

**Official Title:** A Phase 2 interventional, multicenter, randomized, open-label study in three age-descending cohorts to evaluate efficacy, safety and tolerability of KAF156 and Lumefantrine-SDF combination in the treatment of acute uncomplicated *Plasmodium falciparum* Malaria in a pediatric population

**NCT Number:** NCT04546633

**Document Date:** Protocol Amendment 1: 29 Jul 2021

Novartis Research and Development

KAF156

Clinical Trial Protocol CKAF156A2203

**A Phase 2 interventional, multicenter, randomized, open-label study in three age-descending cohorts to evaluate efficacy, safety and tolerability of KAF156 and Lumefantrine-SDF combination in the treatment of acute uncomplicated *Plasmodium falciparum* Malaria in a pediatric population**

Document type:	Amended Protocol Version
EUDRACT number:	2021-003583-27
Version number:	01 (Clean)
Clinical Trial Phase:	II
Release date:	29-Jul-2021

Property of Novartis  
Confidential

May not be used, divulged, published, or otherwise disclosed  
without the consent of Novartis

Clinical Trial Protocol Template Version 2.0 dated 01-Aug-2018



## Table of contents

Table of contents .....	2
List of tables .....	5
List of figures .....	6
List of abbreviations .....	7
Glossary of terms .....	9
Amendment 1 (29-Jul-2021) .....	11
Protocol summary .....	15
1 Introduction .....	18
1.1 Background .....	18
1.2 Purpose .....	19
2 Objectives and endpoints .....	20
3 Study design .....	21
4 Rationale .....	26
4.1 Rationale for study design .....	26
4.2 Rationale for dose/regimen and duration of treatment .....	27
4.3 Rationale for choice of control drugs (comparator/placebo) .....	28
4.4 Purpose and timing of interim analyses/design adaptations .....	29
4.5 Risks and benefits .....	29
4.6 Rationale for Public Health Emergency mitigation procedures .....	30
5 Population .....	30
5.1 Inclusion criteria .....	30
5.2 Exclusion criteria .....	31
6 Treatment .....	33
6.1 Study treatment .....	33
6.1.1 Investigational and control drugs .....	33
6.1.2 Additional study treatments .....	34
6.1.3 Treatment arms/group .....	34
6.1.4 Treatment duration .....	35
6.2 Other treatment(s) .....	35
6.2.1 Concomitant therapy .....	35
6.2.2 Prohibited medication .....	36
6.2.3 Rescue medication .....	38
6.3 Patient numbering, treatment assignment, randomization .....	39
6.3.1 Patient numbering .....	39
6.3.2 Treatment assignment, randomization .....	39

6.4	Treatment blinding.....	40
6.5	Dose escalation and dose modification.....	40
6.5.1	Dose modifications.....	40
6.6	Additional treatment guidance.....	41
6.6.1	Treatment compliance.....	41
6.6.2	Emergency breaking of assigned treatment code.....	41
6.7	Preparation and dispensation .....	41
6.7.1	Handling of study treatment and additional treatment.....	41
6.7.2	Instruction for prescribing and taking study treatment .....	42
7	Informed consent procedures .....	43
8	Visit schedule and assessments .....	45
8.1	Screening .....	62
8.1.1	Information to be collected on screening failures .....	62
8.2	Patient demographics/other baseline characteristics .....	62
8.3	Efficacy.....	63
8.3.1	Parasitemia assessment (details provided in the Laboratory Manual) .....	63
8.3.2	Blood sample for molecular diagnostic purposes .....	64
8.3.3	Appropriateness of efficacy assessments .....	64
8.4	Safety .....	64
8.4.1	Laboratory evaluations.....	66
8.4.2	Electrocardiogram .....	66
8.4.3	Pregnancy and assessments of fertility in Run-in Cohort .....	67
8.4.4	WHO Definitions of treatment failures and Adequate Clinical and Parasitological Response.....	68
8.4.5	Appropriateness of safety measurements.....	68
8.5	Additional assessments.....	69
8.5.1	Pharmacokinetics .....	69
9	Study discontinuation and completion .....	69
9.1	Discontinuation.....	69
9.1.1	Discontinuation of study treatment .....	69
9.1.2	Lost to follow-up.....	70
9.2	Withdrawal of informed consent / Opposition to use data/biological samples .....	71
9.3	Early study termination by the sponsor .....	71
9.4	Study completion and post-study treatment .....	72
10	Safety monitoring and reporting.....	72
10.1	Definition of adverse events and reporting requirements.....	72

10.1.1	Adverse events .....	72
10.1.2	Serious adverse events .....	74
10.1.3	SAE reporting.....	75
10.1.4	Pregnancy reporting .....	76
10.1.5	Reporting of study treatment errors including misuse/abuse.....	76
10.2	Additional Safety Monitoring.....	77
10.2.1	Liver safety monitoring.....	77
10.2.2	Renal safety monitoring .....	78
10.2.3	Data Monitoring Committee .....	78
10.2.4	Cardiac Safety Monitoring.....	78
11	Data Collection and Database management .....	79
11.1	Data collection .....	79
11.2	Database management and quality control .....	79
11.3	Site monitoring .....	80
12	Data analysis and statistical methods .....	81
12.1	Analysis sets .....	81
12.2	Patient demographics and other baseline characteristics.....	82
12.3	Treatments .....	82
12.4	Analysis of the primary endpoint(s) .....	82
12.4.1	Definition of primary endpoint(s) .....	82
12.4.2	Statistical model, hypothesis, and method of analysis.....	83
12.4.3	Handling of missing values/censoring/discontinuations.....	83
12.4.4	Sensitivity analyses .....	83
12.5	Analysis of secondary endpoints .....	84
12.5.1	Efficacy and/or Pharmacodynamic endpoint(s) .....	84
12.5.2	Safety endpoints .....	87
12.5.3	Pharmacokinetics .....	88
12.5.4	PK/PD relationships .....	89
	.....	89
12.7	Interim analyses .....	89
12.8	Sample size calculation.....	90
12.8.1	Primary endpoint(s).....	90
12.8.2	Secondary endpoint(s).....	91
13	Ethical considerations and administrative procedures .....	92
13.1	Regulatory and ethical compliance.....	92
13.2	Responsibilities of the investigator and IRB/IEC.....	93

13.3	Publication of study protocol and results.....	93
13.4	Quality Control and Quality Assurance.....	93
14	Protocol adherence .....	93
14.1	Protocol amendments.....	94
15	References .....	95
16	Appendices .....	97
16.1	Appendix 1: Clinically notable laboratory values and vital signs .....	97
16.2	Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements .....	100
16.3	Appendix 3: Specific Renal Alert Criteria and Actions and Event Follow-up....	102
16.4	Appendix 4: Signs/symptoms of severe/complicated malaria.....	103
16.5	Appendix 5: Cardiac Alert Threshold Values and Actions .....	105
	.....	106

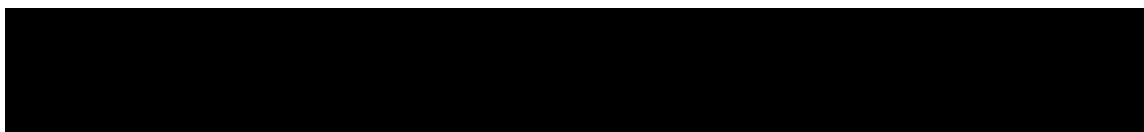
## List of tables

Table 2-1	Objectives and related endpoints .....	20
Table 4-1	Rationale for study design.....	27
Table 6-1	Investigational and control drug.....	33
Table 6-2	KAF156 and LUM-SDF starting dosing scheme in the Run-in Cohort.....	34
Table 6-3	Cohorts 1 and 2: KAF156 and LUM-SDF dosing per weight .....	34
Table 6-4	Cohorts 1 and 2: Coartem <sup>®</sup> dosing per weight.....	35
Table 6-5	Prohibited Medications .....	37
Table 8-1	Assessment Schedule for the Run-in Cohort (treatment groups: KAF156/LUM-SDF QD for 2 days in fed and fasted patients) .....	46
Table 8-2	Assessment Schedule for Cohorts 1 and 2 (treatment groups: KAF156/LUM-SDF QD for 2 days and Coartem <sup>®</sup> BID for 3 days).....	50
Table 8-3	Assessment Schedule for Cohorts 1 and 2 (treatment arms: KAF156/LUM-SDF QD for 3 days and Coartem <sup>®</sup> BID for 3 days).....	56
Table 8-4	Assessments & Specifications.....	65
Table 8-5	Local laboratory evaluations .....	66
Table 10-1	Guidance for capturing the study treatment errors including misuse/abuse .....	77
Table 12-1	Non-compartmental pharmacokinetic parameters .....	89
Table 16-1	Criteria for notably abnormal vital signs .....	97
Table 16-2	Liver event and laboratory trigger definitions .....	100

Table 16-3	Follow-up requirements for liver events and laboratory triggers.....	100
Table 16-4	Specific Renal Alert Criteria and Actions.....	102
Table 16-5	Renal Event follow-up .....	103
Table 16-6	Cardiac alert threshold values and actions .....	105

## List of figures

Figure 3-1	Patient Flow within a Cohort .....	24
Figure 3-2	Study Design .....	26



## List of abbreviations

ACPR	Adequate clinical and parasitological response
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BID	Twice a day
BMI	Body Mass Index
BUN	Blood urea nitrogen
CFR	Code of Federal Regulation
CMO&PS	Chief Medical Office and Patient Safety
CO	Country Office
CQ	Chloroquine
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTC	Common Toxicity Criteria
CTT	Clinical Trial Team
DDE	Direct data entry
DHP	Data handling plan
DMC	Data Monitoring Committee
DMP	Data management plan
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ETF	Early treatment failure
FAS	Full Analysis Set
FBC	Full Blood Count
FCT	Fever clearance time
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GNF	Genomics Institute of the Novartis Research Foundation
H	Hour
HIV	Human immunodeficiency virus
HR	Heart rate
HTS	High through-put screening
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board

IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine system
LCF	Late clinical failure
LFT	Liver function test
LLOQ	Lower limit of quantification
LPF	Late parasitological failure
LTF	Late treatment failure
LUM-SDF	Lumefantrine-Solid Dispersion Formulation
MedDRA	Medical dictionary for regulatory activities
Mg	Milligram(s)
mL	Milliliter(s)
NI	Non-inferiority
NITD	Novartis Institute of Tropical Diseases
NSAIDs	Non-steroidal anti-inflammatory drugs
OHP	Offsite healthcare professional
PBPK	Physiologically Based Pharmacokinetic
PCR	Polymerase chain reaction
PCT	Parasite clearance time
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PPS	Per-Protocol Set
PYR	Pyrimethamine
QD	Once a day
QTcF	QT interval corrected by Fridericia's formula
RAS	Randomized Analysis Set
RBC	Red blood cell(s)
RSI	Reference safety information
SAE	Serious adverse event
sCR	Serum creatinine
SD	Standard deviation
SDF	Solid dispersion formulation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SMQ	Standardized MedDRA Query
SNPs	Single-nucleotide polymorphisms
SoC	Standard of care
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	Total bilirubin
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell(s)
WHO	World Health Organization

## Glossary of terms

Assessment	A procedure used to generate data required by the study.
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A specific group of patients fulfilling certain criteria.
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial.
Discontinuation from study	Point/time when the patient permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the patient permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Patient agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
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	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 source data/documents used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last patient
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol). The action of enrolling one or more patients
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant.
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with "investigational new drug" or "test substance".
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system.
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the patient's home.
Off-site healthcare Professional	A qualified healthcare professional, such as include those used in the study e.g. Nurse, Phlebotomist, Physician, who performs certain protocol procedures for the patient in an off-site location such as a patient's home.
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	An individual with the condition of interest.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization	The process of assigning trial patients to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment.
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location
Screen Failure	A patient who is screened but is not treated or randomized.
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug/treatment	Any drug (or combination of drugs) administered to the patient as part of the required study procedures; includes investigational drug, 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.
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the patient is not at the investigative site where the investigator will conduct the trial.
Patient number	A unique number assigned to each patient upon signing the informed consent. This number is the definitive, unique identifier for the patient and should be used to identify the patient throughout the study for all data collected, sample labels, etc.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points.
Withdrawal of consent (WoC) / Opposition to use of data / biological samples	<p>Withdrawal of consent from the study occurs when the patient or legal guardian explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation.</p> <p>Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.</p>

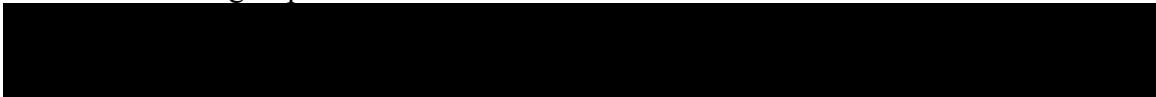
## Amendment 1 (29-Jul-2021)

### Amendment rationale

- Changes have been implemented due to the availability of data from another ongoing study (CKAF156A2202). The changes are related to safety and efficacy data of KAF156 combined with LUM-SDF in pediatric patients (2 to <12 years of age).
- Study CKAF156A2202 was set up to assess safety and efficacy of different doses of KAF156 and LUM-SDF in combination, in acute malaria patients of 2 years and older. In a first part, patients 12 years and older received one of 6 different dose regimens of KAF156/LUM-SDF or control (Coartem®). Interim assessment showed that all KAF156/LUM-SDF dose-cohorts met the primary efficacy endpoint, and that safety/tolerability was comparable to control for all cohorts. These results confirmed the positive risk-benefit balance and justify additional exploration in younger patients in a second part of the study where 3 dose regimens of KAF156/LUM-SDF or control (Coartem®) are currently assessed in patients 11 to 2 years of age. The final outcome of the study is expected to be available by 4Q2021, before the start of KAF156A2203 Cohort 1.
- The following changes are implemented under this amendment:
  - The age transition has been streamlined in Cohort 1 as safety and efficacy data in patients 2 to <12 years of age will already be available.
  - Food effect on KAF156 and lumefantrine exposures will be assessed in the Run-in Cohort only (12 years to < 18 years). It will no longer be assessed in the lower age groups.
  - A control group has been added in Cohorts 1 and 2 to evaluate the efficacy of KAF156 combined with LUM-SDF by demonstrating its non-inferiority to Coartem®.
  - Editorial changes have been added to cover for potential Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits.

### Changes to the protocol

- **Glossary of terms:** The following terms have been added: Clinical Trial Team, Coded data, discontinuation from study, discontinuation from study treatment, electronic data capture, end of the clinical trial, off-site, off-site healthcare professional, randomization, remote, tele-visit, opposition to use of data/biological samples.
- **Protocol summary:** The primary objective has been modified to add non-inferiority to standard of care (i.e., Coartem®). The control group added in Cohorts 1 and 2 and the associated changes in the study design have been described in the following sections of the table: Title, Primary and Secondary objectives, Study treatment and Data analysis, Inclusion criteria. For Cohorts 1 and 2, lower limit of parasite count required for inclusion criteria increased to 1,500 parasites/μL.
- **Section 1.2:** The reference product Coartem® to be used as comparator in Cohorts 1 and 2 (i.e., patients 6 months to <12 years of age) has been added. Option to change dose regimen of KAF156/LUM-SDF after analysis of the Run-in Cohort has been added (i.e., either 2-day or 3-day regimen).

- **Section 2:** Non-inferiority to Coartem<sup>®</sup> has been added to the primary objective. Comparison between fasted and fed patients has been removed for Cohorts 1 and 2 in the secondary objectives (fasted vs fed patients compared in the Run-in Cohort only). Secondary objectives have been rephrased.
  - **Section 3:** Study design has been modified.
    - Description of study design has been modified to indicate that it is now a parallel-group and non-inferiority study
    - Sample size has been modified to reflect the new study design
    - In the Run-in Cohort, an optional 3<sup>rd</sup> repeat has been added in case confirmation of same dose/food condition is required on lumefantrine and KAF156 exposures.
    - In Cohorts 1 and 2, the fasted group has been replaced by a control group (Coartem<sup>®</sup>), and the age transition and DMC review have been streamlined. The optional repeat of the first 24 patients of Cohort 1 with a different KAF156/LUM-SDF dose has been removed. An option to terminate Cohort 2 and re-allocate patients to Cohort 1 has been added (in case an optimal dose is not identified after the DMC review in Cohort 2). Sample size of Cohorts 1 and 2 was adjusted to fit new design/objective.
    - Clinical Trial Team has been blinded to treatments of Cohorts 1 and 2.
    - For Cohorts 1 and 2, lower limit of parasite count required for inclusion criteria increased to 1,500 parasites/ $\mu$ L.
    - Clarification on re-screening has been added
    - Text related to Public Health emergency has been added
  - **Section 4:** Text describing the control group in Cohorts 1 and 2 has been added to different sub-sections of Section 4. Modified sections are:
    - Section 4.1 (rationale for study design updated, Table 4-1 modified: randomization, data review check, stratification, non-inferiority)
    - Section 4.2 (rationale for dose/regimen updated)
    - Section 4.3 (rationale for choice of control drugs added)
    - Section 4.4 (timing for DMC review modified)
    - Section 4.5 (risks and benefits modified to include control group)
    - Section 4.6 (rationale for public health emergency mitigation procedures has been added)
  - **Section 5:** Sample size modified to reflect change in primary objective and streamlining of study design. For Cohorts 1 and 2, lower limit of parasite count required for inclusion criteria increased to 1,500 parasites/ $\mu$ L.
  - **Section 6.1:** Coartem<sup>®</sup> study treatment has been added to different sub-sections;
    - Section 6.1.1: Table 6-1
    - Section 6.1.2: Additional study treatments
    - Section 6.1.3: Treatment groups and Table 6-4 (dosing per body weight)
    - Section 6.1.4: Treatment duration
  - **Section 6.2.2:** Prohibited medication section adjusted to include the Coartem treatment group
- 

- **Section 6.3.2:** Treatment assignment and randomization modified to include the control group in Cohorts 1 and 2.
  - **Section 6.4:** Treatment blinding modified (Clinical Trial Team blinded during Cohorts 1 and 2).
  - **Section 6.7.2:** Instruction for prescribing and taking Coartem<sup>®</sup> added.
  - **Section 7:** The list of ICFs to be used in the study and text related to public health emergency have been added.
  - **Section 8:** Text related to public health emergency added.
  - **Table 8-1:** Table of assessments modified and two separate tables added:
    - Table 8-1 modified: visit schedule and assessment for the Run-in Cohort only
    - Table 8-2 added and footnotes modified: visit schedule and assessment for Cohorts 1 and 2 if a 2-day KAF156/LUM-SDF regimen is selected after the analysis of the Run-in Cohort
    - Table 8-3 added and footnotes modified: For Cohorts 1 and 2 if a 3-day KAF156/LUM-SDF regimen is selected after the analysis of the Run-in Cohort.
    - Some corrections have been done on timepoints for collection of [REDACTED] PCR genotyping.
    - ECG time points have been clarified, when to perform prior to drug administration, aligned with PK schedule
  - **Section 8.1:** Clarification on re-screening has been added.
  - **Section 8.4:** Text related to public health emergency added
  - **Section 8.4.1:** In Table 8-5, Chemistry has been corrected. In addition, it has been clarified that based on the outcomes of the Run-in cohort and study CKAF156A2202, laboratory evaluations done and the frequency of blood draws may be reduced in patients <12 years old (Cohorts 1 and 2).
  - **Section 8.4.2:** Clarification on the ECG procedure and QT correction formula to be used for different age groups added.
  - **Section 9:** Editorial changes related to withdrawal of informed consent, opposition to use data, biological samples added. And Section 9.1.2 Lost to follow-up has been added.
  - **Section 10:** Coartem<sup>®</sup> related information has been added, plus clarification text.
  - **Section 12:** The data analysis and statistical methods have been modified to reflect the changes implemented: different treatment groups in Run-in Cohort and in Cohorts 1 and 2, non-inferiority added to primary objective, streamline of age transition, sample size changes. Changes have been implemented in the following sections:
    - Section 12.3: Treatments
    - Section 12.4: Analysis of the primary endpoint(s)
    - Section 12.5: Analysis of secondary endpoint(s)  
[REDACTED]
    - Section 12.7: Interim Analyses
    - Section 12.8: Sample size calculation
-

- **Section 16.1 Appendix 1:** Editorial change (error with bullet point and space)
- **Section 16.2 Appendix 2:** Editorial change, consistency with Appendix 1.
- **Section 16.6 Appendix 6:** Blood sampling tables removed as blood sampling volumes will be indicated in the Laboratory Manual.

