrawal from study participation. Also, if a patient vomits study drugs and needs to take a replacement medication, the site staff need to notify IRT.

[redacted]

[15] Screen Epoch has 2 parts: a Pre-Screening Part (Study Visit 1) to successfully identify the correct patients to be screened for this clinical study, and a Screening Part (Study Visit 99) in which further assessments will take place.

Table 6-2 12-Lead ECG assessments (triplicate) for all patients (PK Run-in Part, Part A and Part B)

Epoch	Screen		Treatment[1]																Follow-up						UNS
Visit Numbers[2]	1	99	101							102				199 EOT Epoch / premature discontinuation					201	202	203	204	205	299 End of Follow up / PSW	
Study Day			1							2				3					4	5	8	15	29	43	
Window			±0 day							±0 day				±0 day					±0 day	+1 day	±1 day	±2 day	±4 days	±4 days	
Time (post-dose) in hours	-24 to < 0		0	1	3	6	8	12	18	24	27	30	36	48	51	54	60	68	72	96	168	336	672	1008	
KAF-LUM SDF 1D cohort		x			x	x			x[3]	x		x[3]									x			x	
KAF-LUM SDF 2D cohort		x				x[3]				x	x	x		x							x			x	
KAF-LUM SDF 3D cohort		x				x[3]				x				x	x	x			x		x			x	
Coartem cohort		x				x[3]												x			x			x	

Note: ECG's should be taken in triplicate within 5 minutes after resting for at least 10 minutes 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 to < 24 h ± 30 min; ≥ 24 to 72 h ± 2 h; > 72 h ± 24 h.

UNS = Unscheduled visit

EOT = End of Treatment

PSW = Premature Study Withdrawal

X = assessment to be recorded on clinical data base

[1] Patients will be admitted to the hospital on Day 1 and will remain in the hospital under close supervision until they are discharged by the investigator or designee on Day 4.

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

[3] ECG assessment at this time point to be done for patients in Part A only, ECG assessments will be repeated in case of abnormalities.

[redacted]

Table 6-3 PK sampling schedule for patients involved in RICH PK sampling (PK Run-in Part and Part A)

Epoch	Screen		Treatment[1]																Follow-up						UNS
Visit Numbers[2]	1	99	101							102				199 EOT Epoch / premature discontinuation					201	202	203	204	205	299 End of Follow up / PSW	
Study Day			1							2				3					4	5	8	15	29	43	
Window			±0 day							±0 day				±0 day					±0 day	+1 day	±1 day	±2 day	±4 days	±4 days	
Time (post-dose) in hours	-24 to < 0		0	1	3	6	8	12	18	24	27	30	36	48	51	54	60	68	72	96	168	336	672	1008	
KAF-LUM SDF 1D cohort			x[3]	x	x	x		x	x	x		x		x						x	x				
KAF-LUM SDF 2D cohort			x[3]	x	x	x		x		x	x	x	x	x					x	x	x				
KAF-LUM SDF 3D cohort			x[3]	x	x	x		x		x				x	x	x			x	x	x	x			

Notes: A) Each PK sample will be 1mL blood. Further details on sample collection, numbering, processing and shipment can be found in the Site Operations Manual. B) 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 to < 24 h ± 30 min; ≥ 24 to 72 h ± 2 h; > 72 h ± 24 h.

UNS = Unscheduled visit

EOT = End of Treatment

PSW = Premature Study Withdrawal

X = assessment to be recorded on clinical data base

[1] Patients will be admitted to the hospital on Day 1 and will remain in the hospital under close supervision until they are discharged by the investigator or designee on Day 4.

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

[3] PK sampling at Visit 101 should be done in a range of 15 min to 1 min prior to dosing.

[redacted]

Table 6-4 PK sampling schedule for patients NOT involved in RICH PK sampling (Part A and Part B)

Epoch	Screen		Treatment[1]																Follow-up						UNS
Visit Numbers[2]	1	99	101							102				199 EOT Epoch / premature discontinuation					201	202	203	204	205	299 End of Follow up / PSW	
Study Day			1							2				3					4	5	8	15	29	43	
Window			±0 day							±0 day				±0 day					±0 day	+1 day	±1 day	±2 day	±4 days	±4 days	
Time (post-dose) in hours	-24 to < 0		0	1	3	6	8	12	18	24	27	30	36	48	51	54	60	68	72	96	168	336	672	1008	
KAF-LUM SDF 1D cohort					x	x			x[3]	x		x[3]									x				
KAF-LUM SDF 2D cohort					x[3]	x[3]				x	x	x		x							x				
KAF-LUM SDF 3D cohort					x[3]	x[3]				x				x	x	x			x		x				
Coartem cohort						x[3]				x				x				x			x				

Note: 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 to < 24 h ± 30 min; ≥ 24 to 72 h ± 2 h; > 72 h ± 24 h.

UNS = Unscheduled visit

EOT = End of Treatment

PSW = Premature Study Withdrawal

X = assessment to be recorded on clinical data base

[1] Patients will be admitted to the hospital on Day 1 and will remain in the hospital under close supervision until they are discharged by the investigator or designee on Day 4.

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

[3] PK sampling at these time points to be done only for patients in Part A.