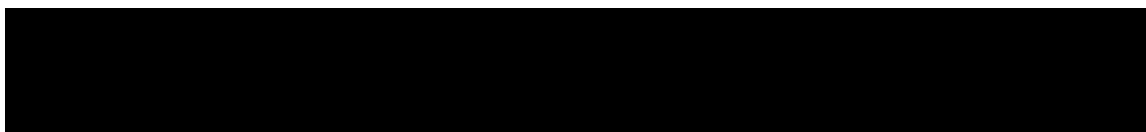
Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through colored font for deletions and colored underlined for insertions.

### **IRBs/IECs**

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

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

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



## Protocol summary

<b>Protocol number</b>	CKAF156A2203
<b>Full Title</b>	A Phase 2 interventional, multicenter, randomized, open-label study in three age-descending cohorts to evaluate efficacy, safety and tolerability of KAF156 and Lumefantrine Solid Dispersion Formulation (LUM-SDF) combination in the treatment of acute uncomplicated <i>Plasmodium falciparum</i> Malaria in a pediatric population
<b>Brief title</b>	Efficacy, safety and tolerability of KAF156 in combination with LUM-SDF in pediatric population with uncomplicated <i>Plasmodium falciparum</i> malaria
<b>Sponsor and Clinical Phase</b>	Novartis Phase 2
<b>Investigation type</b>	Drug
<b>Study type</b>	Interventional
<b>Purpose and rationale</b>	This study aims to determine the efficacy, safety and tolerability of the investigational drug KAF156 in combination with a solid dispersion formulation of lumefantrine (LUM-SDF) in pediatric patients (6 months to < 18 years of age) with uncomplicated <i>P. falciparum</i> malaria. There is an unmet medical need for anti-malarial treatment with a new mechanism of action to reduce the probability of developing resistance, and for a duration shorter than 3 days of treatment and/or reduced pill burden.
<b>Primary Objective(s)</b>	The primary objective of this study is to evaluate the efficacy of KAF156 combined with LUM-SDF compared to Coartem® (non-inferiority trial) for the treatment of uncomplicated malaria caused by <i>P. falciparum</i> in children 6 months to < 12 years old.
<b>Secondary Objectives</b>	Objective 1: To investigate the effect of food on lumefantrine bioavailability in patients 12 to < 18 years old (Run-in Cohort). Objective 2: To investigate the effect of food on KAF156 bioavailability in patients 12 to < 18 years old (Run-in Cohort). Objective 3: To evaluate safety and tolerability of KAF156/LUM-SDF in pediatric patients (6 months to <18 years old). Objective 4: To assess PK of KAF156 and lumefantrine in pediatric patients (6 months to <12 years). Objective 5: To evaluate the efficacy of KAF156 combined with LUM-SDF by assessing uncorrected and corrected adequate clinical and parasitological response (ACPR) at different time points as well as fever- and parasite- clearance times.
<b>Study design</b>	This will be a multicenter, open-label, randomized study in pediatric patients with confirmed uncomplicated <i>P. falciparum</i> malaria.
<b>Population</b>	The study population will consist of male and female patients (Run-in Cohort: 12 to < 18 years old and ≥ 35.0 kg; Cohort 1: 2 to < 12 years old and ≥ 10.0 kg; Cohort 2: 6 months to < 2 years old, weight ≥ 5.0 kg) with confirmed uncomplicated <i>P. falciparum</i> malaria. In the Run-In Cohort, patients will have malaria symptoms and <i>P. falciparum</i> counts of ≥ 1,000 and ≤ 150,000 parasites/μL at pre-screening. In Cohort 1 and Cohort 2, patients will have malaria symptoms and <i>P. falciparum</i> counts of ≥ 1,500 and ≤ 150,000 parasites/μL at pre-screening.

<b>Key Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• In Run-in Cohort: Male and female patients 12 to &lt; 18 years of age, with a body weight <math>\geq 35.0</math> kg; In Cohort 1: Male and female patients 2 to &lt; 12 years of age, with a body weight <math>\geq 10.0</math> kg; In Cohort 2: Male and female patients 6 months to &lt; 2 years of age, with a body weight <math>\geq 5.0</math> kg</li> <li>• Microscopic confirmation of <i>P. falciparum</i> by Giemsa-stained thick and thin films</li> <li>• <i>P. falciparum</i> parasitemia of <math>\geq 1,000</math> and <math>\leq 150,000</math> parasites/<math>\mu</math>L at the time of pre-screening for Run-in Cohort</li> <li>• <i>P. falciparum</i> parasitemia of <math>\geq 1,500</math> and <math>\leq 150,000</math> parasites/<math>\mu</math>L at the time of pre-screening for Cohorts 1 and 2</li> <li>• Axillary temperature <math>\geq 37.5</math> °C or oral/tympanic/rectal temperature <math>\geq 38.0</math> °C; or history of fever during the previous 24 hours (at least documented verbally)</li> <li>• Written informed consent has been obtained from parent / legal guardian before any assessment is performed. If the parent / legal guardian is unable to read and write, then a witnessed consent according to local ethical standards is permitted. Patients who are capable of providing assent, must provide assent with parental/legal guardian consent or as per local ethical guidelines</li> <li>• The patient and his/her parent/legal guardian is able to understand and comply with protocol requirements, instructions and protocol-stated restrictions and is likely to complete the study as planned.</li> </ul>
<b>Key Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• Mixed Plasmodium infections as per light microscopy results</li> <li>• Signs and symptoms of severe malaria according to the World Health Organization (WHO 2015)</li> <li>• Patients with concurrent febrile illnesses (e.g., typhoid fever, known or suspected COVID19)</li> <li>• Repeated 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 in the 24 hours prior to inclusion in the study)</li> <li>• Clinically relevant abnormalities of electrolyte balance which require correction, e.g., hypokalemia, hypocalcemia or hypomagnesemia</li> <li>• Anemia (hemoglobin level &lt; 7 g/dL)</li> <li>• Patients of child bearing potential, defined as all girls post first menarche (except for Run-in Cohort)</li> <li>• Pregnant or nursing (lactating) patients</li> <li>• Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs (e.g., HIV patients on ART therapy or TB patients on treatment), 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: <ul style="list-style-type: none"> <li>• Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) &gt; 3 x the upper limit of normal range (ULN), regardless of the level of total bilirubin</li> <li>• AST/ALT &gt; 1.5 and <math>\leq 2 \times</math> ULN and total bilirubin is &gt; ULN</li> <li>• Total bilirubin &gt; 2 x ULN regardless of the level of AST/ALT</li> </ul> </li> <li>• 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)</li> <li>• 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.</li> </ul>

<b>Study treatment</b>	<ul style="list-style-type: none"> <li>Run-in Cohort (12 to &lt; 18 years): <ul style="list-style-type: none"> <li>Treatment group 1 (starting dose in the Run-in Cohort): KAF156 400 mg and LUM-SDF 240 mg (adult dose) once daily (QD) for 2 days under fasting condition</li> <li>Treatment group 2 (starting dose in the Run-in Cohort): KAF156 400 mg and LUM-SDF 240 mg (adult dose) once daily (QD) for 2 days under fed condition</li> </ul> </li> <li>Cohort 1 (2 to &lt;12 years old): <ul style="list-style-type: none"> <li>Treatment group 1: The selected dose and dose regimen of KAF156 and LUM-SDF (i.e., 2-day or 3-day) after the Run-in Cohort</li> <li>Treatment group 2: Coartem® twice a day for 3 days (as per product label)</li> </ul> </li> <li>Cohort 2 (6 months to &lt;2 years old): <ul style="list-style-type: none"> <li>Treatment group 1: The selected dose and dose regimen of KAF156 and LUM-SDF (i.e., 2-day or 3-day) after the Run-in Cohort</li> <li>Treatment group 2: Coartem® twice a day for 3 days (as per product label)</li> </ul> </li> </ul>
<b>Efficacy assessments</b>	Parasitaemia
<b>Pharmacokinetic assessments</b>	<ul style="list-style-type: none"> <li>PK parameters of study drug (e.g. AUC, Cmax, C168 h and Tmax)</li> </ul>
<b>Key safety assessments</b>	<ul style="list-style-type: none"> <li>Physical examination and malaria signs and symptoms</li> <li>Vital signs</li> <li>Body temperature</li> <li>Monitoring of laboratory parameters in blood and urine</li> <li>Electrocardiogram (ECG)</li> <li>Adverse event (AE) monitoring.</li> </ul>
<b>Data analysis</b>	<p>For ACPR (Polymerase chain reaction (PCR) corrected and uncorrected ACPR at Days 15, 29 and 43), 2-sided 95% confidence intervals will be constructed using the exact (Clopper-Pearson) method for each treatment group by cohort and for Cohorts 1 and 2 pooled. If Cohort 2 does not stop early after the first 24 patients, two-sided 95% confidence interval (CI) for the difference between two treatment groups for Cohorts 1 and 2 pooled will be provided based on Mantel-Haenszel estimate of the common risk difference stratified by cohort. In case that Cohort 2 stops early, such as after the first 24 patients, two-sided 95% CI for the difference between the two treatment groups will be provided for Cohort 1 alone using the Wilson uncorrected method. For parasite clearance time (PCT) and fever clearance time (FCT), descriptive statistics (mean, standard error, median, quartiles) will be presented using the Kaplan-Meier method for each treatment group by cohort and for Cohorts 1 and 2 pooled. In case that Cohort 2 stops early, objectives for PCT and FCT will be assessed using Cohort 1 data alone. For PK parameters of KAF156 and lumefantrine, such as AUC, Cmax, etc., two-sided 90% confidence intervals will be calculated for each treatment group and for between treatment relative difference (ratio) for relevant common PK parameters by cohort and Cohorts 1 and 2 pooled using normal or log-normal approximation as applicable.</p>
<b>Key words</b>	<i>Plasmodium falciparum</i> malaria, KAF156, LUM-SDF, children

## 1 Introduction

### 1.1 Background

Malaria caused by *Plasmodium falciparum* is one of the leading causes of death in the developing world.

In 2018, an estimated 228 million cases of malaria and 405,000 deaths occurred worldwide: 93% of malaria cases and 94% of malaria deaths were in the African Region; and about half of all malaria deaths came from six countries (Nigeria, Democratic Republic of the Congo, Tanzania, Angola, Mozambique and Niger) (WHO 2019). Children aged under 5 years are the most vulnerable group affected by malaria, which accounted for 67% (272 000) of all malaria deaths worldwide in 2018 (WHO 2019).

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.

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, Ménard 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 et al 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 (Conrad and Rosenthal 2019, Ménard 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 mechanisms of actions.

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 possibly less than 3-day administration can improve treatment success and reduce probability of developing resistance via improved adherence and thus accelerate malaria eradication.

KAF156 (Ganaplacide) 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 in development. The mechanism of action of KAF156 is still being characterized, but may be related to a previously uncharacterized gene (*P. 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 gametocytocidal 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 of *P. vivax* infections. Also, KAF156 is equally potent against drug-sensitive and a broad panel of drug resistant malaria strains (Kuhlen et al 2014; Koller et al 2018).

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 is 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 day regimen, a two day or a three day regimen will be evaluated (based on the outcomes of the run-in cohort).

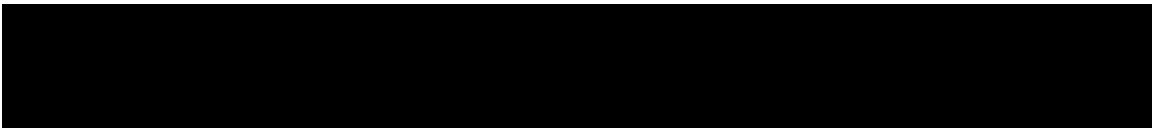
Lumefantrine-Solid Dispersion Formulation (LUM-SDF) will be used as partner drug in this study. In contrast to the conventional lumefantrine formulation, LUM-SDF has an improved bioavailability and less food effect, leading to an exposure which allows for a potentially curative once daily two-day regimen. KAF156 does not have a food effect. KAF156 and LUM-SDF in combination were assessed in a Phase 2b dose finding study (CKAF156A2202, Part A). Outcomes of the interim assessment in acute malaria patients of 12 years and older under fasted condition showed that all doses were efficacious, safe and well tolerated.

## 1.2 Purpose

This Phase 2 study aims to evaluate the efficacy, safety and tolerability of the investigational drug KAF156 and a Solid Dispersion Formulation of lumefantrine (LUM-SDF) when administered in combination once daily in pediatric patients 6 months to < 18 years of age with uncomplicated *Plasmodium falciparum* malaria. After completion of the Run-in cohort in patients 12 to <18 years, a reference product Coartem® will be used as comparator in patients 6 months to <12 years of age. In addition, pharmacokinetics (PK) of the drug combination will also be evaluated.

There will be three age-descending cohorts: Run-in Cohort (12 years to < 18 years), Cohort 1 (2 years to < 12 years) and Cohort 2 (6 months to < 2 years).

It is important to understand the impact of food on exposure. In adult healthy volunteers, LUM-SDF alone has shown a food effect whereas KAF156 does not have a food effect. This new study will first explore the effect of food on lumefantrine and KAF156 PK in malaria patients



12 to < 18 years old with malaria caused by *P. falciparum*. Based on the data from the Run-in Cohort, recommendation on dose, dosing regimen, dosage administration (with food) and duration will be provided before younger patients in Cohorts 1 and 2 are dosed with KAF156/LUM-SDF.

Then, efficacy, safety, tolerability and PK of the combination of KAF156/LUM-SDF in comparison with Coartem® will be evaluated in younger patients, in Cohort 1 of patients 2 to < 12 years old and Cohort 2 of patients 6 months to < 2 years old.

## 2 Objectives and endpoints

**Table 2-1 Objectives and related endpoints**

Objective(s)	Endpoint(s)
Primary objective(s)	Endpoint(s) for primary objective(s)
<ul style="list-style-type: none"> <li>To evaluate the efficacy of KAF156 combined with LUM-SDF compared to Coartem® (non-inferiority trial) for the treatment of uncomplicated malaria caused by <i>P. falciparum</i> in children 6 months to &lt; 12 years.</li> </ul>	<ul style="list-style-type: none"> <li>PCR-corrected adequate clinical and parasitological response (ACPR) at Day 29 (i.e., 28 days post-dose) (Cohorts 1 and 2 pooled).</li> </ul>
Secondary objective(s)	Endpoint(s) for secondary objective(s)
<ul style="list-style-type: none"> <li>To investigate the effect of food on KAF156 bioavailability in patients 12 to &lt; 18 years old (Run-in Cohort).</li> <li>To investigate the effect of food on lumefantrine bioavailability in patients 12 to &lt; 18 years old (Run-in Cohort).</li> <li>To evaluate safety and tolerability of KAF156/LUM-SDF in pediatric patients (6 months to &lt;18 years old).</li> <li>To assess PK of KAF156 and lumefantrine in pediatric patients (6 months to &lt;12 years old).</li> <li>To evaluate the efficacy of KAF156 combined with LUM-SDF by assessing uncorrected and corrected ACPR at different time points as well as fever- and parasite- clearance times.</li> </ul>	<ul style="list-style-type: none"> <li>KAF156 PK parameters such as AUC, Tmax and Cmax (Run-in Cohort).</li> <li>LUM PK parameters such as AUC, Tmax and Cmax (Run-in Cohort).</li> <li>Standard safety/tolerability assessments: Adverse events (AE)/serious adverse events (SAE) incidence and severity, laboratory abnormalities and electrocardiogram (ECG) abnormalities.</li> <li>KAF156 and lumefantrine: PK parameters such as AUC, Cmax (LUM Cmax for Cohorts 1 and 2), C168 h and Tmax.</li> <li>PCR-corrected adequate clinical and parasitological response (ACPR) at Day 15, Day 29 (Run-in Cohort) and Day 43, and the uncorrected ACPR at Day 15, Day 29, and Day 43.</li> <li>Incidence rate of recrudescence and reinfection at Days 15, 29 and 43.</li> <li>Parasite and fever clearance times (PCT and FCT).</li> </ul>

Objective(s)	Endpoint(s)

### 3 Study design

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

The study has a Run-in Cohort and a main part with two sequential age-descending cohorts: Cohort 1 and Cohort 2.

#### Run-in Cohort:

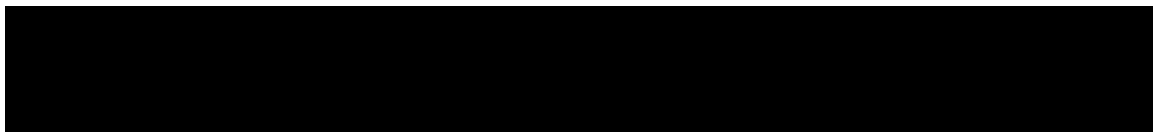
Male and female adolescent patients (12 to < 18 years old and  $\geq 35$  kg) will be enrolled in the Run-in Cohort. Twenty four patients (up to 96 in case of dose/food-adaptation) will be dosed with KAF156 400 mg and LUM-SDF 240 mg QD (once daily) for 2 days under fasted or fed conditions (Figure 3-1 and Figure 3-2).

The food effect of a standard meal (as defined in Section 6.7.2) on lumefantrine and KAF156 exposures will be evaluated in 24 patients first and may be repeated up to three times if dose or food adaption is required or if confirmation of same dose or food condition is required (based on integrated assessments of efficacy, safety and exposure). After the Run-in cohort, a dose and dosing regimen (2-day or 3-day) will be selected with the appropriate food recommendation for patients <12 years of age. Following this evaluation of drug-exposure, all investigators will be informed of the results and dosing/food recommendation will be implemented accordingly. Randomization will be stratified by country.

#### Cohorts 1 and 2:

Approximately 220 (up to 268 in case Cohort 2 stops early and additional patients are enrolled in Cohort 1) male and female pediatric patients (6 months to < 12 years old) will be randomized to the study. There will be two sequential age-descending cohorts of approximately 140 patients for Cohort 1 and 80 patients for Cohort 2: Cohort 1 will include children 2 to < 12 years and Cohort 2 will include children 6 months to < 2 years (Figure 3-1 and Figure 3-2). In the event that Cohort 2 is stopped early, such as after the first 24 patients, 80 additional patients will be enrolled in Cohort 1. Randomization will be stratified by age group (6 years to < 12 and 2 to < 6 years) and country for Cohort 1, and by country for Cohort 2. Children will have a body weight  $\geq 10$  kg in Cohort 1 and  $\geq 5$  kg in Cohort 2.

The Screening Period for the three cohorts will consist of two visits: a Pre-Screening visit and a Screening visit.



- **Pre-Screening visit:** Pre-screening is a key element to successfully identify the right patients to be screened for this clinical study. During pre-screening, a *P. falciparum* parasite count will be obtained. Patients in the Run-in cohort should have a *P. falciparum* parasitemia of  $\geq 1,000$  and  $\leq 150,000$  parasites/ $\mu$ L at the time of the pre-screening visit to be further screened. Patients Cohort 1 and Cohort 2 should have a *P. falciparum* parasitemia of  $\geq 1,500$  and  $\leq 150,000$  parasites/ $\mu$ L at the time of the pre-screening visit to be further screened.
- **Screening visit:** Further screening assessments will take place as soon as the pre-screening *P. falciparum* parasitemia outcome is available and only if outcome is in the pre-defined range ( $\geq 1,000$  and  $\leq 150,000$  parasites/ $\mu$ L in Run-In Cohort and  $\geq 1,500$  and  $\leq 150,000$  parasites/ $\mu$ L in Cohort 1 and Cohort 2 ).

It is not permissible to re-screen a patient within the same malaria episode if s/he fails the initial pre-screening or screening. Re-screening of a patient may occur in case the patient is returning to the study site for a new malaria episode. In this case, the patient will be assigned a new study number.