[redacted]

Table 6-5 Overview of specific CRF pages

Epoch	Screen		Treatment[1]																Follow-up						UNS
Visit Numbers[2]	1	99	101							102				199 EOT Epoch / premature discontinuation					201	202	203	204	205	299 End of Follow up / PSW	
Study Day			1							2				3					4	5	8	15	29	43	
Window			±0 day							±0 day				±0 day					±0 day	+1 day	±1 day	±2 day	±4 days	±4 days	
Time (post-dose) in hours	-24 to < 0		0	1	3	6	8	12	18	24	27	30	36	48	51	54	60	68	72	96	168	336	672	1008	
Screening Epoch disposition page[9]	x	x																							
Treatment completion[3]			x				x[4]			x[5]			x[4]	x[6]			x[4]								
Treatment Epoch disposition page[7]																		x							
Follow-up Epoch disposition page[8]																								x	

UNS = Unscheduled visit
EOT = End of Treatment
PSW = Premature Study Withdrawal
X = assessment to be recorded on clinical data base

[1] Patients will be admitted to the hospital on Day 1 and will remain in the hospital under close supervision until they are discharged by the investigator or designee on Day 4.

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

[3] To be completed at the last study drug administration.

[4] Comparator only (Coartem®).

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

[6] Not applicable to 1 and 2-day treatment regimens.

[7] To be completed at End of Treatment (EOT) Epoch (end of Day 3 or at the time of treatment Epoch discontinuation).

[8] To be completed at end of follow-up Epoch (Day 43 or at the time of follow-up Epoch discontinuation).

[9] The Screen Epoch disposition page is completed at Visit 1 if a patient is a screen failure at Visit 1 and at Visit 99 otherwise.

[redacted]

6.1 Information to be collected on screening failures

All patients/subjects who have signed informed consent but not entered into the next epoch/period will have the study completion page for the screening epoch/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
- Initial medical and treatment history
- Severe malaria
- Vital signs
- Physical exam
- Prior and concomitant medications
- Blood chemistry and hematology
- Thyroid function
- Urinalysis
- Pregnancy test
- Malaria blood film for parasite and gametocyte count
- Blood sampling for 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

Compliance will be assessed by the investigator and/or study personnel at each visit using pill/sachet counts. This information should be captured in the source document at each visit. All study treatment taken must be recorded in the Dosage Administration Record 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.

[redacted]

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 CRF after start of study drug.

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.

6.4 Efficacy

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

6.4.1 Parasitaemia assessment (details provided in the laboratory manual)

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
- Pre-screening/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:

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

- Blood examination during the 43 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

[redacted]

- if *P. falciparum* **gametocytes** are seen, perform a gametocyte count against 1000 leukocytes

The **count should be made for each species and for the *P. falciparum* gametocytes** (White et al 2014). Blood film will be used for gametocyte count, and 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.

[redacted]

6.4.3 Blood sample for molecular diagnostic purposes

Blood will be sampled for parasite genotyping as indicated in the assessment schedule (Table 6-1). At screening, blood sample will be collected in all patients fulfilling eligibility criteria for inclusion in the study. A second blood sample collected as per Table 6-1 will analyzed only in patients showing treatment failure. This will distinguish between recrudescence and new infection. Analysis will be done by a pre-selected central laboratory.

Microscopic species identification (parasitaemia) will be confirmed and determined with PCR-based methods on blood retained from samples collected at the time of withdrawal.

All parasite samples at baseline will also be screened for specific genes/single-nucleotide polymorphisms (SNPs) that are known as markers for *P. falciparum* resistance.

During the analysis process no human DNA will be amplified or analyzed by any means.

6.4.4 Appropriateness of efficacy assessments

The microscopy examination methods to quantify the malaria parasite and gametocyte 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.

[redacted]

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. In addition, body height in centimeters (cm) and body weight to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes will be measured during the complete physical examination at screening.

An ***abbreviated*** physical examination will be performed at all other visits starting from Day 1 including the examination of general appearance and vital signs. Body weight to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes will be measured at Study End only (Day 43 or earlier in case of premature patient withdrawal from study participation).

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 (Table 6-1).
In particular in Part B pediatric patients need to be examined for signs of dehydration.

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 Body temperature

Body temperature will be monitored as indicated in the study assessment schedule table and recorded on the clinical data base. Fever monitoring will be done every 6 hours until resolution of fever, defined as being afebrile for 24 hours.

Fever Clearance is defined (in patients with an increased temperature at baseline) as the time of the first measurement of axillary temperature of < 37.5°C (or < 38.0°C for alternative routes). Fever clearance will be concluded following confirmation of temperature < 37.5°C (or < 38.0°C for alternative routes) on the subsequent measurement for at least 24 hours.

Patients who entered in the study on the basis of history of fever and did not subsequently have an increased body temperature measurement indicating presence of fever pre-dose will not be included in the analysis of fever clearance time (FCT).

[redacted]

6.5.4 Laboratory evaluations

A local laboratory will be preferably used for analysis of all specimens collected except for PCR (parasite identification and resistance markers), 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 at screening, 24 and 48 hours post-dose, Day 5 and then at each following Study visit up to end of study.

6.5.4.1 Hematology

Hemoglobin, hematocrit (packed-cell volume - PCV), 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'). Red blood cell count (RBC), reticulocytes count and haptoglobin levels will be performed in case of significant hemoglobin drop > 2g/dL or hemoglobin levels ≤ 5g/dL (will be optional depending on site equipment). Assessments will be done as indicated in the study assessment schedule table.

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, ALP, BUN, INR, sodium, potassium, magnesium, calcium, chloride, total protein and albumin.

Thyroid Stimulating Hormone (TSH) and free thyroxine T4 are tested at screening, after 336 hours, and at study completion only.

At screening, results of the thyroid test are not mandatory for eligibility into the study.

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, except for children ≤ 6 years, when Bazett formula (QTcB) is recommended.

[redacted]

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.

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 2-3 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 pregnancy test in urine will be performed at the screening visit and at study completion. Any female aged 8 years and above is considered a woman of child-bearing potential (WOCBP), and must be included among female patients undergoing obligatory pregnancy testing during the study.

6.5.7 Appropriateness of safety measurements

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

6.5.8 WHO definition

Definition of treatment failures

Early Treatment Failures (ETF)

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

[redacted]

Late Clinical Failure (LCF)

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

Late Parasitological Failure (LPF)

- Presence of parasitaemia on any day from Day 8 to Day 43 and axillary temperature < 37.5ºC without previously meeting any of the criteria of Early Treatment Failure or Late Clinical Failure

Adequate Clinical and Parasitological Response (ACPR):

Absence of parasitaemia on Day 43 irrespective of axillary temperature, without previously meeting any of the criteria of Early Treatment Failure or Late Treatment Failure or Late Parasitological Failure.

In this study, "absence of parasitaemia on Day 43" has been adapted to "absence of parasitaemia on Day 29" based on the short half-life of the study drugs.

Note: The first day of treatment with study medication is defined as Day 1 while the day prior to the first day of treatment is defined as Day -1. Compared to WHO (2015) 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, Day 29 in this protocol corresponds to Day 28 by WHO (2015).

Signs/symptoms indicative of severe/complicated malaria

Danger signs:

1. not able to drink or breast feed
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 or Blantyre coma score < 3 in children)
- 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)

[redacted]

- Hypoglycemia (blood or plasma glucose < 2.2 mmol/L; < 40 mg/dL)
- Severe malarial anemia (haemoglobin concentration ≤ 5 g/dL or a haematocrit of ≤ 15% in children < 12 years of age (< 7 g/dL and < 20% respectively 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)
- 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 < 70 mm Hg in children or < 80 mm Hg in adults with evidence of impaired perfusion)
- Hyperparasitaemia (*P. falciparum* parasitaemia > 10%)

[redacted]

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.

[redacted]

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.

Study drug/treatment includes investigational drugs i.e. KAF156 (200 mg, 400 mg and 800 mg), LUM-SDF (480 mg and 960 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 Terminology 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 criterion 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 serious adverse event (SAE - see Section 7.2 for definition of SAE) and which seriousness criteria have been met.
- action taken regarding study 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 given
- 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)

[redacted]

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 Investigator Brochure (IB). This information will be included in the patient informed consent and should 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, for example, via an Investigator Notification (IN) or an Aggregate Safety Finding. 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 (e.g., blood transfusion for the treatment of anemia due to malaria)
    - 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.

[redacted]

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 (please refer to Annex IV, ICH-E.2D Guideline).

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

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

Expectedness assessment

Since KAF156 and LUM-SDF will be administered to the patients on the same day, it would only be possible to assess the suspectedness of the reported SAEs to the combination (i.e., KAF156 and LUM-SDF). Hence, the expectedness of the reported SAEs will also be assessed for the combination. KAF156 and LUM-SDF have separate Investigator Brochure (IB) and the respective reference safety information (RSI) will be used. If the reported SAE/s is/are listed in the RSI of either of the product's IB, those will be considered as expected adverse events to the combination product (i.e., KAF156 and LUM-SDF) for reporting purposes. RSI in the LUM-SDF IB is based on the safety profile of Coartem®.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit 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 Serious Adverse Event 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 to the study treatment (KAF156/lumefantrine combination 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

[redacted]

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 Investigator Brochure(s) (IB) or Package Insert (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. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. 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.

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 will require close observation, follow-up monitoring, completion of the specific liver CRF pages and reported as SAE (Section 7.2.2).

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 designated personal 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 liver function test (LFT) within 24 hours to confirm elevation.
  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.

[redacted]

- Discontinuation of the investigational/study 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).
- Report to Novartis as SAE.
- 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 pre-defined checklist. All follow-up information, and the procedures performed must be recorded on appropriate CRF pages, including the liver event overview CRF pages.

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 (uPCR) (if applicable)
  - new onset (≥ 1+), hematuria or glycosuria

Every renal laboratory trigger or renal event as defined in Table 16-1 in Appendix 4 should be followed up by the investigator or designated personnel at the trial site as summarized in Appendix 4.

7.5 Cardiac Safety Monitoring

To ensure patient safety and fully characterize the cardiovascular safety of the investigational drug, a standardized process for identification, monitoring and evaluation of cardiac events is followed.

The following categories of notable ECG changes will be assessed during the course of the study (irrespective of whether classified/reported as (S)AE):

- QTcF increase from pretreatment baseline ≥ 60 ms (QTcB for children ≤ 6 years)
- QTcF > 500 ms (QTcB for children ≤ 6 years)

Resting heart rate:

- ECG of HR < 50/min with > 25% decrease from pretreatment baseline or
- HR < 50/min associated with symptoms

Cardiac rhythm:

- Any cardiac arrhythmia associated with hemodynamical compromise
- Sustained ventricular tachycardia ≥ 30 sec, or ventricular fibrillation

[redacted]

Every cardiac event as defined in Table 15-1 in Appendix 3 should be appropriately documented in the eCRF (both AE and SAE) and followed up by the investigator or designated personnel at the trial site as summarized in Appendix 3.

7.6 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 dose administration record (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 (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

7.7 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 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.

[redacted]

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 drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. 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 will be disclosed.

8.2 Data collection

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

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system 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 electronic Case Report Forms are complete and accurate. After

database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Data management and quality control

Novartis staff (or Contract Research Organization (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. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff or designee that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

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 Interactive Response Technology (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 for each part separately. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis for each part. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

8.4 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be established for this study to review patient safety at several time points. The DMC can recommend to stop the study or a specific cohort in case of serious safety observations which can include a non-acceptable rate of early treatment failures. The DMC will consist minimally of an external clinician with expertise in tropical diseases and external statistician. Regular formal interim assessment to review patient safety will be performed during the study as specified in the DMC charter.

Additional ad-hoc safety review may be requested by DMC or Novartis if needed.

Details of safety analyses will be specified in the analysis plan for the DMC. The DMC will make recommendations to Novartis on any safety issues that are deemed relevant.