All eligible patients will be admitted to the hospital on Day 1. Another *P. falciparum* parasite count will be obtained prior to dosing on Day 1. The outcome of the Day 1 visit parasite count will be used as the baseline count.

In the Run-in Cohort, patients will be randomized into one of the two treatment groups at a starting dose of KAF156 400 mg and LUM-SDF 240 mg:

- Treatment group 1: KAF156 400 mg and LUM-SDF 240 mg QD (once daily) for 2 days in fasted condition
- Treatment group 2: KAF156 400 mg and LUM-SDF 240 mg QD (once daily) for 2 days in fed condition (standard meal as defined in [Section 6.7.2](#)).

Above doses are starting doses for patients  $\geq 35$ kg in the Run-in Cohort (patients 12 to  $<18$  years of age). The selected dose after completion of the Run-in Cohort will be adapted according to body weight if patients are  $<35$ kg in Cohorts 1 and 2 (patients  $<12$  years of age) (see [Section 6.1.3](#)).

In Cohorts 1 and 2, patients will be randomized into one of the two treatment groups:

- Treatment group 1: KAF156 and LUM-SDF QD (once daily) in either a 2-day or 3-day dose regimen. Food recommendation will be issued after the Run-in Cohort based on efficacy, safety, tolerability and PK data).
- Treatment group 2: Coartem® BID (twice a day) for 3 days (will be administered with food and doses will be based on patient's body weight as per product label).

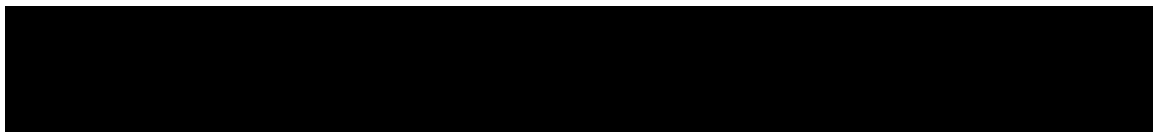
Patients will remain in the hospital under close supervision until they are discharged by the investigator or designee on Day 4. At the discretion of the investigator, patients may stay additional days if needed.

The patients will then be followed-up until Day 43 as outpatients. Visits to assess efficacy, safety, tolerability and PK of KAF156 and LUM-SDF combination will be scheduled during the follow-up period as described in the Assessment Schedule (For Run-in Cohort see [Table 8-1](#); For Cohorts 1 and 2 if a 2 day-KAF156/LUM-SDF treatment is selected see

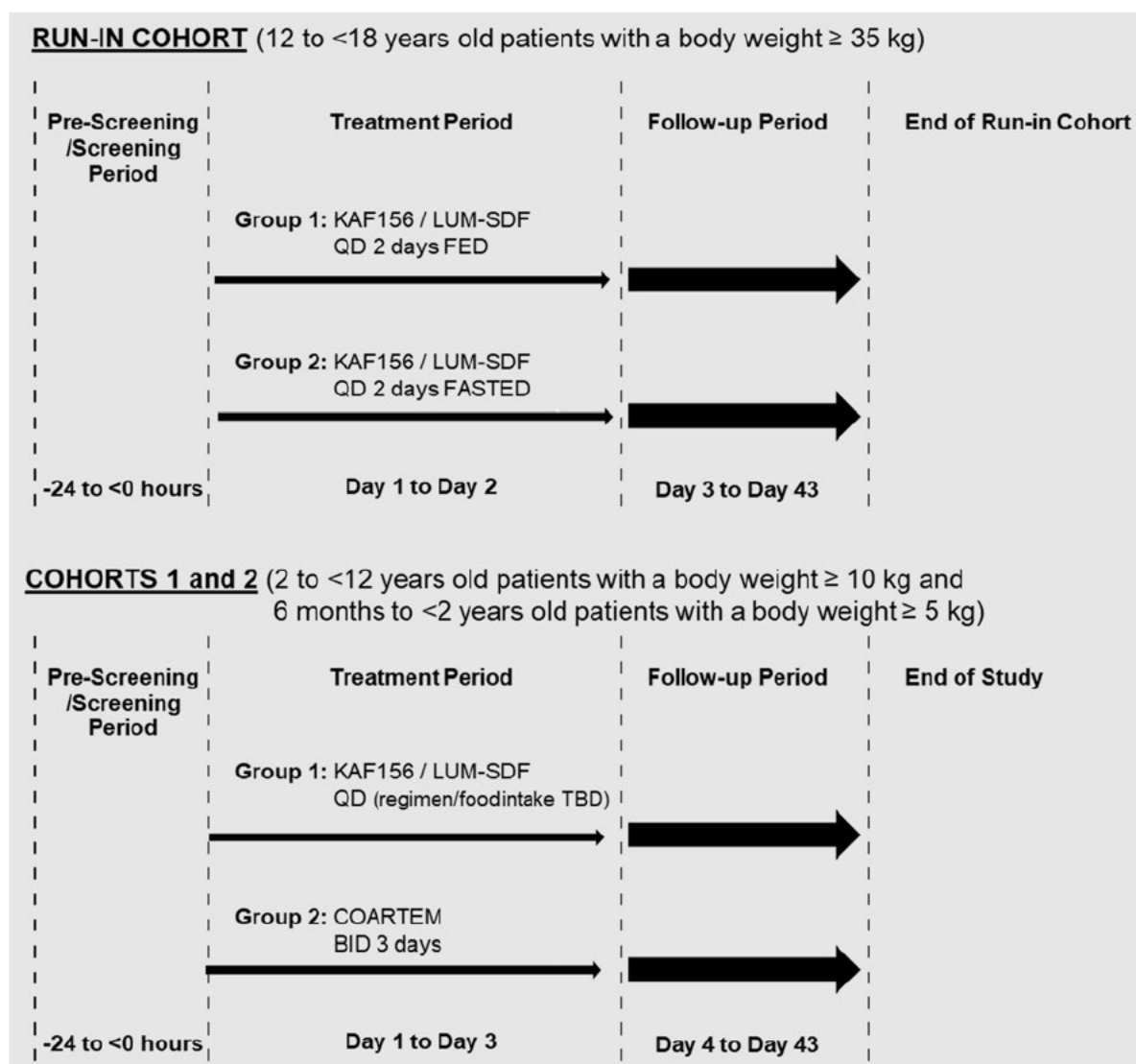
[Table 8-2](#), and if a 3 day-KAF156/LUM-SDF treatment is selected see [Table 8-3](#)). If malaria symptoms re-emerge outside of the scheduled study visits, patients will be instructed to contact the investigator.

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 the start of trial medications and up to 43 days after the last dose of KAF156/LUM-SDF as deemed necessary by the investigator. Lumefantrine-including treatment should preferably be avoided in case of early treatment failure (ETF).

As per [Section 4.6](#), during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the patient's home, may replace on-site study visits, for the duration of the disruption until it is safe for the patient to visit the site again. Sponsor must be consulted before implementation.



**Figure 3-1 Patient Flow within a Cohort**



Sponsor data review checks will be performed during the Run-in Cohort to assess safety, PK exposure and efficacy (Figure 3-2). An independent Data Monitoring Committee (DMC) will review the patient safety, treatment efficacy and PK data throughout the study. Based on these checks, the dose and dosing regimen being considered will be assessed as optimal or not for the cohort. Details of the DMC meetings will be provided in the DMC Charter.

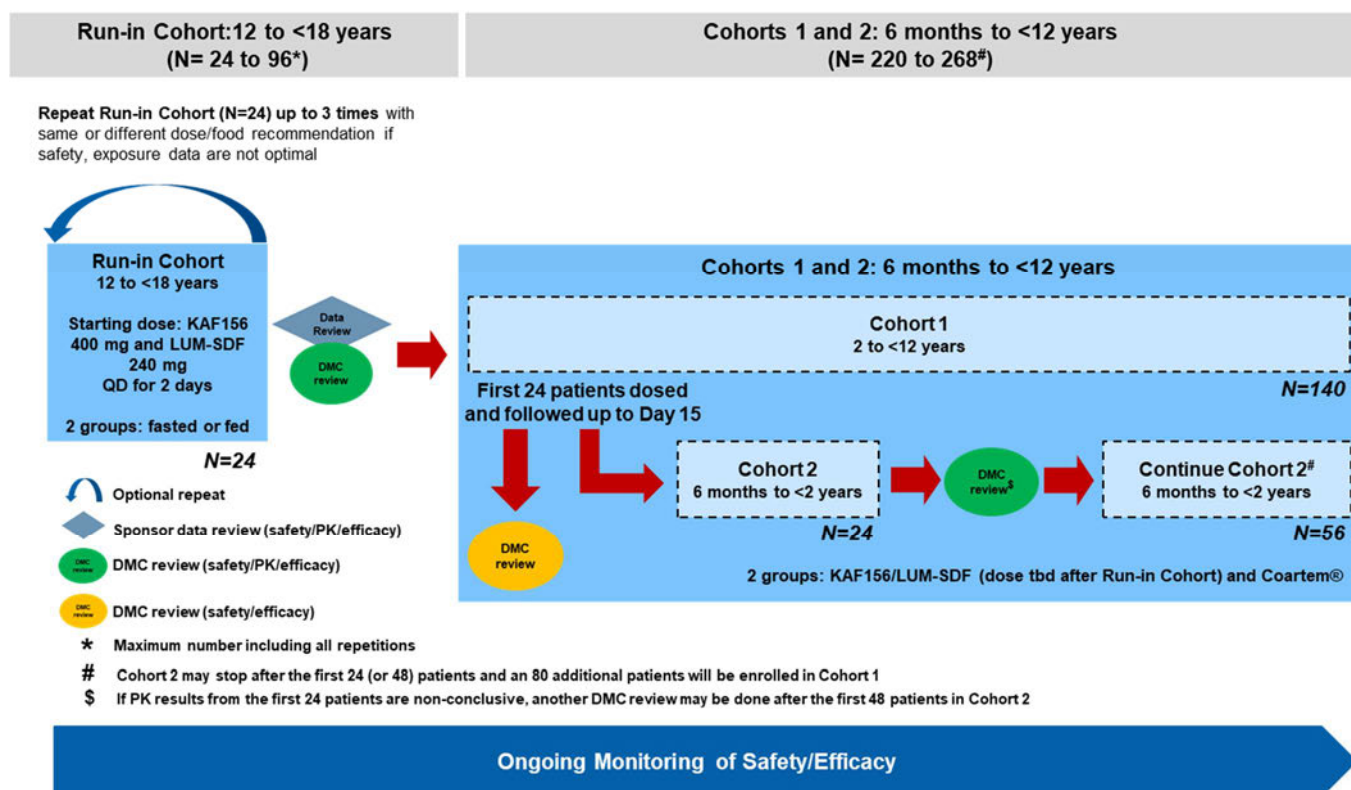
The following Data Review checks are planned:

- Run-in Cohort:** Once the first 24 patients (approximately 12 patients of each treatment group) from the age group 12 to < 18 years have been dosed and followed up to Day 15.
  - If the dose is deemed optimal in the first 24 adolescent patients under fed or fasted conditions (based on safety, treatment efficacy and PK data review as available), then patients from the age group 2 to < 12 years will be randomized (Cohort 1).
  - If the dose is not optimal, then additional 24 patients will be treated. This can be repeated up to three times, using a different dose level or food intake for fed patients

- (as specified in [Section 6.7.2](#)) until an optimal dose or food recommendation are determined. These repeats could also be done with same dose level or food intake in case confirmation is required. Then patients from the age group 2 to < 12 years will be randomized (Cohort 1).
- There will be no enrollment during the Sponsor Data Review and DMC Review (safety, treatment efficacy and PK data). Patient randomization in Cohort 1 will start after an optimal dose and food recommendation are confirmed.
2. **Cohort 1:** Once optimal dose, dosing regimen and food recommendation are confirmed in the Run-in Cohort, 140 patients from the age group 2 to <12 years old will be randomized either to KAF156/LUM-SDF combination group or to the Coartem<sup>®</sup> control group in a 1:1 ratio.
- When the first 24 patients (targeted 12 patients in each treatment group) from the age group 2 to < 12 years are dosed and followed up to Day 15,
  - DMC review (safety and efficacy) of the first 24 patients in Cohort 1 will be done in parallel to completing enrollment in the cohort.
  - randomization of patients aged 6 months to < 2 years in Cohort 2 can start in parallel to the DMC review and in parallel to completing enrollment in Cohort 1
  -
3. **Cohort 2:** Once the first 24 patients (targeted 12 patients in each treatment group i.e., KAF156/LUM-SDF and Coartem<sup>®</sup>) from the age group 6 months to < 2 years have been dosed and followed up to Day 15.
- If the KAF156/LUM-SDF dose is deemed optimal in the first 12 patients from the age group 6 months to 2 years (based on safety, PK, and efficacy data review as available), then the remaining cohort will be randomized so that there are approximately 80 treated patients aged 6 months to < 2 years old.
  - In case results (PK, safety and efficacy data) from the initial 24 patients are non-conclusive, another DMC review may be scheduled after the first 48 patients of Cohort 2 have been dosed and followed up to Day 15.
  - If the dose is not optimal (based on safety, PK and efficacy data review as available), the enrollment for this cohort will be terminated. The 80 patients allocated to Cohort 2 will be re-allocated to Cohort 1.
  - There will be no enrollment during the DMC Review. Patient randomization in Cohort 2 will start again after the dose is confirmed.

The study design, procedures and assessments are the same in all cohorts. PK and ECG assessments for the different treatment groups are shown in the different table of assessments (for Run-in Cohort see [Table 8-1](#); for Cohorts 1 and 2 see [Table 8-2](#) for a 2-day KAF156/LUM-SDF treatment or [Table 8-3](#) for a 3-day KAF156/LUM-SDF treatment). The study design allows for the randomization of up to an additional 72 patients in the Run-in Cohort, therefore, the resulting sample size may vary from approximately 24 to 96 for the Run-in Cohort. Patients treated with a non-optimal dose will also be closely followed up to Day 43. Considering the study dynamics of optional repeats of Run-in Cohort and optional additional Cohort 1 patients (in case of Cohort 2 early termination), the actual overall study sample size may vary between approximately 244 and 364 patients

**Figure 3-2 Study Design**



## 4 Rationale

### 4.1 Rationale for study design

This will be a multicenter, open-label, randomized, parallel-group, non-inferiority (NI) study in a pediatric population with uncomplicated *P. falciparum* malaria. The study has a Run-in Cohort of adolescent patients and a main part in two age-descending cohorts of younger pediatric patients.

The use of a combination regimen with at least two drugs for anti-malaria therapy is well established and recommended by the World Health Organization (WHO 2019). There is an unmet medical need for (i) anti-malarial treatments with new mechanisms of action to cure multi-drug resistant infections and to reduce the probability of rapidly selecting cross-resistant parasites, and (ii) shortened treatment regimens and/or reduced frequency of dosing.

The main objective of this study is to assess efficacy, safety and PK of the combination of KAF156 and LUM-SDF in children aged 6 months to < 12 years of age by demonstrating the NI of the combination of KAF156 and LUM-SDF against Coartem®, a standard of care (SoC) using PCR-corrected ACPR rate at Day 29. The NI margin has been set to 10%. A secondary objective is to investigate the food effect in lumefantrine PK in terms of fold increase for fed vs fasted conditions for treatment of uncomplicated malaria caused by *P. falciparum* in patients 12 to < 18 years old in Run-in Cohort.

Rationale for study design is summarized in the table below.

**Table 4-1 Rationale for study design**

Study Design Aspect	Rationale
Multicenter	To enroll a diverse patient population
Run-in Cohort of adolescent patients followed by 2 sequential age-descending cohorts in children	To investigate food effect on lumefantrine exposure and determine optimal dose in adolescent patients (12 to < 18 years) before going to children population (6 months to < 12 years). Age descending cohorts (2 to < 12 years and 6 months to < 2 years) ensures that the lower age group cohorts are exposed to treatment only after drug exposure and treatment dose from the previous higher age cohort are confirmed to be acceptable.
Randomized	To reduce the risk of selection bias and also the risk of unequal distribution between 2 arms (fasted and fed patients in the Run-in Cohort; KAF156/LUM-SDF and Coartem® in Cohorts 1 and 2)
Open-label	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
Non-inferiority (NI)	Non-inferiority setting will provide the opportunity to perform head-to-head comparison between a KAF/LUM regimen against Coartem®. Generally, NI margin is selected based on the placebo adjusted treatment effect of the SoC as well as the clinical judgement. However, placebo-adjusted treatment effect for Coartem® in terms of PCR-corrected ACPR at Day 29 is not available. 10% NI margin in PCR corrected ACPR at Day 29 is based on clinical judgement as a NI margin of 10% to 12.5% is commonly used in other infection diseases (e.g., FDA 2018 guidance for Complicated Urinary Tract Infections, FDA 2020 guidance for Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia, EMA 2014 Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections, etc.)
Patient participation will be for 43 days	The design of the follow-up (up to Day 43) within each cohort is well established for malaria trials and follows WHO guidelines.
Data review check	Safety, efficacy, and pharmacokinetic exposure check for Run-in and Cohort 2 and safety and efficacy check for Cohort 1 after a limited number of patients (24 patients in each cohort) is instigated to minimize the risk to a larger group of patients. Safety and efficacy data review, as well as exposure above or below a safe and effective range may trigger reduction or increase of the dose.
Stratification	Randomization is stratified by country for the first 24 patients in the Run-in cohort, by age group (6 to < 12 years and 2 to < 6 years) and country in Cohort 1, and by country in Cohort 2 to achieve the equal treatment allocation within age group/a country.

## 4.2 Rationale for dose/regimen and duration of treatment

The doses and regimens of KAF156 combined with LUM-SDF were selected based on expected exposure, efficacy/safety outcomes, known food effect of LUM-SDF and supported by clinical as well as pre-clinical data.

The starting dose to be assessed in the Run-in Cohort of adolescent patients will be KAF156 400 mg combined with LUM-SDF 240 mg QD for 2 days.

Treatment group will be assigned based on food recommendation

- KAF156 400 mg combined with LUM-SDF 240 mg QD for 2 days in fasted patients
- KAF156 400 mg combined with LUM-SDF 240 mg QD for 2 days in fed patients

A range of doses and regimens of KAF156 combined with LUM-SDF were assessed in a Phase 2b study (CKAF156A2202) under fasting condition. Outcomes of the interim assessment of this dose finding study showed that single dose of 400 mg KAF156 with 960 mg LUM-SDF under fasting condition demonstrated polymerase chain reaction (PCR)-corrected ACPR at Day 29 of > 90% with lower limit of 2-sided 95% CI >80%. Also, with increasing dose and the duration of treatment (i.e., 2 days and 3 days) a higher ACPR was observed and safety and tolerability were not compromised.

Based on preliminary exposure-response analysis of CKAF156A2202 study data it was determined that lumefantrine Day 8 concentrations correlate with PCR-corrected ACPR<sub>29</sub>. Preliminary data from an ongoing relative bioavailability study in healthy volunteers (LUM566X2102) showed that lumefantrine exposure was around 3-7 fold higher depending on food type (6-7 fold with standard diet and 3-4 fold with whole milk). This food effect is expected to be lower in patients. Nevertheless, if the KAF156 / LUM-SDF combination is administered with food there is a potential for achieving higher lumefantrine exposure than under fasting condition.

In this study, CKAF156A2203, a two day treatment of 400 mg KAF156 and 240 mg LUM-SDF (adult dose) has been selected as the starting dose in the Run-in Cohort. This dose is expected to result in high PCR-corrected ACPR at Day 29 with or without food (also supported by preliminary exposure response modeling). After the first 24 patients in the Run-in Cohort have been dosed and followed up to Day 15, the dose (and food intake in the fed arm) may be adjusted to achieve optimal exposures for safety and efficacy. In Cohorts 1 and 2, the selected doses of KAF156 and LUM-SDF will be adapted for body weight as detailed in [Section 6.1.3](#). The data from this study CKAF156A2203 together with the data from the ongoing Phase 2b study CKAF156A2202, where treatments are given under fasting condition, are expected to provide sufficient information to characterize the exposure-response relationship for ACPR<sub>29</sub> and to inform the selection of the dose/regimen for benefit/risk assessment in Phase 3 and beyond.

The weight bands for dose adjustment are mainly based on clinical recommendation for Coartem<sup>®</sup> which contains lumefantrine. KAF156 and LUM-SDF would eventually be a fixed dose combination and therefore the ratio of KAF156 and LUM-SDF will be kept the same across the weight bands unless clinical data suggest otherwise. KAF156, like lumefantrine, is metabolized predominantly by CYP3A4 and there is no additional data suggesting that KAF156 will behave significantly different in this study's population; additionally in study CKAF156A2202, KAF156 was dosed in patient >2 years under fasting conditions using the weight bands proposed in this study.

In Cohorts 1 and 2, the efficacy of KAF156 combined with LUM-SDF will be assessed by demonstrating its non-inferiority to Coartem<sup>®</sup>. Coartem<sup>®</sup> will be administered with food and doses will be based on patient's body weight as per product label.

#### **4.3 Rationale for choice of control drugs (comparator/placebo)**

The control treatment used in Cohorts 1 and 2 of this study is Coartem<sup>®</sup>, the artemisinin-based combination therapy artemether-lumefantrine. Coartem<sup>®</sup> is widely used for *P. falciparum* malaria and has a well-characterized safety and efficacy profile ([Hamed and Grueninger 2012](#)).

In addition, Coartem<sup>®</sup> contain the same partner drug as in the current study (lumefantrine). For these reasons, Coartem<sup>®</sup> is considered the appropriate comparator treatment for this study.

#### 4.4 Purpose and timing of interim analyses/design adaptations

There will be no formal interim analysis, but the following interim assessments (DMC Review) are planned in order to minimize risks for this vulnerable patient population. Additional DMC Review may be conducted during the study as deemed necessary.

- 1) In the Run-in Cohort, once the first 24 adolescent patients (approximately 12 patients in each treatment group) from the age group 12 to < 18 years have been dosed and followed up to Day 15.
- 2) In Cohort 1, once the first 24 patients (approximately 12 patients of each treatment group) from the age group 2 to < 12 years have been dosed and followed up to Day 15.
- 3) In Cohort 2, once the first 24 patients (approximately 12 patients of each treatment group) from the age group 6 months to < 2 years have been dosed and followed up to Day 15.
- 4) Optional: In Cohort 2, once the first 48 patients (approximately 24 patients of each treatment group) from the age group 6 months to < 2 years have been dosed and followed up to Day 15 in case PK results from the initial 24 patients are non-conclusive.

Note: additional DMC review will be conducted if the first 24 patients are repeated in Run-in cohort or in case of special safety observations. The interim assessments in the Run-in Cohort including repeats will be reviewed by Sponsor first (Data Review) followed by DMC.

#### 4.5 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. In particular, interim results of a recent study (CKAF156A2202 Interim Assessment) in 349 acute malaria patients  $\geq 12$  years, showed that the combination of KAF156 and LUM-SDF achieved parasite clearance at Day 29 in > 90% of patients with safety/tolerability comparable to control (artemether-lumefantrine). 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.

In this 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 ETF (see [Section 6.2.3](#)), recrudescence or new infection will be managed with standard-of-care pharmacotherapy. This may minimize the likelihood of resistance emergence or spread. [REDACTED]

Appropriate patient eligibility criteria and specific stopping rules are included in the protocol.

[REDACTED]

Only after food effect on lumefantrine exposure is investigated in 24 (and potentially up to 96) adolescent patients aged 12 to < 18 years will the study treatment be assessed in younger population. The assessment of the data will be through Sponsor Data Review of the Run-in Cohort (including safety and drug exposure as available) and DMC Review.

Only after the first 24 patients aged 2 years to < 12 years (approximately 12 patients of each treatment group) have been dosed and followed up to Day 15 will the lower aged patients from 6 months to < 2 years be dosed.

In addition, only after DMC Review of the first 24 patients aged 6 months to < 2 years (approximately 12 patients of each treatment group) will additional patients in that age group be dosed.

Safety and efficacy data from study CKAF156A2202 with KAF156/LUM-SDF in children 2 to <12 years treated under fasting condition will be available before the start of Cohort 1. This data will support the dose selection for Cohort 1.

#### **4.6 Rationale for Public Health Emergency mitigation procedures**

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure patient safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

### **5 Population**

The study population will consist of male and female patients (Run-in Cohort: 12 to < 18 years old and  $\geq 35.0$  kg; Cohort 1: 2 to < 12 years old and  $\geq 10.0$  kg; Cohort 2: 6 months to < 2 years old, weight  $\geq 5.0$  kg) with confirmed uncomplicated *P. falciparum* malaria. In the Run-in Cohort, patients will have malaria symptoms and *P. falciparum* counts of  $\geq 1,000$  and  $\leq 150,000$  parasites/ $\mu$ L at pre-screening. In Cohort 1 and Cohort 2, patients will have malaria symptoms and *P. falciparum* counts of  $\geq 1,500$  and  $\leq 150,000$  parasites/ $\mu$ L at pre-screening. Approximately 244 patients will be enrolled with a potential of enrolling up to 364 patients if there is a need to repeat enrollment of the Run-in Cohort and if Cohort 2 stops early after the DMC review.

#### **5.1 Inclusion criteria**

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

1. In Run-in Cohort: Male and female patients 12 to < 18 years of age, with a body weight  $\geq 35.0$  kg  
In Cohort 1: Male and female patients 2 to < 12 years of age, with a body weight  $\geq 10.0$  kg  
In Cohort 2: Male and female patients 6 months to < 2 years of age, with a body weight  $\geq 5.0$  kg
2. Microscopic confirmation of *P. falciparum* by Giemsa-stained thick and thin films

3. *P. falciparum* parasitemia of  $\geq 1,000$  and  $\leq 150,000$  parasites/ $\mu\text{L}$  at the time of pre-screening for the Run-in Cohort; and *P. falciparum* parasitemia of  $\geq 1,500$  and  $\leq 150,000$  parasites/ $\mu\text{L}$  at the time of pre-screening for Cohorts 1 and 2
4. Axillary temperature  $\geq 37.5$  °C or oral/tympanic/rectal temperature  $\geq 38.0$  °C; or history of fever during the previous 24 hours (at least documented verbally)
5. Written informed consent has been obtained from parent / legal guardian before any assessment is performed. If the parent/legal guardian is unable to read and write, then a witnessed consent according to local ethical standards is permitted. Patients who are capable of providing assent, must provide assent with parental/legal guardian consent or as per local ethical guidelines
6. The patient and his/her parent/legal guardian is able to understand and comply with protocol requirements, instructions and protocol-stated restrictions and is likely to complete the study as planned

## 5.2 Exclusion criteria

Patients meeting **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.

1. Mixed *Plasmodium* infections as per light microscopy results
2. Signs and symptoms of severe malaria according to [WHO 2015](#) (see [Section 16.4](#))
3. Significant, non-plasmodial co-infections including tuberculosis
4. Patients with concurrent febrile illnesses (e.g., typhoid fever, known or suspected COVID19)
5. 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
6. Major congenital defects
7. Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection or family history of congenital or hereditary immunodeficiency
8. Immunosuppressive therapy (steroids, immune modulators or immune suppressors) within 3 months prior to recruitment. (For corticosteroids, this will mean prednisone, or equivalent,  $\geq 0.5$  mg/kg/day. Inhaled and topical steroids are allowed)
9. Repeated 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 in the 24 hours prior to inclusion in the study)
10. Active duodenal ulcer, ulcerative colitis, Crohn's disease, chronic (i.e.,  $> 2$  weeks) use of non-steroidal anti-inflammatory drugs (NSAIDs)
11. Clinically relevant abnormalities of electrolyte balance which require correction, e.g., hypokalemia, hypocalcemia or hypomagnesemia
12. Anemia (hemoglobin level  $< 7$  g/dL)
13. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs (e.g., HIV patients on ART therapy or TB patients on treatment), 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:

- $AST/ALT > 3 \times$  the upper limit of normal range (ULN), regardless of the level of total bilirubin
  - $AST/ALT > 1.5$  and  $\leq 2 \times$  ULN and total bilirubin is  $> ULN$
  - Total bilirubin  $> 2 \times$  ULN regardless of the level of AST/ALT
14. Resting QT interval corrected by Fridericia's formula (QTcF)  $> 450$  ms at screening
  15. Creatinine  $> 2 \times$  ULN in the absence of dehydration. In case of dehydration, creatinine should be  $< 2 \times$  ULN after oral/parenteral rehydration
  16. Any severe disease condition which might prohibit participation in this study
  17. Known chronic underlying disease such as sickle cell disease, and severe cardiac, renal, or hepatic impairment
  18. Known active or uncontrolled thyroid disease
  19. Inability to swallow oral medication (in tablet and/or liquid form)
  20. 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)
  21. Use of other investigational drugs within 30 days of dosing or until the expected pharmacodynamic effect has returned to baseline, whichever is longer
  22. Patients taking medications prohibited by the protocol
  23. Previous participation in any malaria vaccine study or received malaria vaccine in any other circumstance within 3 months of dosing
  24. 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
  25. Use of agents known to prolong the QT interval unless it can be permanently discontinued for the duration of study
  26. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes

**For the Run-in Cohort only:**

27. Pregnant or nursing (lactating) patients
28. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing of investigational drug. Basic 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 m prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps).
- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS)

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 not of child bearing potential if they 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.

**For Cohorts 1 and 2 only:**

29. Patients of child bearing potential, defined as all girls post first menarche (except for Run-in Cohort)

## **6 Treatment**

### **6.1 Study treatment**

Novartis will supply the following Investigational products as open-label patient-specific supplies.

- KAF156 50 mg and 100 mg (tablets in bottles)
- LUM-SDF 60 mg, 120 mg and 240 mg (powder in sachets)
- Coartem<sup>®</sup> 20/120 mg (dispersible tablets in blister pack) (for Cohorts 1 and 2)

New strengths may need to be considered as per cohort requirement.

#### **6.1.1 Investigational and control drugs**

**Table 6-1 Investigational and control drug**

<b>Investigational/ Control Drug (Name and Strength)</b>	<b>Pharmaceutical Dosage Form</b>	<b>Route of Administration</b>	<b>Supply Type</b>	<b>Sponsor (global or local)</b>
KAF156 50 mg	Tablet	Oral	Open label patient packs; bottles	Sponsor (global)
KAF156 100 mg	Tablet	Oral	Open label patient packs; bottles	Sponsor (global)
LUM-SDF (LUM566) 60 mg	Powder	Oral	Open label patient packs; sachets	Sponsor (global)

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
LUM-SDF (LUM566) 120 mg	Powder	Oral	Open label patient packs; sachets	Sponsor (global)
LUM- SDF (LUM566) 240 mg	Powder	Oral	Open label patient packs; sachets	Sponsor (global)
Coartem® 20/120 mg	Dispersible tablet	Oral	Open label; blister pack	Sponsor (global)

### 6.1.2 Additional study treatments

No other treatment beyond the investigational drug and control drug are included in this trial.

### 6.1.3 Treatment arms/group

Patients will be assigned to one of the 2 treatment groups in a ratio of 1:1 per cohort as follows:

- The starting dose of KAF156 and LUM-SDF for the Run-in Cohort (12 to < 18 years) will be as per Table 6-2. After the Run-in Cohort, a dose and food recommendation will be selected for children < 12 years old.
- Children in Cohorts 1 and 2 (Cohort 1: 2 to < 12 years; Cohort 2: 6 months to < 2 years) who are randomized to KAF156 and LUM-SDF combination will take a proportion of the selected dose per weight group as in Table 6-3.
- Children in Cohorts 1 and 2 (Cohort 1: 2 to < 12 years; Cohort 2: 6 months to < 2 years) who are randomized to Coartem® will take a proportion of the selected dose per weight group as in Table 6-4.

**Table 6-2 KAF156 and LUM-SDF starting dosing scheme in the Run-in Cohort**

Group	Treatment*	Dosing Regimen
1	KAF156 400 mg & LUM-SDF 240 mg Fasted	QD 2 Days
2	KAF156 400 mg & LUM-SDF 240 mg Fed (standard meal)	QD 2 Days

\*The above "full" doses are for patients with a body weight ≥35kg

**Table 6-3 Cohorts 1 and 2: KAF156 and LUM-SDF dosing per weight**

Weight Range	KAF156 and LUM-SDF
≥ 35 kg	full dose QD
25 to < 35 kg	0.75 of the full dose QD
15 to < 25 kg	0.50 of the full dose QD
5 to < 15 kg	0.25 of the full dose QD

**Table 6-4 Cohorts 1 and 2: Coartem® dosing per weight**

	Artemether/Lumefantrine
≥ 35 kg	80/480 mg BID
25 to < 35 kg	60/360 mg BID
15 to < 25 kg	40/240 mg BID
5 to < 15 kg	20/120 mg BID

#### **6.1.4 Treatment duration**

The duration of the treatment with KAF156/LUM-SDF will be two days (once daily/QD) for an individual patient in the Run-in Cohort.

The duration of treatment with KAF156/LUM-SDF in Cohorts 1 and 2 will be either two days or three days once daily/QD, depending on the outcome of the of the Run-in Cohort and KAF156A2202 study.

Coartem® will be given twice a day (BID) for three days as per the product label.

#### **6.2 Other treatment(s)**

No additional treatment beyond investigational drug is included in this trial.

Rescue medication can be provided by the investigator according to local practices. Lumefantrine-including treatment should preferably be avoided if the patient requires therapy for ETF ([Section 6.2.3](#)).

##### **6.2.1 Concomitant therapy**

Prior medications are defined as drugs taken and stopped prior to the 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 study medication and the last day of study visit (including those which were started pre-baseline and continued into the treatment period or follow-up 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 to the first dose, it has to be reported as prior medication.

Metoclopramide is contraindicated from the period prior to the 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 antibiotics, new-quinolones included, with anti-malarial activity should be prohibited.

The investigator must instruct the patient (or parent/legal guardian) 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 before allowing a new medication to be started.

## 6.2.2 Prohibited medication

### 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 who has developed ETF or late treatment failure or failed to respond to standard-of-care. Lumefantrine-including treatments should be avoided as therapy for ETF, unless there is no alternative.
- **Drugs 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.*

### Drug with potential for pharmacokinetic interaction:

- **Drugs/supplements impacting KAF156 and lumefantrine / Coartem<sup>®</sup> exposure:** Drugs or supplements which are known CYP3A inhibitors (e.g., erythromycin, ketoconazole, itraconazole, cimetidine) or CYP3A inducers (e.g. rifampin, phenobarbital, St John's wort) etc. should not be used during study and within 14 days prior to dosing.
- **Drugs/Supplements which can be impacted by KAF156 and lumefantrine/Coartem<sup>®</sup>:** 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 6-5](#) 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 6-5 Prohibited Medications**

CYP Enzymes/transporter	Sensitive substrates <sup>a</sup>	Substrates with narrow therapeutic range <sup>b</sup>
<b>CYP2D6</b>	Atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine	Thioridazine, neuroleptics, flecainide, metoprolol, and tricyclic antidepressants such as imipramine, amitriptyline, clomipramine
<b>CYP3A</b>	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
<b>CYP2B6<sup>c</sup></b>	Bupropion, efavirenz	
<b>CYP2C8</b>	Repaglinide <sup>d</sup>	Paclitaxel
<b>CYP2C9</b>	Celecoxib	Warfarin, phenytoin
<b>OATP1B1</b>	Bosentan, pravastatin	
<sup>a</sup> Sensitive CYP substrates refers to drugs whose plasma area under the curve (AUC) values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor. <sup>b</sup> 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). <sup>c</sup> 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. <sup>d</sup> 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, clindamycin, etc.), with the exception of the use of topical antibiotics, the patient will be followed up until the end of the study.

For the period specified, use of the treatments in [Table 6-4](#) is not allowed in:

- patients
- the persons providing breast milk to the patients (if the prohibited drug is known to be secreted significantly in breastmilk)

These restrictions result from potential confounding of efficacy or from drug interactions.

### 6.2.3 Rescue medication

The following circumstances warrant discontinuation of study treatment and the implementation of rescue medication:

#### Early Treatment Failure (ETF)

- Development of danger signs or severe malaria on Day 2, Day 3, Day 4 in the presence of parasitemia.
- Parasitemia on Day 3 higher than Day 1 count irrespective of axillary temperature
- Parasitemia on Day 4 with axillary temperature  $\geq 37.5^{\circ}\text{C}$
- Parasitemia 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 parasitemia without previously meeting any of the criteria of ETF
- Presence of parasitemia and axillary temperature  $\geq 37.5^{\circ}\text{C}$  on any day from Day 5 to Day 43 without previously meeting any of the criteria of ETF.

#### Late Parasitological Failure (LPF)

- Presence of parasitemia on any day from Day 8 to Day 43 and axillary temperature  $< 37.5^{\circ}\text{C}$  without previously meeting any of the criteria of ETF or LCF.

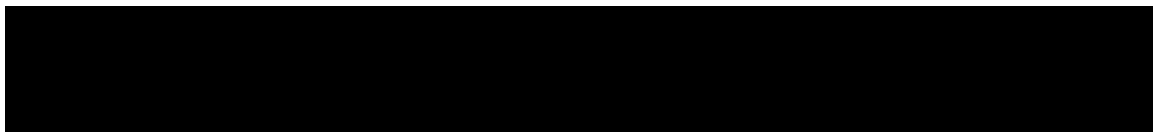
Patients having signs/symptoms of hypersensitivity after the first dose should not be administered with the second dose.

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 the start of trial medications and up to Day 43 as deemed necessary by the investigator. Lumefantrine-including treatment should preferably be avoided if the patient requires therapy for 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 these patients 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 medication 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 the start of study drug.

### **6.3 Patient numbering, treatment assignment, randomization**

#### **6.3.1 Patient numbering**

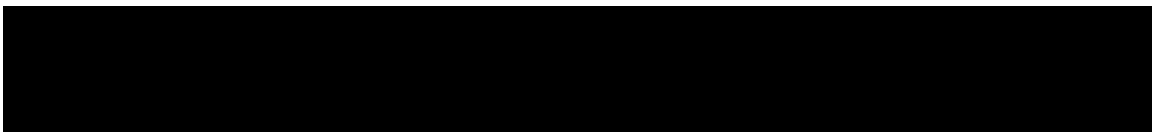
Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient is first enrolled for pre-screening, and is retained as the primary identifier for the patient throughout his/her participation in the trial. The Patient No. consists of the Center Number (assigned by Novartis to the investigative site) with a sequential patient number suffixed to it (assigned by the investigator), so that each patient is numbered uniquely across the entire database. Upon signing the pre-screening informed consent form, the patient is assigned by the investigator to the next sequential Patient No. available. Once assigned to a patient, the Patient Number will not be reused. The site must select the case report/record form (CRF) book with a matching Patient Number from the electronic data capture (EDC) system to enter data.

If the patient fails to be treated for any reason, the Interactive Response Technology (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 Phase Study Disposition CRF.

#### **6.3.2 Treatment assignment, randomization**

All eligible patients will be randomized via Interactive Response Technology (IRT) to one of the 2 treatment groups of each cohort. 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 group and will specify medication number(s). The medication number(s) and the appropriate dose for each medication will be communicated to the caller so that the corresponding investigational drug(s) can be dispensed to the patient. The dose level of a treatment group may be adjusted after the first 24 patients in the Run-in cohort have been dosed. Once the dose level has been adjusted, it becomes a different treatment group and the randomization for the cohort will re-start using the adjusted treatment groups.

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 (fed or fasted in Run-in Cohort and KAF156 and LUM-SDF combination or Coartem<sup>®</sup> in Cohorts 1 and 2), which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supplies team using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug. The IRT will also inform the food condition (fed or fasted) for each patient to the site in the Run-in Cohort.



Study will use country and age group as strata:

Run-in Cohort will be stratified by country; Cohort 1 will be stratified by age group (6 to < 12 and 2 to < 6 years) and country; and finally, Cohort 2 will be stratified by country.