[redacted]

The DMC is accountable to the Sponsor for appropriate monitoring of the study data. Although the DMC may make recommendations to the Sponsor about changes in the conduct of the study, final decisions will be made by Novartis Clinical Development senior management. In the case of early termination, consultation with Health Authorities may be required. Further details of the DMC's composition, organization and responsibilities will be described in the DMC charter.

9 Data analysis

Statistical analyses for PK Run-in Part, Part A and Part B will be performed separately. For key efficacy and safety outcomes, pooled analysis will be performed by pooling Part B with corresponding cohorts in Part A. Unless described separately otherwise, same statistical method will be used for separate analysis and pooled analysis.

For each cohort in Part B, a corresponding cohort in Part A will exist with matching dose and regimen. For statistical analyses and clinical study reporting, treatment group name, instead of cohort number, will be used for both parts and the pooled analysis which will include only those treatment groups with patients in both parts. The following treatment groups will be used (doses for KAF156 in Part A may be adapted according to Table 3-1):

- KAF156 400 mg/LUM-SDF 960 mg QD 1 day
- KAF156 800 mg/LUM-SDF 960 mg QD 1 day
- KAF156 400 mg/LUM-SDF 960 mg QD 2 days
- KAF156 200 mg/LUM-SDF 480 mg QD 3 days
- KAF156 400 mg/LUM-SDF 480 mg QD 3 days
- KAF156 400 mg/LUM-SDF 960 mg QD 3 days
- Coartem®

Efficacy data from the PK Run-in Part will not be pooled with the data from other cohorts. The PK analysis will be performed separately for this cohort.

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.

[redacted]

Safety set (SS)

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)

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

- did not have any important protocol deviations
- took at least 80% of randomized study medication(s). If a patient vomited the original dose but did not vomit the replacement dose, the patient is considered as taking the dose of study medication. Except for patients who are assigned to Coartem® cohort, this requires that all patients take all KAF156 and LUM-SDF dosages as assigned
- did not take other antimalarial medications prior to Day 29 for reasons other than rescue medication given for signs and symptoms of infection with *P. falciparum* or unsatisfactory therapeutic effect, and
- met at least one of the following criteria: (a) classified as treatment failure before Day 8 (see Section 6.5.8), (b) absent from parasitaemia at Day 29 or later, or (c) had valid PCR evaluations at baseline and at the time point with parasitaemia if parasitaemia is present at Day 8 or later.

Important protocol deviations for exclusion from PPS will be identified by the clinical team before database lock for each part.

PK analysis set

All subjects in the safety analysis set who had evaluable pharmacokinetic parameter data.

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 treatment group, as well as overall, using the FAS and PPS.

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 treatment group and drug (KAF156, LUM-SDF, or Coartem®). The percentage will be calculated based on the planned number of doses per treatment group. Percentage of patients with study drug vomiting and dose replacement will be presented by treatment group. Average daily dosage and total dosage (in mg) of each drug (KAF156, LUM-SDF, Coartem®) will be summarized by treatment group.

[redacted]

9.3.2 Prior and concomitant medication

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

Prior and concomitant medications will be summarized by treatment group in separate tables. Concomitant rescue and other anti-malarial medications will also be summarized by treatment group. Medications will be presented in alphabetical order, by ATC codes and grouped by anatomical main group (the first level of the ATC codes). Tables will also show the overall number and percentage of subjects receiving at least one drug of a particular ATC code and at least one drug in a particular anatomical main group.

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.

9.4 Analysis of the primary variable(s)

The PK Run-in Part will be separately analyzed. The primary objective for the PK Run-in Part is to investigate the pharmacokinetic interaction potential between KAF156 and LUM-SDF. The analyses of PK parameters of KAF156 and LUM-SDF are detailed in Section 9.5.4.

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

The primary efficacy objective in Part B is to determine if the selected dose combination regimens from Part A is effective in children down to 2 years.

Data in Part B will be pooled with the corresponding cohort data in Part A to determine which KAF156 and LUM-SDF dose combination can be carried forward to Phase 3 studies.

9.4.1 Primary Variable(s)

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

A patient is considered as PCR-corrected ACPR at Day 29 if the patient does not meet any of the criteria of early treatment failure (up to Day 4), late clinical failure (Day 5 to Day 29) or late parasitological failure (Day 8 to Day 29), and is absence of parasitaemia on Day 29 irrespective of axillary temperature unless the presence of parasitaemia after 7 days is due to reinfection based on PCR.

A presence of parasitaemia after 7 days of treatment initiation (Day 8 or later) is considered as a reinfection only if the parasitaemia is clear before Day 8 and none of the parasite strain(s) detected on Day 8 or later matche with the parasite strain at baseline based on PCR genotyping.

[redacted]

Treatment failures after 7 days due to reinfection based on PCR genotyping are not considered as failure for PCR-corrected analyses but will be considered as failure for PCR uncorrected analyses.

9.4.2 Statistical model, hypothesis, and method of analysis

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

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

9.4.3 Handling of missing values/censoring/discontinuations

No missing data are expected for the primary efficacy analysis based on PPS since patients who are not evaluable for the primary efficacy variable are excluded from PPS. See Section 9.4.4 for missing data handling for the supportive analysis using FAS.

9.4.4 Sensitivity analyses

The primary efficacy variable will be performed based on the FAS using the statistical method specified in Section 9.4.2. Missing primary efficacy variable will be handled as follows:

- 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 (from the day of rescue use onwards).
- 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* or for the treatment of *P. falciparum* gametocytes (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 if (a) they did not have a parasite count at Day 29 unless these patients could be classified as cured based on absence of parasitemia at later time, or (b) they did not have valid PCR evaluations at baseline and Day 29 if parasitemia was present at Day 29.