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

## **6.4 Treatment blinding**

This study is randomized and open label. Treatment and food condition during the Run-in cohort will be open to patients/patients' parents/legal guardian, investigators staff and study monitors, as well as to the Clinical Trial Team (CTT) to allow continuous review of safety, drug exposure and efficacy data in pediatric population. However, since the primary and secondary objectives of the trial are mainly based on laboratory assessments, this should not bias the efficacy and the safety endpoint assessments. In order to minimize the potential impact of treatment knowledge, treatment allocation and PK concentration, the CTT (particularly clinicians, statisticians, programmers) will not assess aggregate data by treatment prior to the scheduled data review/DMC review checks and final analysis. Thereafter during Cohorts 1 and 2, treatment/food condition will be open to patients/patients' parents/legal guardian, investigators staff and study monitors but will be blinded to the Clinical Trial Team (CTT). If necessary, the pharmacokineticist will be unblinded for PK/drug exposure data only. Further details on data handling are documented in the appropriate data handling plan (DHP)/data management plan (DMP).

Summaries of safety and efficacy results by treatment arm will be prepared only for Data Review checks (see [Section 3](#)) and additional Data Monitoring Committee (DMC) assessments.

## **6.5 Dose escalation and dose modification**

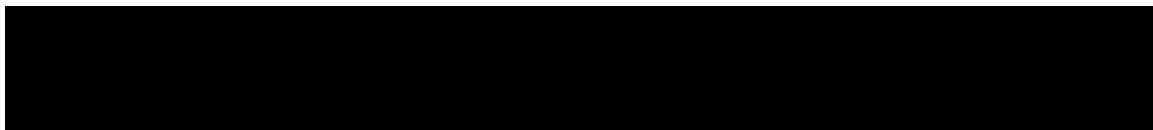
No dose adjustments other than according to body weight group as described above (see [Section 6.1.3](#)) are permitted. No intra-patient dose modification is allowed. However, dose can be adjusted following Sponsor Data Review check and DMC Review (safety, drug exposure and efficacy data as available) of the Run-in Cohort.

Patients who vomit within 1 hour of trial drug administration will be given a replacement dose, and IRT must be notified (see [Section 6.7.2](#)).

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

### **6.5.1 Dose modifications**

Dose will be adjusted according to body weight as described above (see [Section 6.1.3](#)). In addition, the dose may be adjusted following Sponsor Data Review check and DMC Review (safety, drug exposure and efficacy data as available) of the Run-in Cohort. No other dose adjustments than described above are permitted.



## **6.6 Additional treatment guidance**

### **6.6.1 Treatment 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.

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 dose 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.

### **6.6.2 Emergency breaking of assigned treatment code**

Not applicable since this is an open-label study

## **6.7 Preparation and dispensation**

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 or other such relevant document) for that patient's unique patient number.

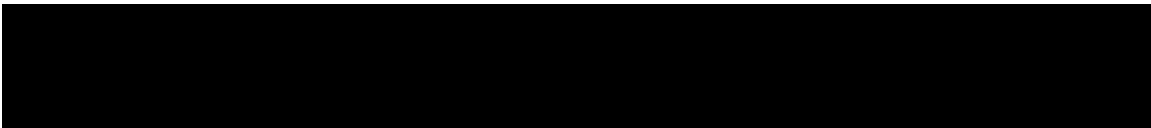
If a patient vomits study drugs within 1 hour of intake, a replacement dose will be given to the patient and the investigator or designee will notify IRT.

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

### **6.7.1 Handling of study treatment and additional treatment**

#### **6.7.1.1 Handling of study treatment**

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



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

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

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

#### **6.7.1.2 Handling of additional treatment**

No additional treatment other than the investigational study drug is required per protocol.

#### **6.7.2 Instruction for prescribing and taking study treatment**

##### **KAF156 and LUM-SDF**

Patients will take the KAF156 and LUM-SDF according to the assigned dose level and dosing regimen of the KAF156 and LUM-SDF combination.

LUM-SDF will be given as a dispersible powder directly in the mouth 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 some water. Administration of LUM-SDF and KAF156 must be done under study staff supervision.

Each patient's mouth must be examined to verify 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 alternative treatment preferably not containing lumefantrine.

Patients who will be administered treatment under fasting condition should be fasted at least 4 hours before and 4 hours after KAF156/LUM-SDF administration. However, these patients can receive non-fatty liquids such as orange juice prior to 1 hour of dosing and 1 hour after dosing. All food intake has to be recorded appropriately. Water can be provided ad-libitum.

Patients who will be administered treatment with food should have food within 30 min (preferably prior to dose) of dose administration.

Patients in the Run-in Cohort who have been randomized to the Fed group should consume food containing 400-500 calories and 20-30 g of fat (standard meal).

This recommendation for food may be adapted based on the evaluation of the food effect in the Run-in Cohort. Such change will be based on the observed C<sub>max</sub> of lumefantrine. All investigators will be informed in case of an adaptation in food recommendation.

## 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 6-4](#).

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.

For all treatment groups, food intake information will be collected only on each dosing day, i.e., time of last food intake before dosing, time of the 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 < 100 calories, ~ 1 g of fat)
4. Light meal (estimate of 100-300 calories, 5-10 g of fat)
  - 4a. ~250 mL of whole milk
  - 4b. Breastfed/formula milk
  - 4c. Porridge
  - 4d. Pancake
  - 4e. Other
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)

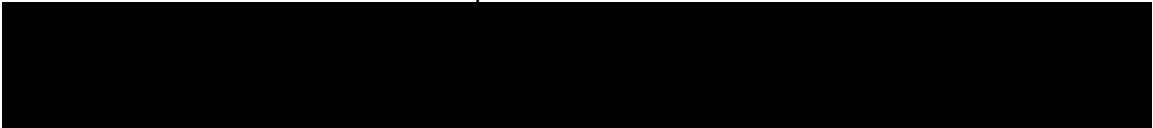
A low fat vehicle such as orange juice may be used for drug administration in children who are unable to take the medication normally with water.

## 7 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent or, if applicable after such consent has been provided by a legally acceptable representative(s) of the patient.

If applicable, in cases where the patient's representative(s) gives consent (if allowed according to local requirements), the patient must be informed about the study to the extent possible given his/her level of understanding. If the patient is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

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 International Conference on Harmonization (ICH) E6 GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's 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 investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the patient.

The following informed consent forms (ICFs) are included in the study:

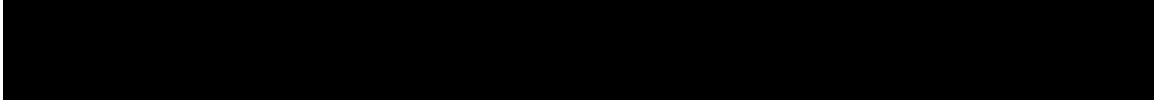
1. Pre-screening parental ICF
2. Pre-screening assent (for ages 7 to <18 years)
3. Main short parental / legal guardian ICF
4. Main child assent form (for ages 7 to < 12 years)
5. Main adolescent assent form (for ages 12 < 18 years)
6. Main short ICF for participants who turn 18 years old during the course of the study
7. Pregnancy follow up ICF for participants who become pregnant during the course of the study

In addition, there is an ICF guidance form whose purpose is to provide more detailed information to the PI. The PI will use the information for the consenting process with the patient / parent / legal guardian. The patient / parent/legal guardian will be given a copy of the ICF guidance. Patient 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 treatment. If there is any question that the patient will not reliably comply, they must not be entered in the study.

A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

The study includes the option for the patient to have certain study procedures performed off-site by an off-site healthcare professional instead of at the study site. The type of procedures will first need to be discussed with the Sponsor before implementation by the Principal Investigator / site staff. The patient and/or legal guardian will need to provide a separate informed consent signature if they agree to have procedures performed off-site. It is required as part of this protocol that the Investigator presents this option to the patient and/or legal guardian, as permitted by national and local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

As per [Section 4.6](#), during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may



conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Health Authority. Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

## 8 Visit schedule and assessments

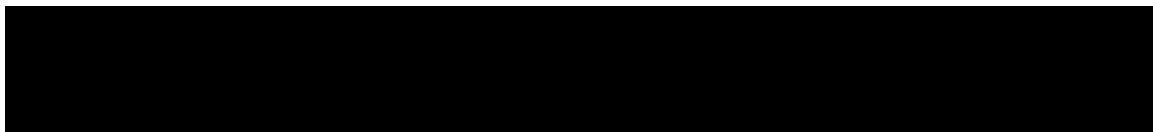
Assessment schedule lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

Patients should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time 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 (EOS) visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

As per [Section 4.6](#), during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing. Sponsor must be consulted before implementation.

Depending on the final KAF156 and LUM-SDF regimen selected for Cohorts 1 and 2, patients would be assessed according to [Table 8-2](#) if KAF156 and LUM-SDF combination is given for 2 days or according to [Table 8-3](#) if KAF156 and LUM-SDF combination is given for 3 days.

The “X” in the table of assessments below denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The “S” in the table denotes the assessments that are only in the participant’s source documentation and do not need to be recorded in the clinical database.

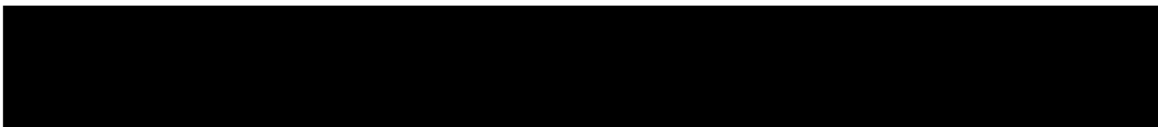


**Table 8-1 Assessment Schedule for the Run-in Cohort (treatment groups: KAF156/LUM-SDF QD for 2 days in fed and fasted patients)**

Period	Screening		Treatment																Follow-up	
Visit Name	Pre-Screening	Screening	Day 1								Day 2								Day 3	Day 4
Days	-1	-1	1								2								3	4
Time (post-dose)	-	-	0h	1h	3h	4h	5h	6h	8h	12h	24h	25h	27h	28h	29h	30h	32h	36h	48h	72h
Pre-screening Informed Consent	X																			
Pre-screening Inclusion criteria	X																			
Demography	X																			
Malaria blood film for asexual parasite counts	X		X					X		X	X							X	X	X
Adverse events			X																	
Contact IRT	X		X								X									
Informed consent		X																		
Inclusion / Exclusion criteria		X																		
Medical history/current medical conditions		X																		
Prior and concomitant medications		X	X								X								X	X
Signs and symptoms of severe malaria		S	S								S								S	S
Physical Examination		S	S								S								S	S
Blood Pressure		X	X								X								X	X
Body Temperature <sup>1</sup>		X	X								X					X		X	X	X

Period	Screening		Treatment																	Follow-up	
Visit Name	Pre-Screening	Screening	Day 1									Day 2								Day 3	Day 4
Days	-1	-1	1									2								3	4
Time (post-dose)	-	-	0h	1h	3h	4h	5h	6h	8h	12h	24h	25h	27h	28h	29h	30h	32h	36h	48h	72h	
Body Height		X																			
Pulse rate		X	X								X								X	X	
Body Weight		X	X								X										
Clinical Chemistry		X									X								X		
Hematology		X									X								X		
Thyroid function		X																			
Urinalysis		X									X								X		
Pregnancy test (Run-in Cohort only) <sup>2</sup>		X																			
Blood sampling for parasite PCR genotyping <sup>3,4</sup>		X									X								X	X	
Drug administration record			X								X										
Meal record			X									X									
PK sampling for Run-in Cohort <sup>3,5,6</sup>		X		X	X	X	X	X	X		X <sup>7</sup>	X	X	X	X	X	X		X	X	
Electrocardiogram (ECG)		X			X			X			X		X			X			X	X	
Overnight Hospital Stay		S	S									S								S	

Period	Follow-up					UNS
Visit Name	Day 5	Day 8	Day 15	Day 29	Day 43 / EOS	UNS
Days	5	8	15	29	43	1 to 43
Time (post-dose)	96h	168h	336h	672h	1008h	-
Pre-screening Informed Consent						
Pre-screening Inclusion criteria						
Demography						
Malaria blood film for asexual parasite counts	X	X	X	X	X	X
Adverse events	X					
Contact IRT	X	X	X	X	X	
Informed consent						
Inclusion / Exclusion criteria						
Medical history/current medical conditions						
Prior and concomitant medications	X	X	X	X	X	X
Signs and symptoms of severe malaria	S	S	S	S	S	S
Physical Examination	S	S	S	S	S	
Blood Pressure	X	X	X	X	X	X
Body Temperature <sup>1</sup>	X	X	X	X	X	X
Body Height						
Pulse rate	X	X	X	X	X	X
Body Weight					X	X
Clinical Chemistry		X		X	X	X
Hematology		X		X	X	X
Thyroid function			X		X	
Urinalysis		X		X	X	X
Pregnancy test (Run-in Cohort only) <sup>2</sup>						
Blood sampling for parasite PCR genotyping <sup>3,4</sup>		X	X	X	X	X



Period	Follow-up					UNS
Visit Name	Day 5	Day 8	Day 15	Day 29	Day 43 / EOS	UNS
Days	5	8	15	29	43	1 to 43
Time (post-dose)	96h	168h	336h	672h	1008h	-
Drug administration record						
Meal record						
PK sampling for Run-in Cohort <sup>3,5,6</sup>		X				
Electrocardiogram (ECG)		X			X	
Overnight Hospital Stay						

<sup>1</sup> Fever monitoring will be done every 6 hours until resolution of fever, defined as being afebrile for 24 hours.

<sup>2</sup> Run-in Cohort: The patient's menstrual and contraceptive history will be taken and a urine  $\beta$ -hCG pregnancy test will be performed at screening to exclude pregnancy and at end of study. Results must confirm negative before dosing.

<sup>3</sup> The number of samples/blood draws and total blood volume collected will remain under the limits recommended in this population ([Howie 2011](#)).

<sup>4</sup> PCR will be used for genotyping to establish malaria recrudescence/reinfection. [REDACTED]. 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.

<sup>5</sup> Also applies to any repeats

<sup>6</sup> a) Further details on sample collection, numbering, processing and shipment can be found in the Laboratory Manual. b) Missed PK sampling time should be taken as soon as possible and actual time should be recorded. For Scheduled time  $\leq 2 \text{ h} \pm 10 \text{ min}$ ;  $2 \text{ to} < 24 \text{ h} \pm 30 \text{ min}$ ;  $\geq 24 \text{ to } 72 \text{ h} \pm 2 \text{ h}$ ;  $> 72 \text{ h} \pm 24 \text{ h}$ .

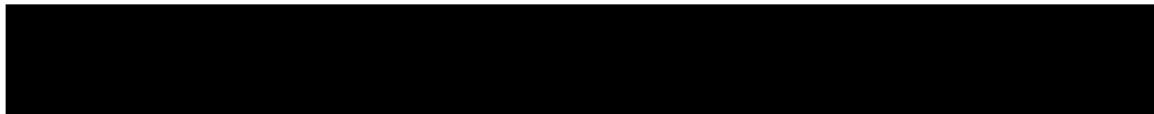
<sup>7</sup> The PK sample at 24 h should be collected prior to the drug administration.



[illegible]

Period	Screening		Treatment																			Follow-up	
Visit Name	Pre-Screening	Screening	Day 1									Day 2								Day 3			Day 4
Days	-1	-1	1									2								3			4
Time (post-dose)	-	-	0h	1h	3h	4h	5h	6h	8h	12h	24h	25h	27h	28h	29h	30h	32h	36h	48h	60h	68h	72h	
Medical history/current medical conditions		X																					
Prior and concomitant medications		X	X									X								X			X
Signs and symptoms of severe malaria		S	S									S								S			S
Physical Examination		S	S <sup>11</sup>								S <sup>11</sup>								S <sup>12</sup>			S	
Blood Pressure		X	X <sup>11</sup>								X <sup>11</sup>								X <sup>12</sup>			X	
Body Temperature <sup>1</sup>		X	X <sup>11</sup>								X <sup>11</sup>					X		X <sup>12</sup>	X <sup>12</sup>			X	
Body Height		X																					
Pulse rate		X	X <sup>11</sup>								X <sup>11</sup>								X <sup>12</sup>			X	
Body Weight		X	X								X												
Clinical Chemistry <sup>13</sup>		X									X <sup>11</sup>								X <sup>12</sup>				
Hematology <sup>13</sup>		X									X <sup>11</sup>								X <sup>12</sup>				
Thyroid function <sup>13</sup>		X																					
Urinalysis		X									X <sup>11</sup>								X <sup>12</sup>				
Blood sampling for parasite PCR genotyping <sup>3,4</sup>			X <sup>11</sup>																				
Drug administration record for KAF156/LUM-SDF			X								X												
Drug administration record for Coartem <sup>®2</sup>			X						X		X							X	X	X			

Period	Screening		Treatment																			Follow-up	
Visit Name	Pre-Screening	Screening	Day 1									Day 2								Day 3			Day 4
Days	-1	-1	1									2								3			4
Time (post-dose)	-	-	0h	1h	3h	4h	5h	6h	8h	12h	24h	25h	27h	28h	29h	30h	32h	36h	48h	60h	68h	72h	
Meal record			X									X								X <sup>2</sup>			
PK sampling for patient ages 6 to <12 years in Cohort 1 dosed with KAF156/LUM-SDF QD for 2 days <sup>3,5,6</sup>					X			X			X <sup>7</sup>		X			X			X			X	
PK sampling for patient ages 2 to <6 years in Cohort 1 and 6 months to <2 years in Cohort 2 dosed with KAF156/LUM-SDF QD for 2 days <sup>3,5,6</sup>								X			X <sup>7</sup>		X			X			X			X	
PK sampling for Coartem <sup>®</sup> arm											X <sup>7</sup>								X <sup>7</sup>		X		
Electrocardiogram (ECG) in patients dosed with KAF156/LUM-SDF QD for 2 days		X									X <sup>10</sup>		X			X			X			X	



Period	Screening		Treatment																				Follow-up
Visit Name	Pre-Screening	Screening	Day 1									Day 2									Day 3		Day 4
Days	-1	-1	1									2									3		4
Time (post-dose)	-	-	0h	1h	3h	4h	5h	6h	8h	12h	24h	25h	27h	28h	29h	30h	32h	36h	48h	60h	68h	72h	
Electrocardiogram (ECG) in patients dosed with Coartem®		X																	X <sup>10</sup>		X		
Overnight Hospital Stay		S	S									S										S	

Period	Follow-up					UNS
Visit Name	Day 5	Day 8	Day 15	Day 29	Day 43 / EOS	UNS
Days	5	8	15	29	43	1 to 43
Time (post-dose)	96h	168h	336h	672h	1008h	-
Pre-screening Informed Consent						
Pre-screening Inclusion criteria						
Demography						
Malaria blood film for asexual parasite counts	X	X	X	X	X	X
Adverse events	X					
Contact IRT	X	X	X	X	X	
Informed consent						
Inclusion / Exclusion criteria						
Medical history/current medical conditions						
Prior and concomitant medications	X	X	X	X	X	X
Signs and symptoms of severe malaria	S	S	S	S	S	S
Physical Examination	S	S	S	S	S	
Blood Pressure	X	X	X	X	X	X
Body Temperature <sup>1</sup>	X	X	X	X	X	X

Period	Follow-up					UNS
Visit Name	Day 5	Day 8	Day 15	Day 29	Day 43 / EOS	UNS
Days	5	8	15	29	43	1 to 43
Time (post-dose)	96h	168h	336h	672h	1008h	-
Body Height					X <sup>9</sup>	
Pulse rate	X	X	X	X	X	X
Body Weight					X	X
Clinical Chemistry <sup>13</sup>		X		X	X	X
Hematology <sup>13</sup>		X		X	X	X
Thyroid function <sup>13</sup>			X		X	
Urinalysis		X		X	X	X
Pregnancy test (Run-in Cohort only) <sup>2</sup>					X	
Blood sampling for parasite PCR genotyping <sup>3,4</sup>		X	X	X	X	X
Drug administration record						
Meal record						
PK sampling for patient ages 6 to <12 years in Cohort 1 dosed with KAF156/LUM-SDF QD for 2 days <sup>3,5,6</sup>		X				
PK sampling for patient ages 2 to <6 years in Cohort 1 and 6 months to <2 years in Cohort 2 dosed with KAF156/LUM-SDF QD for 2 days <sup>3,5,6</sup>		X				
PK sampling for patients dosed with Coartem <sup>®</sup>		X				
Electrocardiogram (ECG) for patients dosed with KAF156/LUM-SDF QD for 2 days		X			X	
Electrocardiogram (ECG) for patients dosed with Coartem <sup>®</sup>		X			X	
Overnight Hospital Stay						

<sup>1</sup> Fever monitoring will be done every 6 hours until resolution of fever, defined as being afebrile for 24 hours.

<sup>2</sup> Cohorts 1 and 2: Comparator only (Coartem<sup>®</sup>). Coartem<sup>®</sup> will be given at 0, 8, 24, 36, 48 and 60 hours. For all drug administrations actual time should be recorded.

<sup>3</sup> The number of samples/blood draws and total blood volume collected will remain under the limits recommended in this population (Howie 2011).

<sup>4</sup> PCR will be used for genotyping to establish malaria recrudescence/reinfection. . At screening, blood

Period	Follow-up					UNS
Visit Name	Day 5	Day 8	Day 15	Day 29	Day 43 / EOS	UNS
Days	5	8	15	29	43	1 to 43
Time (post-dose)	96h	168h	336h	672h	1008h	-

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.

<sup>5</sup> Also applies to any repeats

<sup>6</sup> a) Further details on sample collection, numbering, processing and shipment can be found in the Laboratory Manual. b) Missed PK sampling time should be taken as soon as possible and actual time should be recorded. For Scheduled time  $\leq 2 \text{ h} \pm 10 \text{ min}$ ;  $2 < 24 \text{ h} \pm 30 \text{ min}$ ;  $\geq 24 \text{ to } 72 \text{ h} \pm 2 \text{ h}$ ;  $> 72 \text{ h} \pm 24 \text{ h}$ .

<sup>7</sup> For KAF156/LUM-SDF, the PK sample at 24 h should be collected prior to the drug administration. For Coartem<sup>®</sup>, the PK sample at 24 h and 48 h should be collected prior to the drug administration

<sup>9</sup> Body height will be measured at Study End in Cohort 2 only

<sup>10</sup> For KAF156/LUM-SDF, ECG at 24 h should be performed prior to drug administration. For Coartem, ECG at 48 h should be performed prior to the drug administration.

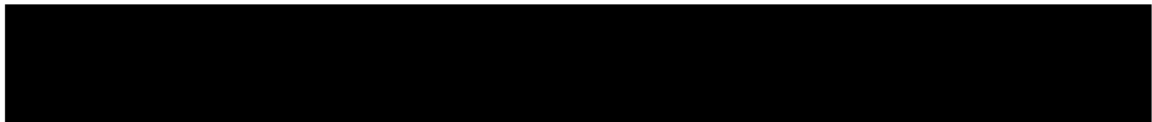
<sup>11</sup> To be done before administration of study treatment.

<sup>12</sup> To be done before administration of comparator only (Coartem®).

<sup>13</sup> Based on the outcomes of the Run-in cohort and study CKA156A2202, laboratory evaluations done (Table 8-5) and the frequency of blood draws may be reduced.

**Table 8-3 Assessment Schedule for Cohorts 1 and 2 (treatment arms: KAF156/LUM-SDF QD for 3 days and Coartem® BID for 3 days)**

Period	Screening		Treatment																						Follow-up
Visit Name	Pre-Screening	Screening	Day 1								Day 2								Day 3						Day 4
Days	-1	-1	1								2								3						4
Time (post-dose)	-	-	0h	1h	3h	4h	5h	6h	8h	12h	24h	25h	27h	28h	29h	30h	32h	36h	48h	51h	54h	60h	68h	72h	
Pre-screening Informed Consent	X																								
Pre-screening Inclusion criteria	X																								
Demography	X																								
Malaria blood film for asexual parasite counts	X		X <sup>11</sup>					X		X	X <sup>11</sup>							X <sup>12</sup>	X <sup>11</sup>					X	
Adverse events	X																								
Contact IRT	X		X						X <sup>2</sup>		X							X <sup>2</sup>	X <sup>2</sup>				X <sup>2</sup>		
Informed consent		X																							
Inclusion / Exclusion criteria		X																							



Period	Screening		Treatment																						Follow-up
Visit Name	Pre-Screening	Screening	Day 1								Day 2								Day 3					Day 4	
Days	-1	-1	1								2								3					4	
Time (post-dose)	-	-	0h	1h	3h	4h	5h	6h	8h	12h	24h	25h	27h	28h	29h	30h	32h	36h	48h	51h	54h	60h	68h	72h	
Medical history/current medical conditions		X																							
Prior and concomitant medications		X	X								X								X					X	
Signs and symptoms of severe malaria		S	S								S								S					S	
Physical Examination		S	S <sup>11</sup>								S <sup>11</sup>								S <sup>11</sup>					S	
Blood Pressure		X	X <sup>11</sup>								X <sup>11</sup>								X <sup>11</sup>					X	
Body Temperature <sup>1</sup>		X	X <sup>11</sup>								X <sup>11</sup>					X		X	X <sup>11</sup>					X	
Body Height		X																							
Pulse rate		X	X <sup>11</sup>								X <sup>11</sup>								X <sup>11</sup>					X	
Body Weight		X	X								X								X						
Clinical Chemistry <sup>13</sup>		X									X <sup>11</sup>								X <sup>11</sup>						
Hematology <sup>13</sup>		X									X <sup>11</sup>								X <sup>11</sup>						
Thyroid function <sup>13</sup>		X																							
Urinalysis		X									X <sup>11</sup>								X <sup>11</sup>						



Period	Screening		Treatment																				Follow-up	
Visit Name	Pre-Screening	Screening	Day 1								Day 2								Day 3					Day 4
Days	-1	-1	1								2								3					4
Time (post-dose)	-	-	0h	1h	3h	4h	5h	6h	8h	12h	24h	25h	27h	28h	29h	30h	32h	36h	48h	51h	54h	60h	68h	72h
Blood sampling for parasite PCR genotyping [REDACTED]			X																					
Drug administration record for KAF156/LUM-SDF			X								X								X					
Drug administration record for Coartem® <sup>2</sup>			X						X		X							X	X			X		
Meal record			X								X								X					
PK sampling for patient ages 6 to <12 years in Cohort 1 dosed with KAF156/LUM-SDF QD for 3 days <sup>3,5,6</sup>					X			X			X <sup>7</sup>								X <sup>7</sup>	X	X			X

[REDACTED]

Period	Screening		Treatment																						Follow-up
Visit Name	Pre-Screening	Screening	Day 1									Day 2								Day 3					Day 4
Days	-1	-1	1									2								3					4
Time (post-dose)	-	-	0h	1h	3h	4h	5h	6h	8h	12h	24h	25h	27h	28h	29h	30h	32h	36h	48h	51h	54h	60h	68h	72h	
PK sampling for patient ages 2 to <6 years in Cohort 1 and 6 months to <2 years in Cohort 2 dosed with KAF156/LUM-SDF QD for 3 days <sup>3,5,6</sup>											X <sup>7</sup>								X <sup>7</sup>	X	X			X	
PK sampling for Coartem® arm											X <sup>7</sup>								X <sup>7</sup>				X		
Electrocardiogram (ECG) in patients dosed with KAF156/LUM-SDF QD for 3 days		X									X <sup>10</sup>		X			X			X <sup>10</sup>	X	X			X	
Electrocardiogram (ECG) in patients dosed with Coartem®		X																	X <sup>10</sup>				X		
Overnight Hospital Stay		S	S									S										S			



Period	Follow-up					UNS
Visit Name	Day 5	Day 8	Day 15	Day 29	Day 43 / EOS	UNS
Days	5	8	15	29	43	1 to 43
Time (post-dose)	96h	168h	336h	672h	1008h	-
Pre-screening Informed Consent						
Pre-screening Inclusion criteria						
Demography						
Malaria blood film for asexual parasite counts	X	X	X	X	X	X
Adverse events	X					
Contact IRT	X	X	X	X	X	
Informed consent						
Inclusion / Exclusion criteria						
Medical history/current medical conditions						
Prior and concomitant medications	X	X	X	X	X	X
Signs and symptoms of severe malaria	S	S	S	S	S	S
Physical Examination	S	S	S	S	S	
Blood Pressure	X	X	X	X	X	X
Body Temperature <sup>1</sup>	X	X	X	X	X	X
Body Height					X <sup>9</sup>	
Pulse rate	X	X	X	X	X	X
Body Weight					X	X
Clinical Chemistry <sup>13</sup>		X		X	X	X
Hematology <sup>13</sup>		X		X	X	X
Thyroid function <sup>13</sup>			X		X	
Urinalysis		X		X	X	X
Pregnancy test (Run-in Cohort only) <sup>2</sup>					X	
Blood sampling for parasite PCR genotyping <sup>3,4</sup>		X	X	X	X	X
Drug administration record						
Meal record						

<sup>1</sup> Fever monitoring will be done every 6 hours until resolution of fever, defined as being afebrile for 24 hours.

<sup>2</sup> Cohorts 1 and 2: 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.

<sup>3</sup> The number of samples/blood draws and total blood volume collected will remain under the limits recommended in this population (Howie 2011).

<sup>4</sup> PCR will be used for genotyping to establish malaria recrudescence/reinfection. [REDACTED] 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.

<sup>5</sup> Also applies to any repeats

<sup>6</sup> a) Further details on sample collection, numbering, processing and shipment can be found in the Laboratory Manual. b) Missed PK sampling time should be taken as soon as possible and actual time should be recorded. For Scheduled time  $\leq 2 \text{ h} \pm 10 \text{ min}$ ;  $2 \text{ to} < 24 \text{ h} \pm 30 \text{ min}$ ;  $\geq 24 \text{ to } 72 \text{ h} \pm 2 \text{ h}$ ;  $> 72 \text{ h} \pm 24 \text{ h}$ .

<sup>7</sup> For both KAF156/LUM-SDF and Coartem®, the PK sample at 24 h and 48 h should be collected prior to the drug administration.

[REDACTED]

<sup>9</sup> Body height will be measured at Study End in Cohort 2 only

<sup>10</sup> For KAF156/LUM-SDF the ECG at 24 h and 48 h and for Coartem at 48 should be performed prior to drug administration.

<sup>11</sup> Blood samples to be collected before administration of study treatment.

<sup>12</sup> To be done before administration of comparator only (Coartem®).

<sup>13</sup> Based on the outcomes of the Run-in cohort and study CKAF156A2202, laboratory evaluations done (Table 8-5) and the frequency of blood draws may be reduced.

## **8.1 Screening**

Patients in the Run-In Cohort should have a *P. falciparum* parasitemia of  $\geq 1,000$  and  $\leq 150,000$  parasites/ $\mu\text{L}$  at the time of pre-screening.

Patients in Cohort 1 and Cohort 2 should have a *P. falciparum* parasitemia of  $\geq 1,500$  and  $\leq 150,000$  parasites/ $\mu\text{L}$  at the time of pre-screening.

It is not permissible to re-screen a patient within the same malaria episode if s/he fails the initial pre-screening or screening. Re-screening of a patient may occur in case the patient is returning to the study site for a new malaria episode. A new study number will be issued to the patient.

### **8.1.1 Information to be collected on screening failures**

Patients who sign an informed consent form and subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the applicable CRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a serious adverse event during the screening phase (see SAE section for reporting details). Adverse events that are not SAEs will be followed by the investigator and collected only as source data.

Patients who sign an informed consent and are considered eligible but fail to be started on treatment for any reason will be considered an early terminator. The reason for early termination should be captured on the appropriate CRF.

## **8.2 Patient demographics/other baseline characteristics**

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

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

- Age
- Gender
- Child bearing potential for females (post first menarche)
- Body weight
- Body height
- Body temperature
- Initial medical and treatment history
- Signs and symptoms of severe malaria
- Vital signs
- Physical exam
- Prior and concomitant medications
- Blood chemistry and hematology as specified above
- Thyroid function
- Urinalysis

- Pregnancy test (Run-in Cohort only)
- Malaria blood film for asexual parasite [REDACTED] counts and species differentiation
- Blood sampling for parasite genotyping
- Medical history/current medical conditions
- Triplicate 12-lead ECG
- PK sampling for Run-in Cohort

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.

### 8.3 Efficacy

Efficacy assessments will be based on the PCR-corrected and uncorrected Adequate Clinical and Parasitological Response (ACPR) at Days 15, 29 and 43, the incidence rate of recrudescence and reinfection at Days 15, 29 and 43, and the PCT and FCT.

#### 8.3.1 Parasitemia assessment (details provided in the Laboratory Manual)

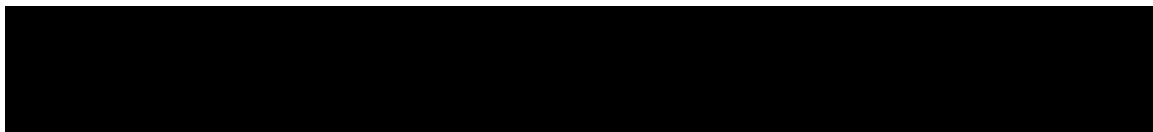
Blood sampling for parasitology can be done by means of finger prick except when the timing for parasitology assessments coincide with time for clinical laboratory tests, in which case, blood sample can be taken from the venous blood collected for clinical laboratory analyses.

##### 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 at 1,000 magnification
- 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 *P. falciparum* 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 [REDACTED] 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:

Number of *Plasmodium* parasites x actual leukocytes (WBC)

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



- 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]

The count should be made for each species [REDACTED]  
(White et al 2014). [REDACTED]

[REDACTED]. Thick (and thin blood) films will be prepared as specified in the assessment schedule table and evaluated by standard techniques (Giemsa stain and light microscopy). This will be the definitive test for a positive *P. falciparum* infection. The parasite counts can also be quantified in percentage (per 1,000) of red cells on the thin film.

[REDACTED]

### 8.3.2 Blood sample for molecular diagnostic purposes

Blood will be sampled for parasite genotyping as indicated in the assessment schedule (Table 8-1, Table 8-2, Table 8-3). At screening, a blood sample will be collected from all patients fulfilling eligibility criteria for inclusion in the study. A second blood sample collected as per assessment schedule will be analyzed only in patients showing treatment failure. This will be used to distinguish between recrudescence and new infection. Molecular analysis will be done by a pre-selected central laboratory.

[REDACTED]

[REDACTED]

### 8.3.3 Appropriateness of efficacy assessments

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

## 8.4 Safety

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

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section (Section 10.1).

[REDACTED]

As per [Section 4.6](#), during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur as per the visit schedule or more frequently for safety monitoring and discussion of the participant's health status until it is safe for the participant to visit the site again.

**Table 8-4 Assessments & Specifications**

Assessment	Specification
Physical examination and malaria signs and symptoms	<p>A <b>complete</b> physical examination will be performed by the investigational staff <i>at screening</i> and will 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.</p> <p>An <b>abbreviated</b> 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). Body height in centimeters (cm) will be also measured at Study End in Cohort 2.</p> <p>A full assessment of <b>malaria signs and symptoms</b> will be made alongside the physical examinations at time points described in the assessment schedule for all patients table (<a href="#">Table 8-1</a>). In particular, pediatric patients need to be examined for signs of dehydration.</p> <p>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 the first administration of investigational drug which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the eCRF.</p>
Vital signs	<p>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.</p> <p>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.</p>
Body temperature	<p>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.</p> <p><b>Fever clearance</b> is defined (in patients with an increased temperature at baseline) as the time of the first measurement of axillary temperature of &lt; 37.5°C (or &lt; 38.0°C for alternative routes). Fever clearance will be concluded following confirmation of temperature &lt; 37.5°C (or &lt; 38.0°C for alternative routes) on the subsequent measurement for at least 24 hours.</p> <p>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 FCT.</p>

### 8.4.1 Laboratory evaluations

A local laboratory or a micro-sampling device can be used for analysis of safety labs (hematology, blood chemistry, and urinalysis). Blood sampling volumes should be collected as per the laboratory manual. The number of samples/blood draws and total blood volume collected will remain under the limits recommended in this population (Howie 2011). Based on the outcomes of the Run-in cohort and study CKAF156A2202, laboratory evaluations done (Table 8-5) and the frequency of blood draws (Table 8-2 and Table 8-3) may be reduced in patients <12 years old (Cohorts 1 and 2). If this is the case, all investigators will be informed before the start of Cohort 1.

A central laboratory will be used for PCR (parasite identification [REDACTED]), ECG, and PK measurements. 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 tables.

Clinically notable laboratory findings are defined in Section 16.1.

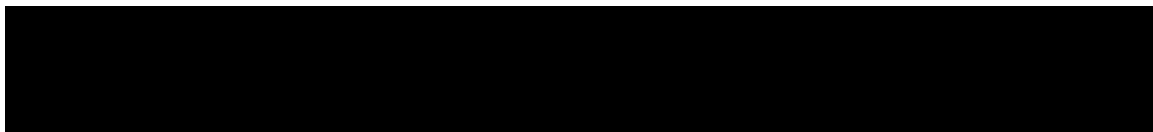
**Table 8-5 Local laboratory evaluations**

Test Category	Test Name
Hematology	Hemoglobin, hematocrit (packed-cell volume - PCV), platelets, white blood cell (WBC) count with differential (as much as possible, neutrophil, lymphocyte and eosinophils counts will be performed while basophils and monocytes can be aggregated as 'other'). Red blood cell count (RBC), reticulocyte 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).
Chemistry	<p>Routine blood chemistry testing will be performed according to the visit schedule in order to monitor the general medical condition of the patient.</p> <p>This includes: Glucose, creatinine (serum), transaminases (ALT/Serum glutamic pyruvic transaminase (SGPT) and AST/Serum glutamic oxaloacetic transaminase (SGOT)), serum-γ-glutamyl transferase (GGT), Total and direct bilirubin, Alkaline Phosphatase (ALP), Blood Urea Nitrogen (BUN), prothrombin time International Normalized Ratio (INR), sodium, potassium, magnesium, calcium, chloride, total protein and albumin.</p> <p>Thyroid stimulating hormone (TSH) and free thyroxine T4 are tested at screening, Day 15 and at study completion only.</p> <p>At screening, results of the thyroid test are not mandatory for eligibility into the study.</p>
Urinalysis	Dipstick measurements for specific gravity, protein, glucose and hematuria. Microscopy will be performed and urine sediment will be assessed in case of an abnormal dipstick test.

### 8.4.2 Electrocardiogram

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) must be used for clinical decisions, e.g. at the Screening visit(s) to assess eligibility.



Triplicate 12 lead ECGs are to be collected with ECG machines supplied by the central laboratory and recorded approximately 2 minutes apart. The mean QTcF value for each visit will be calculated from the triplicate ECGs for each participant. 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. Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated.

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 10.1.2](#). 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  $\geq 60$  ms from baseline occur at any time, the patient should be assessed at the site and appropriate safety procedures (e.g., blood sampling and 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.

Any post-dose average QTcF > 500 ms will result in patient discontinuation from the treatment if there is a planned subsequent treatment.

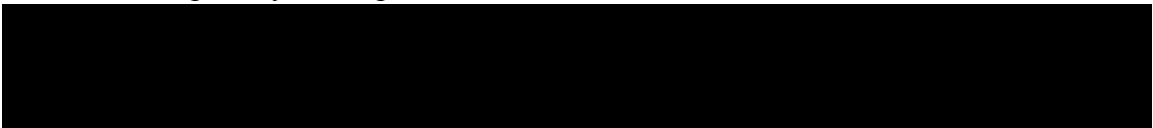
Assessments will be done as indicated in the study assessment ([Table 8-1](#)). All ECGs will be assessed centrally by an independent and blinded (with age of patient identified) cardiologist.