In addition, for the FAS, the proportion of patients with PCR-corrected ACPR at Day 29 and 95% CI will be also estimated using the Kaplan-Meier method (Stepniewska and White 2006 and WHO 2015) which uses treatment failure as the event and treats missing data as censored instead of treatment failure. The PCR-corrected ACPR rate at Day 29 is estimated by the survival function at Day 29. Patients who had a new infection (i.e., reinfection) with *P. falciparum* or other species without *P. falciparum* recrudescence on or after Day 8 will be censored at the time of the first PCR that indicate the infection; patients who took antimalarial

[redacted]

medications for reinfection or reasons other than rescue medication given for signs and symptoms of infection with *P. falciparum* or unsatisfactory therapeutic effect will be censored at the first time of such antimalarial medications; other patients without treatment failure will be censored at the time of last parasitemia assessment.

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

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

Secondary efficacy variables include:

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

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

9.5.1.1 PCR-corrected ACPR and uncorrected ACPR

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

Data will be handled as follows:

- Treatment failures after 7 days (i.e., 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 (from the day of rescue use onwards). 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* or for the treatment of *P. falciparum* gametocytes (e.g. primaquine, certain

[redacted]

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., Day 15, etc.) if (a) they did not have a parasite count at that visit unless these patients could be classified as cured based on absence of parasitaemia at a later time (e.g., 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., Visit Day 15).

In addition, PCR-corrected ACPR rate will be calculated and plotted using the Kaplan-Meier method for each treatment group in the FAS (see Section 9.4.4).

9.5.1.2 Treatment failure related parameters

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

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

The above parameters will be determined using the uncorrected 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 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.

9.5.1.4 Recrudescence and reinfection

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

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 and reinfection at Days 15, 29 and 43 will be estimated by Kaplan-Meier method based on the subset of FAS patients who have clearance of initial infection by Day 7. Time to event (recrudescence or reinfection) will be calculated from the

[redacted]

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.

The following additional analyses will be performed for each part and the pooled Part A and Part B:

- For PCR corrected and uncorrected ACPR rates, the 95% confidence intervals for the difference between each test group (KAF156/LUM-SDF combination) and the control (Coartem®) will be provided using the Wilson uncorrected method. For the pooled analysis, the treatment differences versus control will be evaluated using a Mantel-Haenszel estimate of the common risk difference stratified by Part (see SAS manual version 13.2 Pages 2681-2682, 2014).
- For PCT and FCT, the difference between each test group and control will be evaluated using a log-rank test. Patients who did not experience a clearance will be censored at the time of last relevant assessment (parasite or fever). For the pooled analysis, the log-rank test will be stratified by Part.

9.5.2 Safety variables

All safety parameters will be analyzed based on the safety.

9.5.2.1 Adverse event

The number and percentage of patients who report adverse events will be summarized by treatment group 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, serious adverse events, adverse event causing study drug discontinuation, adverse events by severity and causality will be presented by treatment group. 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 and treatment group.

In addition, shift tables will be provided in order to compare a patient's baseline laboratory evaluation relative to each study visit. 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 a categorical analysis will be provided. These summaries will be presented by laboratory test group and treatment group.

[redacted]

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) for each treatment group.

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 by treatment group.

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, QTcB (QT interval corrected for heart rate according to Bazett) and QTcF (QT interval corrected for heart rate according to Fredericia) for each treatment group. 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 ≥ 30 ms and ≥ 60 ms) will be tabulated at each time point and at the maximum value by treatment group in the form of a categorical analysis.

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

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

[redacted]

9.7 Interim assessments

PK Run-in Part: For the patients in the PK Run-in KAF156 200 mg/LUM-SDF 960 mg cohort, PK analyses will be performed on the samples collected in the first 24 hours. AUC_{0-24}, for KAF156 and lumefantrine will be calculated and compared with the expected values when one drug was given alone. Dosing in Part A will subsequently proceed according to the algorithm specified in Table 3-1. 12 patients with evaluable PK data are needed in the PK Run-in cohort.

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

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

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

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

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

9.8 Sample size calculation

Sample size for PK run-in cohort

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

In a POC Study, the standard deviation for log $AUC_{0\text{-}24h}$ was 0.26 and 0.27 for 10 *P. falciparum* patients treated with KAF156 400 mg QD 3 days and for 18 *P. falciparum* patients treated with KAF156 800 mg QD, respectively. The corresponding standard deviation for log Cmax was 0.205 and 0.215, respectively.

Table 9-1 Sample size and width of 2-sided 90% CI for log AUC_{0_24h} and log Cmax

Standard deviation (in log)	n	Target half width of 2-sided 90% CI	Half width in terms of ratio (anti-log)	Probability that observed half width of 2-sided 90% CI is ≤ the target
0.21	9	0.153	1.17	0.80
0.21	12	0.126	1.13	0.80
0.21	10	0.150	1.16	0.80

[redacted]

Standard deviation (in log)	n	Target half width of 2-sided 90% CI	Half width in terms of ratio (anti-log)	Probability that observed half width of 2-sided 90% CI is ≤ the target
0.26	9	0.200	1.22	0.80
0.26	12	0.155	1.17	0.80
0.26	13	0.150	1.16	0.80
0.26	12	0.150	1.16	0.70
0.27	9	0.200	1.22	0.80
0.27	12	0.161	1.17	0.80
0.27	14	0.150	1.16	0.80
0.27	12	0.150	1.16	0.68

Based on nQuery Table MOC1-1.nqa.

A sample size of 12 patients will provide 80% probability that the observed half width of 2-sided 90% CI for log AUC_{0_24h} is ≤0.155 or 1.17 in terms of ratio. A sample size of 12 patients will provide 80% probability that the observed half width of 2-sided 90% CI for log Cmax is ≤0.126, or 1.13 in terms of ratio. The target half widths of 2-sided 90% CI in Table 9-1 are about 1.2 in terms of ratio, which is smaller than 1.4 used for dose adjustment in Table 3-1.