#### **8.4.3 Pregnancy and assessments of fertility in Run-in Cohort**

A pregnancy test in urine will be performed at the screening visit and at study completion in the Run-in Cohort.

Patients of child-bearing potential are defined as all females physiologically capable of becoming pregnant. This includes female pediatric patients who are menarchal or who become menarchal during the study. Serum pregnancy test will be performed for all females of child-bearing potential according to the protocol assessment schedule (See [Table 8-1](#)).

All menarchal girls and their parents/caregivers should be informed about the potential risks of pregnancy and the need to prevent pregnancy during the study treatment. It is important to be sensitive in introducing this issue, as understanding and comprehension of puberty, sexual activity, pregnancy and contraception is influenced by age, as well as factors such as precocity, socio (educational) economic and familial background. These discussions with the patient and her parents/caregivers are therefore best performed by investigators familiar with the pediatric patient and her family and should be guided by requirements of the local regulatory authorities. These discussions should take into account the socio-economic, cultural factors and religious beliefs of the adolescent participant and her family. The investigator should also discuss the management of the pregnancy test results with the patient and her parents/caregivers. The privacy of the patient should be considered in accordance with the local law and ethics.



Additional pregnancy tests may be performed at the investigator's discretion during the study. Patients becoming pregnant must be discontinued from study drug. However, a patient may choose to remain in the study should she become pregnant, and be followed according to the protocol-defined study visits.

#### **8.4.4 WHO Definitions of treatment failures and Adequate Clinical and Parasitological Response**

##### **Early Treatment Failures (ETF)**

- Development of danger signs or severe malaria on Day 2, Day 3, Day 4 in the presence of parasitemia.
- Parasitemia on Day 3 higher than Day 1 count irrespective of axillary temperature.
- Parasitemia on Day 4 with axillary temperature  $\geq 37.5^{\circ}\text{C}$ .
- Parasitemia 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 parasitemia without previously meeting any of the criteria of ETF.
- Presence of parasitemia and axillary temperature  $\geq 37.5^{\circ}\text{C}$  on any day from Day 5 to Day 43 without previously meeting any of the criteria of ETF.

##### **Late Parasitological Failure (LPF)**

- Presence of parasitemia on any day from Day 8 to Day 43 and axillary temperature  $< 37.5^{\circ}\text{C}$  without previously meeting any of the criteria of ETF or LCF.

##### **Adequate Clinical and Parasitological Response (ACPR):**

Absence of parasitemia on Day 43 irrespective of axillary temperature, without previously meeting any of the criteria of ETF or LTF or LPF.

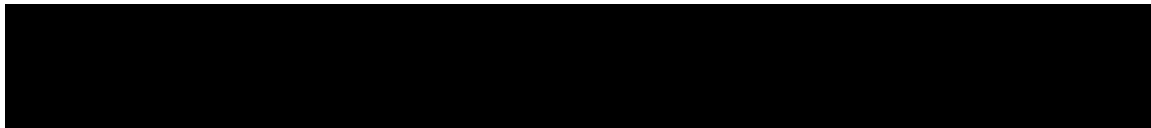
In this study, “absence of parasitemia on Day 43” has been adapted to “absence of parasitemia on Day 29” based on the short half-life of the study drugs.

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](#).

See [Section 16.4](#) for signs/symptoms indicative of severe/complicated malaria

#### **8.4.5 Appropriateness of safety measurements**

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



## 8.5 Additional assessments

### 8.5.1 Pharmacokinetics

PK samples will be collected at the visits defined in the assessment schedule ([Table 8-1](#), [Table 8-2](#), [Table 8-3](#)). Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing, and shipment.

The number of samples/blood draws and total blood volume collected should not exceed those stated in the protocol and laboratory manual.

Pharmacokinetic (PK) samples will be obtained and evaluated in all patients. KAF156 and lumefantrine exposures will be determined by a validated LC-MS/MS method; the anticipated Lower Limit of Quantification (LLOQ) is 5 and 50 ng/mL for KAF156 and lumefantrine, respectively.

KAF156 and lumefantrine concentrations will be expressed in mass per volume units and will refer to the free base. Concentrations below the LLOQ will be reported as “zero” and missing data will be labeled as such in the Bioanalytical Data Report.

Pharmacokinetic (PK) samples will be obtained and evaluated in all patients at all dose levels/regimen. Parameters such as AUC, C<sub>max</sub>, T<sub>max</sub>, C<sub>168</sub> (Day 8 concentration.) etc. will be determined using non-compartmental method for both KAF156 and LUM.

## 9 Study discontinuation and completion

### 9.1 Discontinuation

#### 9.1.1 Discontinuation of study treatment

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the patient's premature discontinuation of study treatment and record this information. Patients who discontinue from study treatment agree to return for end of treatment follow-up visits indicated in the Assessment Schedule (refer to [Section 8](#)).

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. This telephone contact should preferably be done according to the study visit schedule.

Patients will be treated under hospital supervision during the treatment period. Discontinuation of study treatment for a patient occurs when study drug is permanently stopped earlier than the

protocol planned duration, and discontinuation can be initiated by either the patient or the investigator.

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
- Use of prohibited treatment as per recommendations in [Table 6-4](#)
- Any situation in which continued 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
- 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.
- Any laboratory abnormalities that in the judgement 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 [Section 16.2](#)))
- Deviation from the planned dose regimen for the study drug (e.g., vomiting of the replacement dose within 2 hours of intake)

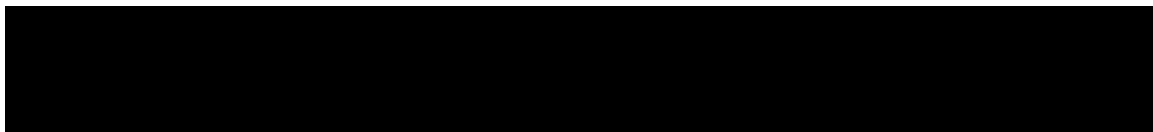
Patients who discontinue study drug for any of the above reasons may be given rescue medication at the discretion of the investigator and will be followed for the whole study duration until Day 43.

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

If a patient is tested positive to COVID19 during the course of the study, the patient may not be available for laboratory or clinical evaluation (as per the local guidelines in management of COVID19). However, all the efforts should be made to follow the patients for safety until end of the study. In case of non-availability, the patient should be considered as discontinued from the study with COVID19 as the reason for discontinuation.

### **9.1.2 Lost to follow-up**

For patients 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 patient, 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.



## **9.2 Withdrawal of informed consent / Opposition to use data/biological samples**

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent/opposition to use data/biological samples occurs only when a patient:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use patient's data and biological samples)
- No longer wishes to receive study treatment and
- Does not want any further visits or assessments (including further study related contacts)

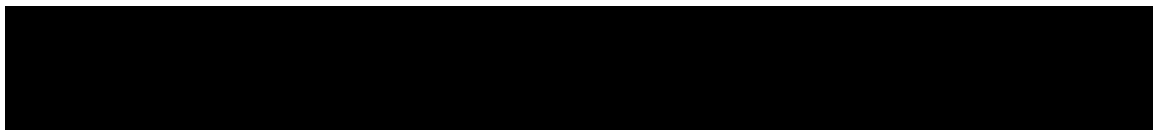
This request should be in writing (depending on local regulations) and recorded in the source documentation

In this situation:

- The investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw their consent / opposition to use data/biological samples 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.
- If the patient agrees, a final evaluation at the time of the patient's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table ([Section 8](#)).
- Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition..

## **9.3 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 (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the patient welfare and safety. Should early termination be necessary, patients 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 or sponsor depending on the local regulation will be responsible for informing Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.



## 9.4 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 and may recommend stopping a cohort or the study early for safety reasons.

## 10 Safety monitoring and reporting

### 10.1 Definition of adverse events and reporting requirements

#### 10.1.1 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, patient or clinical investigation subject *after providing written informed consent* for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

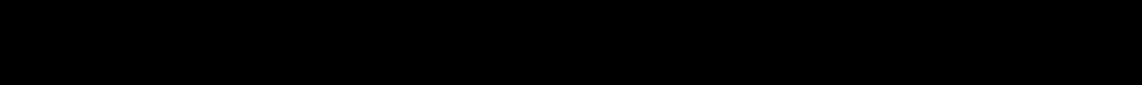
In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

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

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from



baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in [Section 16.1](#).

Study drug/treatment includes investigational drugs i.e. KAF156 and LUM-SDF and the comparator 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 10.1.2](#) 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).

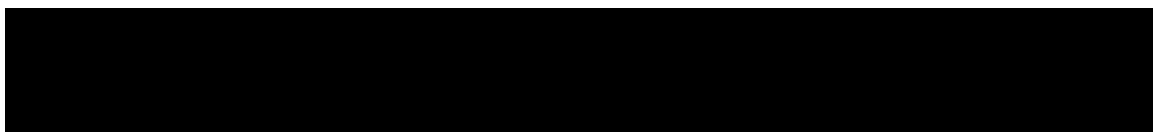
There may be cases where a CTCAE with a grade of 4 (life-threatening) may not necessarily be an SAE (e.g. certain laboratory abnormalities in the absence of meeting other seriousness criteria).

- its relationship to the study treatment (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 10.1.2](#) 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 10.1.2](#) for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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



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

Information about common side effects already known about the investigational drugs (KAF156 and LUM-SDF) can be found in the IBs and for the comparator (Coartem®) in the Prescribing Information. 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.

#### **10.1.2 Serious adverse events**

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:

- fatal
- life-threatening

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 the ICH-E2D Guidelines).

- 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
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
  - 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
- Is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

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. Such events should be considered as “medically significant.” 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 (please refer to the ICH-E2D Guidelines).

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

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

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

### **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 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. For Coartem® the Prescribing Information will serve as reference for the assessment of expectedness/listedness.

### **10.1.3 SAE reporting**

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until Study Day 43 must be reported to Novartis/ safety immediately, without undue delay, under no circumstances later than within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the eSAE with paper backup Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

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.

If the SAE is not previously documented in the Investigator’s Brochures (IB) (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety (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 ECs in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the last study visit, should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

#### **10.1.4 Pregnancy reporting**

In the Run-in Cohort, 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 even if unrelated to the pregnancy must be reported on an eSAE form/paper SAE form (as applicable).

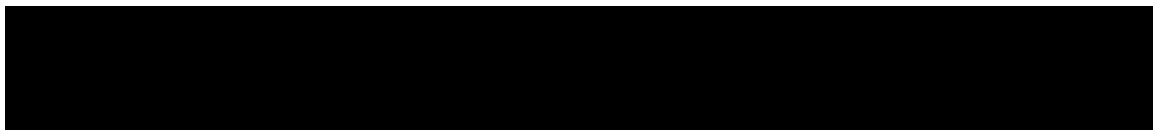
#### **10.1.5 Reporting of study treatment errors including misuse/abuse**

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (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 recorded on the appropriate CRF 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 within 24 hours of Investigator's awareness.



**Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse**

Treatment error type	Document in Dosing CRF (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

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

## 10.2 Additional Safety Monitoring

### 10.2.1 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 AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate CRFs and reported as SAEs.

Please refer to [Table 16-2](#) in [Appendix 2](#) for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in [Section 16.2](#), should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in [Table 16-3](#).

- Repeat liver chemistry tests (i.e. ALT, AST, total bilirubin (TBL), PT/INR, ALP and GGT) to confirm elevation.
- These liver chemistry repeats should be performed using the local laboratory used by the site. Repeated laboratory test results must be reported as appropriate.
- If the initial elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the patient if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should be done. The follow-up should be based on investigator's discretion and can include: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

### 10.2.2 Renal safety monitoring

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

- Serum creatinine (sCR) increase  $\geq 25\%$  compared to baseline during normal hydration status
- Urine protein-creatinine ratio (PCR)  $\geq 1\text{g/g}$  or  $\geq 100\text{ mg/mmol}$ , OR new onset dipstick proteinuria  $\geq 3+$  OR new onset dipstick hematuria  $\geq 3+$  (after excluding menstruation, UTI, extreme exercise, or trauma)

Abnormal renal event findings must be confirmed within 24-48 hours after the first assessment.

Every renal laboratory trigger or renal event as defined in [Table 16-3](#) should be followed up by the investigator or designated personnel at the trial site as summarized in [Section 16.3](#).

### 10.2.3 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of a clinical trial, safety data, drug exposure, and key efficacy variables and recommend to Novartis whether to continue, modify, or terminate a trial.

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between Novartis and the DMC.

### 10.2.4 Cardiac Safety Monitoring

Although QTc extensions and bradycardia are often associated with acute malaria disease and subsequent recovery (fast reduction of fever and heart rate), QTc extensions and bradycardia are also seen as potential side-effects of many anti-malarials. Lumefantrine as part of Coartem<sup>®</sup>, has shown only modest increase of QTc in a dedicated TQT study, and extensive post-marketing surveillance has not shown signs of cardiotoxicity. ECG results from the previous study CKAF156A2202 where the combination of KAF156 and LUM-SDF was evaluated in acute malaria patients  $\geq 12$  years, did not show clinically relevant QTcF extensions and/or bradycardia following treatment. There was however a mild trend towards higher QTcF change from baseline with increasing exposures. Clinical relevance is unknown.

To ensure patient safety in this study and to fully characterize the cardiovascular safety of the investigational drug, a standardized process for identification, monitoring and evaluation of cardiac events by ECG 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  $\geq 60\text{ ms}$
- QTcF  $> 500\text{ ms}$

Resting heart rate:

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

Cardiac rhythm:

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

## **11 Data Collection and Database management**

### **11.1 Data collection**

Designated investigator staff will enter the data required by the protocol into the eCRFs. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 Code of Federal Regulation (CFR) Part 11 requirements; investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate

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

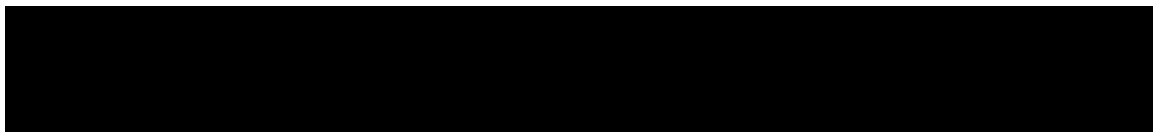
All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

### **11.2 Database management and quality control**

Novartis personnel (or designated Contract Research Organization (CRO)) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Randomization codes and data about all study treatment(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.



Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

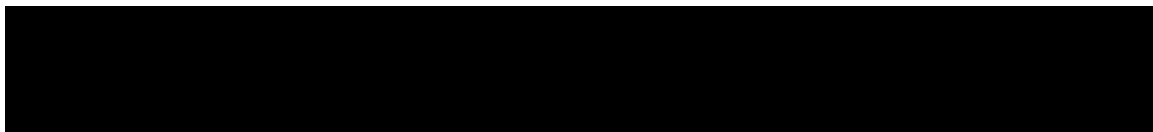
Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be made available for data analysis/moved to restricted area to be accessed by programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

### **11.3 Site monitoring**

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e., eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice (GCP), the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis/sponsor clinical teams to assist with trial oversight.

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, ECGs, and the results of any other tests or assessments. All information on CRFs 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 data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patient will be disclosed.



## 12 Data analysis and statistical methods

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

The dose level of KAF156 and LUM-SDF in the Run-in Cohort (12 to <18 years) may be adjusted after the first 24 patients have been dosed in this cohorts. Once the dose level has been adjusted, it becomes a different treatment group. The KAF156/LUM-SDF based treatment group will be labeled to include both the full dose level of the study drugs and food intake designation for KAF156 and LUM-SDF combination based treatment group (such as KAF156 400 mg & LUM-SDF 240 mg QDx2 with food, etc.). Since the the Run-in Cohort has different treatment groups (i.e. fed vs fasting) from Cohorts 1 and 2 (KAF156/LUM-DSF vs Coartem®), the Run-in Cohort will be analyzed separately from Cohorts 1 and 2. Statistical analysis will in general include Cohorts 1 and 2 pooled in addition to each cohort separately. In case that Cohort 2 stops early, such as after the first 24 patients, the study objectives will be assessed based on Cohort 1 data alone.

### 12.1 Analysis sets

The Randomized Analysis Set (RAS) consists of all randomized patients.

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization and who are treated with at least one dose of study drug with baseline *P. falciparum* asexual parasite count >0. According to the intent to treat principle, patients will be analyzed according to the treatment they have been assigned to during the randomization procedure.

The Safety Set includes all patients who received at least one dose of study treatment. Patients will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

The Per-Protocol Set (PPS) is a subset of patients of the Full Analysis Set and is characterized by the following criteria:

- did not have important protocol deviations affecting efficacy,
- took at least 80% of study medication,
- did not take non-study drug antimalarial medications prior to Day 29 unless experiencing a treatment failure (ETF, LCF, LPF), and
- PCR corrected ACPR status at Day 29 can be defined

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

The PK set is a subset of the Full Analysis Set who had evaluable PK parameter/concentration data and took at least 80% of study medication.

## **12.2 Patient demographics and other baseline characteristics**

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by cohort and treatment group for the FAS and Safety set if Safety set is different from the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation (SD), median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by cohort and treatment group.

## **12.3 Treatments**

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages by cohort and treatment group. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in number of doses to KAF156, LUM-SDF, and Coartem® will be summarized by means of descriptive statistics. Percentage of patients with study drug vomiting and dose replacement will be presented. Average daily dosage and total dosage (in mg) of each drug (KAF156, LUM-SDF, and Coartem®) will be summarized. Meal intake and meal type will be summarized by day.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by cohort and treatment group. Concomitant rescue and other anti-malarial medications will be summarized.

## **12.4 Analysis of the primary endpoint(s)**

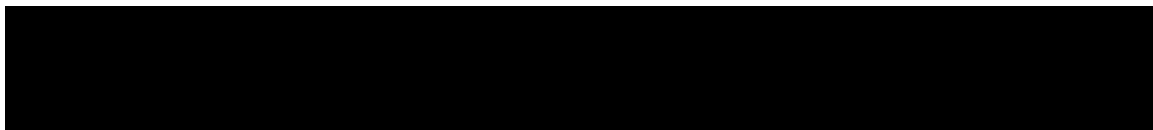
### **12.4.1 Definition of primary endpoint(s)**

The primary efficacy variable is the PCR corrected Adequate Clinical and Parasitological Response (ACPR) at Day 29 (Cohorts 1 and 2 pooled).

In case that Cohort 2 stops early, such as after the first 24 patients, the study objectives will be assessed based on Cohort 1 data alone.

A patient is considered as PCR-corrected ACPR at Day 29 if the patient does not meet any of the criteria of ETF (up to Day 4), LCF (Day 5 to Day 29) or LPF (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 (Day 8 or later) is due to reinfection based on PCR genotyping.

A presence of parasitaemia after 7 days of treatment initiation 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 match with the parasite strain at baseline based on PCR genotyping.



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.

#### 12.4.2 Statistical model, hypothesis, and method of analysis

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

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

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

In case that Cohort 2 stops early, such as after the first 24 patients, two-sided 95% CI for the difference between two treatment groups will be provided for Cohort 1 alone using the Wilson uncorrected method. If the lower limit of 2-sided 95% CI for the difference is greater than -10%, the null hypothesis will be rejected.

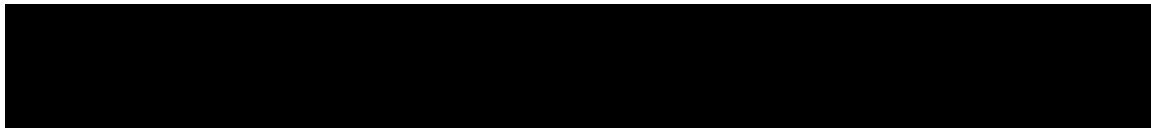
The statistical hypothesis testing will be evaluated based on the PPS.

#### 12.4.3 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 12.4.4](#) for missing data handling for the supportive analysis using FAS.

#### 12.4.4 Sensitivity analyses

- For patients who have a reinfection after 7 days but prior to Day 29 visit, such as at Day 15, the statistical method specified in [Section 12.4.2](#) will be performed by assigning treatment failure to these patients.
- The primary efficacy variable will be performed based on the FAS using the statistical method specified in [Section 12.4.2](#). 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* [REDACTED]



(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 assessment 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 by treatment group and the difference 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 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 the last parasitemia assessment. A two-sided 95% CI for the difference in proportion between the 2 treatment groups will be calculated based on the variance of individual proportion using the Greenwood formula.