Part A

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

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

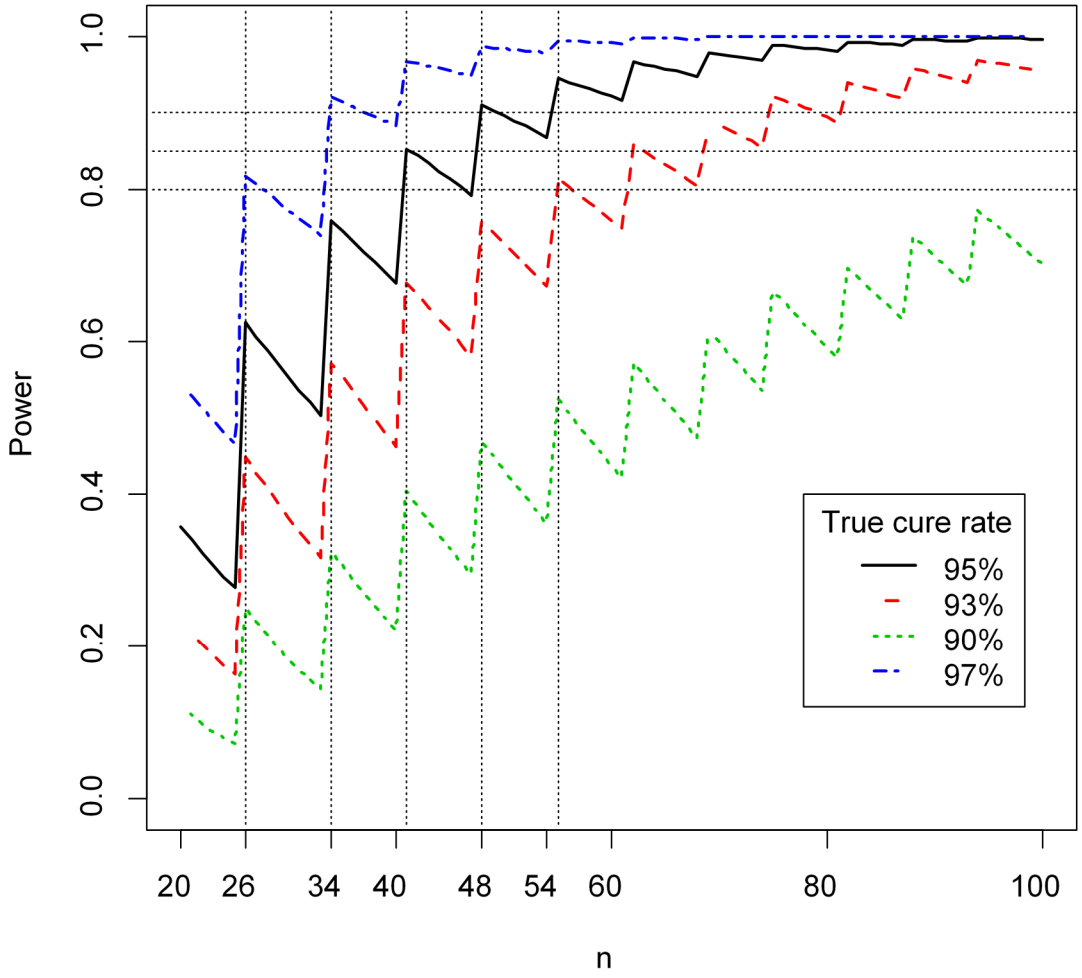
Figure 9-1 plots the power to reject the null hypothesis of at most 80% ACPR rate versus sample size by various true ACPR rates (90%, 93%, 95%, and 97%). Due to the discrete property of binomial distribution, the power increases zigzag with jump at 26, 34, 41, 48, 55, 62, and 68 as the sample size increases. When the sample size is at least 41, the power to reject the null hypothesis of at most 80% ACPR rate is about 80% or higher if the true rate is 95% or higher.

Since there is a 2:1 ratio among different treatment groups, the sample size in the per-protocol analysis set will be targeted to be 42 patients for each KAF156/LUM-SDF dose combination group and 21 patients for the comparator (Coartem®) cohort. This sample size will provide at least 80% power to reject the null hypothesis of at most 80% ACPR rate for the 6 KAF156 dose combinations if the true ACPR rate is at least 95%. If there are multiple KAF156/LUM-SDF dose combinations that are all effective, the less frequent or/and highest KAF156/LUM-SDF

dose combination(s) that is tolerable may be selected for further evaluation. The PK/PD modeling may be used to assist the selection of appropriate dose combination(s) for Part B.

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

Figure 9-1 Power to reject adequate clinical and parasitological response (ACPR) rate less than or equal to 80% based on 2-sided 95% CI by true rate



Part B

The primary objective for this part is to assess the safety and efficacy of the selected KAF156/LUM-SDF dose combination(s) adjusted for body weight in pediatric patients. For the primary efficacy variable of PCR corrected ACPR rate at Day 29 based on the per-protocol analysis set, a sample size of at least 41 patients will provide about 80% power or higher to

[redacted]

reject the null hypothesis of at most 80% ACPR rate based on the lower limit of 2-sided 95% exact confidence interval if the true rate is 95% or higher for a KAF156/LUM-SDF dose combination. Since there is a 2:1 ratio between a KAF156/LUM-SDF dose combination group and the Coartem® cohort, the sample size in the per-protocol analysis set will be targeted to be 42 patients for each KAF156/LUM-SDF dose combination group and 21 patients for the Coartem® cohort. Assuming that 16% of patients will be excluded from the per-protocol analysis set, about 50 pediatric patients will be randomized to yield 42 patients for each KAF156 and LUM-SDF combination and 21 patients for the Coartem® cohort in the per-protocol analysis set.

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, United States (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 Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol,

[redacted]

written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. 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 either submitted for publication and/or 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.

[redacted]

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 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

Ashley EA, Dhorda M, Fairhurst RM et al (2014) Spread of artemisinin resistance in Plasmodium falciparum malaria. N Engl J Med;371(5):411-23.

Dondorp AM, Nosten F, Yi P et al (2009) Artemisinin resistance in Plasmodium falciparum malaria. N Engl J Med.;361(5):455-67.

Flegg JA, Guerin PJ, White NJ, et al (2011) Standardizing the measurement of parasite clearance in falciparum malaria: the parasite clearance estimator. Malar J; 10:339.

Hamed K and Grueninger H (2012) Coartem(®): a decade of patient-centric malaria management. Expert Rev Anti Infect Ther;10(6):645-59.

Held J, Supan C, Salazar CL et al (2015) Ferroquine and artesunate in African adults and children with Plasmodium falciparum malaria: a phase 2, multicentre, randomised, double-blind, dose-ranging, non-inferiority study. Lancet Infect Dis;15(12):1409-19.

Kredo T, Mauff K, Workman L, et al. (2016) The interaction between artemether-lumefantrine and lopinavir/ritonavir-based antiretroviral therapy in HIV-1 infected patients. BMC Infect Dis; 16:30.

Kuhen KL, Chatterjee AK, Rottmann M, et al (2014) KAF156 is an antimalarial clinical candidate with potential for use in prophylaxis, treatment, and prevention of disease transmission. Antimicrob. Agents Chemother;58(9):5060-7.

Lefevre G, Looareesuwan S, Treeprasertsuk S, Krudsood S, Silachamroon U, Gathmann I, Mull R, Bakshi R. 2001. A clinical and pharmacokinetic trial of six doses of artemether-lumefantrine for multidrug-resistant Plasmodium falciparum malaria in Thailand. Am J Trop Med Hyg 64:247–256.

Lefevre G, Carpenter P, Souppart C, et al. (2002) Pharmacokinetics and electrocardiographic pharmacodynamics of artemether-lumefantrine (Riamet) with concomitant administration of ketoconazole in healthy subjects. Br J Clin Pharmacol; 54:485-92.

Leong FJ, Zhao R, Zeng S et al (2014) A first-in-human randomized, double-blind, placebo-controlled, single- and multiple-ascending oral dose study of novel Imidazolopiperazine KAF156 to assess its safety, tolerability, and pharmacokinetics in healthy adult volunteers. Antimicrob. Agents Chemother; 58(11):6437-43.

[redacted]

Ménard D, Khim N, Beghain J et al KARMA Consortium (2016) A Worldwide Map of Plasmodium falciparum K13-Propeller Polymorphisms. N Engl J Med;374(25):2453-64.

SAS Institute Inc. (2014) SAS/STAT® 13.2 User's Guide. Cary, NC: SAS Institute Inc.
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.

Tun KM, Imwong M, Lwin KM et al (2015) Spread of artemisinin-resistant Plasmodium falciparum in Myanmar: a cross-sectional survey of the K13 molecular marker. Lancet Infect Dis;15(4):415-21.

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

WorldWide Antimalaria Resistance Network (WWARN) (2015) Artemether-lumefantrine treatment of uncomplicated Plasmodium falciparum malaria: a systemic review and meta-analysis of day 7 lumefantrine concentrations and therapeutic response using individual patient data. BMC Med; 13:227. doi: 10.1186/s12916-015-0456-7.

World Health Organization (2015) World Malaria Report (http://apps.who.int/iris/bitstream/10665/200018/1/9789241565158_eng.pdf?ua=1).

[redacted]

13 Appendix 1: Clinically notable laboratory and ECG values

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	• 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 drug immediately • Repeat LFTs within 24h • Hospitalize, if clinically appropriate • Establish causality • **Report to Novartis as an SAE** • Complete Liver CRF	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 drug immediately • Repeat LFTs within 24h • Hospitalize if clinically appropriate • Establish causality • **Report to Novartis as an SAE** • Complete Liver CRF	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 drug immediately	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c]

Criteria	Actions required	Follow-up monitoring
	• Repeat LFTs within 24h • Hospitalize, if clinically appropriate • Establish causality • **Report to Novartis as an SAE** • Complete Liver CRF	(frequency twice a week until resolution, stabilize or return to within baseline values)
> 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 • **Report to Novartis as an SAE** • Complete Liver CRF	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 drug immediately • Repeat LFT within 24 hours • Hospitalize if clinically appropriate • Establish causality • **Report to Novartis as an SAE** • Complete Liver CRF	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 24 hours • If elevation is confirmed, initiate close observation of the patient	Monitor LFT until resolution[c] (frequency twice a week until resolution, stabilize or return to within baseline values)
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 24 hours • If elevation persists, establish causality • **Report to Novartis as an SAE** • Complete Liver CRF	Monitor LFT until resolution[c] (frequency twice a week until resolution, stabilize or return to within baseline values)
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 • **Report to Novartis as an SAE** • Complete Liver CRF	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
Jaundice	• Discontinue the study drug immediately • Hospitalize the patient	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency twice a week until

[redacted]

Criteria	Actions required	Follow-up monitoring
	• Establish causality • **Report to Novartis as an SAE** • Complete Liver CRF	resolution, stabilize or return to within baseline values)
Any AE potentially indicative of a liver toxicity* severe events only SMQ AE	• Consider study drug discontinuation • Hospitalization if clinically appropriate • Establish causality • **Report to Novartis as an SAE** • Complete Liver CRF	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

* 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.

[redacted]

15 Appendix 3: Cardiac Alert Threshold Values and Actions

Table 15-1 Cardiac alert threshold values and actions

	Values	Actions
QTcF (QTcB for children ≤ 6 years)	QTcB > 500 ms (< 6 years); QTcF> 500 (≥ 6 years).	If confirmed by two repeat ECG, check and correct the patient's serum potassium and magnesium immediately.
Cardiac rhythm	Sustained ventricular tachycardia lasting 30 sec or more, or ventricular fibrillation, or any hemodynamically compromising cardiac arrhythmia	Report as SAE to Sponsor and transmit to eRT immediately for prompt review. Discontinue patient from study therapy. Monitor ECG hourly until at least 2 consecutive hourly ECGs performed are back to baseline
QTcF (QTcB for children ≤ 6 years)	Increase from baseline ≥ 60 ms	If confirmed by two repeat ECG, check and correct the patient's serum potassium and magnesium immediately.
Resting heart rate	HR < 50/min with > 25% decrease from pretreatment baseline verified by ECG	Report to Sponsor as AE (unless it meets the SAE criteria as described in Section 7.2.1) and transmit to eRT immediately for prompt review.

[redacted]

16 Appendix 4: Renal Alert Criteria and Actions

Table 16-1 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 ≥ 150 mg/g or > 15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider study treatment discontinuation
New dipstick hematuria ≥ 1+ not due to trauma or menstruation	Urine sediment microscopy Perform serum creatinine, ACR
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.	

17 Appendix 5:

Table 17-1 Part A: KAF156 and LUM-SDF dosing scheme in case KAF156 relative exposure factor in PK Run-in vs. the reference mean AUC_{0-24h} (4930 ng*h/mL) is <1.4

Cohort	Treatment	Dose (mg)	Dosing regimen	Daily dosing based on available strengths
1	KAF156 LUM-SDF	400 960	QD 1 day	4 x 100 mg or 2 x 200 mg 2 sachets
2	KAF156 LUM-SDF	800 960	QD 1 day	8 x 100 mg or 4 x 200 mg 2 sachets
3	KAF156 LUM-SDF	400 960	QD 2 days	4 x 100 mg or 2 x 200 mg 2 sachets
4	KAF156 LUM-SDF	200 480	QD 3 days	2 x 100 mg or 1 x 200 mg 1 sachet
5	KAF156 LUM-SDF	400 480	QD 3 days	4 x 100 mg or 2 x 200 mg 1 sachet
6	KAF156 LUM-SDF	400 960	QD 3 days	4 x 100 mg or 2 x 200 mg 2 sachets

Table 17-2 Part A: KAF156 and LUM-SDF dosing scheme in case KAF156 relative exposure factor in PK Run-in vs. the reference mean AUC_{0-24h} (4930 ng*h/mL) is ≥1.4 to <1.8

Cohort	Treatment	Dose (mg)	Dosing regimen	Daily dosing based on available strengths
1	KAF156 LUM-SDF	300 960	QD 1 day	3 x 100 mg 2 sachets
2	KAF156 LUM-SDF	600 960	QD 1 day	6 x 100 mg or 3 x 200 mg 2 sachets
3	KAF156 LUM-SDF	300 960	QD 2 days	3 x 100 mg 2 sachets
4	KAF156 LUM-SDF	150 480	QD 3 days	3 x 50 mg 1 sachet
5	KAF156 LUM-SDF	300 480	QD 3 days	3 x 100 mg 1 sachet
6	KAF156 LUM-SDF	300 960	QD 3 days	3 x 100 mg 2 sachets

[redacted]

Table 17-3 Part A: KAF156 and LUM-SDF dosing scheme in case KAF156 relative exposure factor in PK Run-in vs. the reference mean AUC_{0-24h} (4930 ng*h/mL) is ≥1.8 to <2.5

Cohort	Treatment	Dose (mg)	Dosing regimen	Daily dosing based on available strengths
1	KAF156 LUM-SDF	200 960	QD 1 day	2 x 100 mg or 1 x 200 mg 2 sachets
2	KAF156 LUM-SDF	400 960	QD 1 day	4 x 100 mg or 2 x 200 mg 2 sachets
3	KAF156 LUM-SDF	200 960	QD 2 days	2 x 100 mg or 1 x 200 mg 2 sachets
4	KAF156 LUM-SDF	100 480	QD 3 days	2 x 50 mg or 1 x 100 mg 1 sachet
5	KAF156 LUM-SDF	200 480	QD 3 days	2 x 100 mg or 1 x 200 mg 1 sachet
6	KAF156 LUM-SDF	200 960	QD 3 days	2 x 100 mg or 1 x 200 mg 2 sachets

Table 17-4 Part A: KAF156 and LUM-SDF dosing scheme in case KAF156 relative exposure factor in PK Run-in vs. the reference mean AUC_{0-24h} (4930 ng*h/mL) is ≥2.5 to 4

Cohort	Treatment	Dose (mg)	Dosing regimen	Daily dosing based on available strengths
1	KAF156 LUM-SDF	100 960	QD 1 day	2 x 50 mg or 1 x 100 mg 2 sachets
2	KAF156 LUM-SDF	200 960	QD 1 day	2 x 100 mg or 1 x 200 mg 2 sachets
3	KAF156 LUM-SDF	100 960	QD 2 days	2 x 50 mg or 1 x 100 mg 2 sachets
4	KAF156 LUM-SDF	50 480	QD 3 days	1 x 50 mg 1 sachet
5	KAF156 LUM-SDF	100 480	QD 3 days	2 x 50 mg or 1 x 100 mg 1 sachet
6	KAF156 LUM-SDF	100 960	QD 3 days	2 x 50 mg or 1 x 100 mg 2 sachets

[redacted]