Patients tested positive to COVID19 after Day 29 parasite assessment or after *P. falciparum* re-appearance (recrudescence or new infection) are included in the primary analysis and the sensitivity analyses similarly to other patients. Patients tested positive to COVID19 prior to Day 29 parasite assessment without *P. falciparum* re-appearance are handled similarly to other patients with missing Day 29 parasite assessment (e.g., loss to follow-up), i.e., excluded from PP set but included in FAS. If there are significant number of patients tested positive to COVID19 prior to Day 29 parasite assessment without *P. falciparum* re-appearance, additional sensitivity analyses may be considered.

## 12.5 Analysis of secondary endpoints

### 12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

**Secondary efficacy variables include:**

- PCR-corrected ACPR at Days 15 and 43;
- PCR-corrected ACPR at Day 29 for the Run-in Cohort, Cohort 1, and Cohort 2 separately;
- Uncorrected ACPR at Days 15, 29, and 43;
- 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;
- Time to fever clearance (FCT), defined as time from the first dose until the first time the body temperature decreased below and remained below 37.5°C axillary or 38.0°C oral/tympanic/rectal for at least a further 24 hours;
- Proportion of patients with ETF:

- Proportion of patients with LCF;
- Proportion of patients with LPF;
- Incidence rate of recrudescence and reinfection at 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. Analyses will be performed by cohort and for Cohorts 1 and 2 pooled. Note: difference between KAF156 and LUM-SDF combo and Coartem<sup>®</sup> in PCR-corrected ACPR at Day 29 is the primary efficacy endpoint (see [Section 12.4](#)).

### PCR-corrected ACPR and uncorrected ACPR:

At each visit, the percent of patients with ACPR with 95% confidence intervals will be provided using Clopper-Pearson method for each treatment group and Cohort. For exploratory purpose, 2-sided 95% confidence intervals for the difference at each visit between the 2 treatment groups will be constructed for each Cohort using the Wilson uncorrected method. For the Cohorts 1 and 2 pooled, the treatment difference and 95% CI between KAF156 and LUM-SDF and Coartem<sup>®</sup> will be evaluated using a Mantel-Haenszel estimate of the common risk difference stratified by cohort (see [SAS manual version 13.2 Pages 2681-2682, 2014](#)).

Data will be handled as follows:

- Treatment failures after 7 days (i.e., Day 8) due to new infection (ie, reinfection) based on PCR genotyping are not considered as failure for PCR-corrected analyses.
- For parasitological uncorrected ACPR, patients will be considered as failure on and after the visit when a new infection with *P. falciparum* 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* [REDACTED] (e.g. primaquine, certain antibiotics (sulfonamides, tetracycline, etc.)) will be considered in the analysis as if they had not taken the drug.
- Patients will be counted as failure at a visit (e.g., 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 12.4.4](#)).

Patients tested positive to COVID-19 after a visit or after *P. falciparum* re-appearance (recrudescence or new infection) are included in analysis similarly to other patients. Patients tested positive to COVID-19 prior to a visit without *P. falciparum* re-appearance are handled similarly to other patients with missing visit assessment. If there are significant number of patients tested positive to COVID-19 prior to a visit without *P. falciparum* re-appearance, additional sensitivity analyses may be considered.

### **Treatment failure related parameters:**

For the following parameters, 2-sided 95% confidence intervals will be provided for each treatment group using the Clopper-Pearson method by cohort and for Cohorts 1 and 2 pooled:

- proportion of patients with ETF
- proportion of patients with LCF
- proportion of patients with LPF

In addition, following analysis will be performed. 2-sided 95% confidence intervals for the difference between KAF156 and LUM-SDF combo and Coartem<sup>®</sup> will be provided for Cohorts 1 and 2 pooled using a Mantel-Haenszel estimate of the common risk difference stratified by cohort. 2-sided 95% confidence intervals for the difference between the 2 treatment groups for each Cohort will be constructed using the Wilson uncorrected method.

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.

At each visit, PCR uncorrected failure will be classified into initial infection not cleared, ETF, LCF before Day 8, recrudescence, new infection, negative PCR, missing PCR, or missing assessment. The reason will be tabulated using the FAS.

### **PCT and 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.

For Cohorts 1 and 2 pooled, the treatment difference between KAF156 and LUM-SDF and Coartem<sup>®</sup> will be evaluated at the 2-sided 5% significance level using a log-rank test stratified by cohort. For each cohort, the treatment difference between 2 treatment groups will be evaluated at the 2-sided 5% significance level using a log-rank test.

### **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 time of first study medication to the date of first event if a patient experiences the event and be censored at the time of last parasite assessment if a patient does not experience the event due to whatever reason.

For Cohorts 1 and 2 pooled, the treatment difference between KAF156 and LUM-SDF and Coartem® will be evaluated at the 2-sided 5% significance level using a log-rank test stratified by cohort. For each cohort, the treatment difference between 2 treatment groups will be evaluated at the 2-sided 5% significance level using a log-rank test.

### **12.5.2 Safety endpoints**

For all safety analyses, the safety set will be used. All listings and tables will be presented by cohort and treatment group.

Safety summaries (tables, figures) include all post treatment data with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In particular, summary tables for adverse events (AEs) will summarize using all post-treatment events, with a start date on or after the first treatment (treatment-emergent AEs).

#### **Adverse events:**

All information obtained on adverse events will be displayed by cohort, treatment group, and patients.

The number (and percentage) of patients with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of study treatment but increased in severity based on preferred term) will be summarized in the following ways:

- By cohort, treatment, primary system organ class and preferred term.
- By cohort, treatment, primary system organ class, preferred term and maximum severity.
- By cohort, treatment, Standardized MedDRA Query (SMQ) and preferred term.

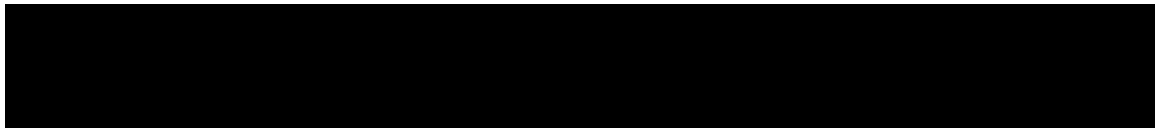
Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation, and adverse events leading to dose adjustment if there are enough events.

The number (and proportion) of patients with adverse events of special interest/related to identified and potential risks will be summarized by cohort and treatment.

A patient with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

#### **Vital signs:**

All vital signs data will be listed by cohort, treatment group, patient, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by cohort, treatment group, and visit/time.



## **12-lead ECG:**

PR, QRS, QT, QTcF, QTcB, and RR intervals will be obtained from 12-lead ECGs for each patient during the study. ECG data will be read and interpreted (centrally).

Categorical Analysis of QT/QTc interval data based on the number of patients meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these patients will be produced (by cohort and treatment group). Post treatment max QTc increase from baseline will be calculated for each patient and 2-sided confidence intervals for the difference between the 2 treatment groups will be calculated using the 80% confidence level for Run-in Cohort and the first 24 patients in Cohort 2 for Data Review checks and the 90% confidence level for all patients in each cohort at the final analysis.

All ECG data will be listed by cohort, treatment group, patient and visit/time, abnormalities will be flagged. Summary statistics will be provided by cohort, treatment group, and visit/time.

## **Clinical laboratory evaluations:**

All laboratory data will be listed by cohort, treatment group, patient, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by cohort, treatment group, and visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst post-treatment value.

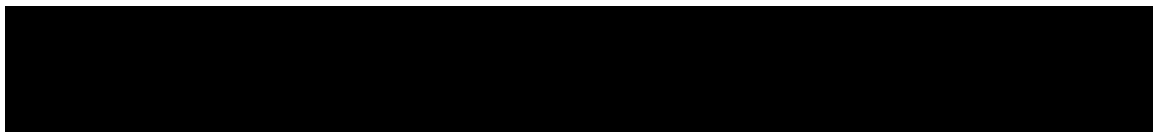
### **12.5.3 Pharmacokinetics**

Plasma concentration data will be listed by cohort, treatment group, patient, and visit/sampling time point. Descriptive summary statistics will be provided by cohort, treatment group, and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. For geometric related mean and CV, concentrations below LLOQ will be included as half of the LLOQ value.

Pharmacokinetic parameters will be listed by cohort, treatment group, and patient. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is  $T_{max}$  where median, minimum, and maximum will be presented.

Two-sided 90% confidence intervals for AUC, C<sub>max</sub> and T<sub>max</sub> PK parameters and C<sub>168</sub> of KAF156 and lumefantrine will be calculated by cohort and treatment group using normal or log-normal approximation as applicable. For relevant common PK parameters (related to KAF156 and lumefantrine for Run-in cohort and related to lumefantrine for Cohorts 1 and 2), two-sided 90% confidence intervals for geometric mean ratio between the 2 treatment groups will be provided by cohort.



**Table 12-1 Non-compartmental pharmacokinetic parameters**

<b>AUC<sub>0-t</sub></b>	The AUC from time zero to time t (e.g. 24h) (µg•h/mL)
<b>C<sub>max</sub></b>	The maximum (peak) observed plasma drug concentration (ng/mL)
<b>T<sub>max</sub></b>	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after last dose administration (time)
<b>C<sub>168</sub></b>	The observed plasma drug concentration at scheduled time point of 168 h post first dose administration (ng/mL)

In addition, the collected data may be analyzed by population PK modeling approach either for this study specifically or after pooling the data with other studies; the broad principles outlined in the Food and Drug Administration (FDA) Guidance for Industry: Population Pharmacokinetics would be followed. The Population PK modeling may not be part of the clinical study report and will be reported separately.

### **PK checking for the Run-in Cohort and the first 24 patients in Cohort 2:**

PK exposure of KAF156 and lumefantrine may be compared between the 2 treatment groups (fasted vs fed) in Run-in Cohort and in Cohort 2 and with the historical clinical data to ensure that exposure are within acceptable range for safety and efficacy. Because this study along with CKAF156A2202 study are part of establishing exposure-response relationship, no specific target exposure is established and all data including safety and efficacy will be considered by the independent data monitoring committee..

#### **12.5.4 PK/PD relationships**

The PK and pharmacodynamics (PD) data obtained in the study may be pooled and an exploratory exposure-response analysis conducted. This analysis may help in identifying if any PK parameter(s) correlate to efficacy outcomes. An exploratory relationship for safety outcomes such as QTc prolongation and PK parameters may also be conducted. The exposure-response analysis may not be part of the clinical study report.

[REDACTED]

[REDACTED]

### **12.7 Interim analyses**

At selected time points during the study (such as the first 24 patients in each cohort, etc., see [Section 3](#)), DMC reports for PK exposure and selected safety endpoints/key efficacy variables will be provided. The DMC reports will be unblinded to the CTT during the Run-in Cohort but be blinded to the CTT during the Cohorts 1 and 2. The DMC reports will be reviewed

[REDACTED]

by the DMC. For Data Review checks during the Run-in Cohort, the unblinded DMC reports will be shared with selected internal/external experts who can contribute to dose adjustment.

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 clinical trial team involved in trial conduct. No further dissemination of DMC reports should occur.

## 12.8 Sample size calculation

### 12.8.1 Primary endpoint(s)

The primary objective is to evaluate the efficacy of KAF156 combined with LUM-SDF by demonstrating non-inferiority to Coartem<sup>®</sup> in PCR corrected ACPR at Day 29 for treatment of uncomplicated malaria caused by *P. falciparum* in children 6 months to < 12 years old. The NI margin ( $\Delta$ ) has been set to 10%. There is no historical Coartem<sup>®</sup> trial that compared Coartem<sup>®</sup> with placebo in PCR corrected ACPR at Day 29 to justify the NI margin statistically. The 10% NI margin in PCR corrected ACPR at Day 29 is based on clinical judgement as a NI margin of 10% to 12.5% is commonly used in other infection diseases (e.g., FDA 2018 guidance for Complicated Urinary Tract Infections, FDA 2020 guidance for Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia, EMA 2014 Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections, etc.).

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

#### **Cohort 2 does not stop early**

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

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

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

additional number of patients will be randomized to match the requirement of PPS. **Cohort 2 stops early**

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

## **12.8.2 Secondary endpoint(s)**

### **Run-in Cohort**

The primary objective in the Run-in Cohort is to investigate the food effect in lumefantrine (LUM) PK in terms of fold increase for fed vs fasted. The key LUM PK variables are C<sub>max</sub>, LUM AUC<sub>0-24h</sub> of last dose, and H168 Concentration. The sample size will be justified based on the precision for estimating the fold increase in LUM PK for fed vs fasted. The fold increase will be estimated using the geometric mean ratio between fed and fasted groups with the precision defined by the half-width of 90% confidence interval for the geometric mean ratio.

It is well known that the distribution of PK parameters, such as AUC or C<sub>max</sub>, is best described by log normal distribution. The geometric mean ratio along with its 90% confidence interval will be calculated first using log value and then anti-log transformed to ratio. The relevant historical data for sample size calculation are the standard deviations of log values. In the phase 2 study CKAF156A2202 Part A, the standard deviations from sparse PK samples of lumefantrine for KAF156 400 mg/LUM-SDF 960 mg QD 2 days (under fasted) were:

- 0.69 for log C<sub>max</sub> of last dose
- 0.77 for log AUC<sub>0-24h</sub> of last dose
- 0.63 for log concentration at 168 hours.

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

For log AUC<sub>0-24h</sub>, assuming that the common standard deviation is 0.77, a sample size of 10 patients per group will provide an 80% probability that the half-width of 2-sided 90% confidence interval for the difference of two log means will be  $\leq 0.693$  or 2 in terms of ratio (nQuery MTC1-1).

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

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

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

After about 24 patients have been randomized in Cohort 2, PK checking along with safety and efficacy will be evaluated to see if the dose level of KAF156 and/or LUM-SDF is appropriate

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


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

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

## **13 Ethical considerations and administrative procedures**

### **13.1 Regulatory and ethical compliance**

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Council for Harmonization (ICH) Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.



### **13.2 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, written informed consent form, consent form updates, patient 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.

### **13.3 Publication of study protocol and results**

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (*defined as last patient last visit*) and finalization of the study report, the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

### **13.4 Quality Control and Quality Assurance**

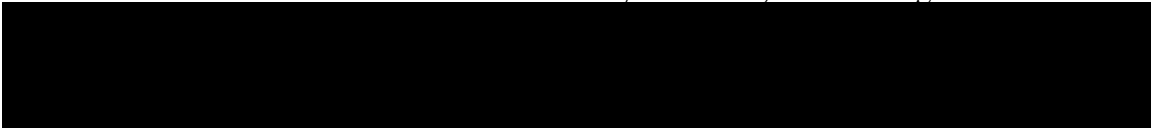
Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, 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 SOPs, and are performed according to written Novartis processes

## **14 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 including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to



Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

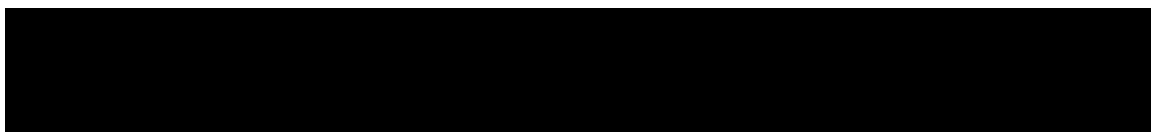
Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and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

#### **14.1 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 required for patient safety 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, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.



## **15 References**

References are available upon request

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.

Conrad MD, Rosenthal PJ (2019) Antimalarial drug resistance in Africa: the calm before the storm? Lancet Infect Dis;19(10):e338-51.

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

Hamed K, 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.

Howie SR (2011) Blood sample volumes in child health research: review of safe limits. Bull World Health Organ;89(1):46–53.

Koller R, Mombo-Ngoma G, Grobusch MP (2018) The early preclinical and clinical development of ganaplacide (KAF156), a novel antimalarial compound. Expert Opin Investig Drugs;27(10):803-10

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.

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 manual (2014) version 13.2:2681-82.

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.

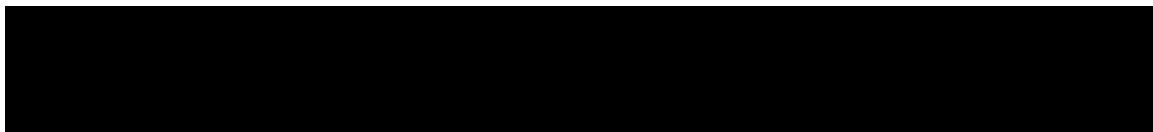
Stepniewska K and White NJ (2006) Some considerations in the design and interpretation of antimalarial drug trials in uncomplicated falciparum malaria. Malaria Journal; 5:127.

WHO (2015) Guidelines for the treatment of malaria  
(<https://.who.int/malaria/publications/atoz/9789241549127/en/>).

WHO (2019) WHO Malaria Report (<https://.who.int/publications-detail/world-malaria-report-2019>).

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 Antimalarial Resistance Network (WWARN) Lumefantrine PK/PD Study Group. Artemether-lumefantrine treatment of uncomplicated *Plasmodium falciparum* malaria: a systematic review and meta-analysis of day 7 lumefantrine concentrations and therapeutic response using individual patient data. *BMC Med*. 2015;13:227. doi: 10.1186/s12916-015-0456-7.



## 16 Appendices

### 16.1 Appendix 1: Clinically notable laboratory values and vital signs

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

#### 1. Hepatic

- ALT or AST  $> 5 \times$  ULN
- TBL  $> 2 \times$  baseline value
- ALT or AST  $> 3 \times$  ULN and INR  $> 1.5$

Potential Hy's Law cases (defined as ALT or AST  $> 3 \times$  ULN and TBL  $> 2 \times$  ULN [mainly conjugated fraction] without notable increase in ALP to  $> 2 \times$  ULN)

- Any clinical event of jaundice (or equivalent term)
- ALT or AST  $> 3 \times$  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)

Criteria for notably abnormal vital signs

**Table 16-1 Criteria for notably abnormal vital signs**

Vital sign		Patient age at visit	
		$< 18$ years	$\geq 18$ years
Systolic blood pressure [mmHg]	High	$\geq 95$ th percentile of the age and height group <sup>1</sup>	$\geq 180$ with increase from updated baseline <sup>5</sup> of $\geq 20$ mmHg
	Low	$\leq 5$ th percentile of the age and height group <sup>1</sup>	$\leq 90$ with decrease from updated baseline <sup>5</sup> of $\geq 20$ mmHg
Diastolic blood pressure [mmHg]	High	$\geq 95$ th percentile of the age and height group <sup>1</sup>	$\geq 105$ with increase from updated baseline <sup>5</sup> of $\geq 15$ mmHg
	Low	$\leq 5$ th percentile of the age and height group <sup>1</sup>	$\leq 50$ with decrease from updated baseline <sup>5</sup> of $\geq 15$ mmHg
Oral body temperature [°C]	High	$\geq 38.4^{\circ}\text{C}$	$\geq 39.1^{\circ}\text{C}$
	Low	$\leq 35.0^{\circ}\text{C}$	$\leq 35.0^{\circ}\text{C}$

Vital sign		Patient age at visit	
		< 18 years	≥ 18 years
Pulse rate [bpm] <sup>2</sup>	High	1-6 months > 160	≥120 with increase from updated baseline <sup>5</sup> of ≥15 bpm
		6-12 months >150	
		12-18 months > 140	
		18-24 months > 135	
		2-3 years > 128	
		3-4 years > 123	
		4-6 years > 117	
		6-8 years > 111	
		8-12 years > 103	
		12-15 years > 96	
		≥ 15 years > 92	
	Low	1-6 months <120	≤50 with decrease from updated baseline <sup>5</sup> of ≥15 bpm
		6-12 months <110	
		12-18 months < 103	
		18-24 months < 98	
		2-3 years < 92	
		3-4 years < 86	
		4-6 years < 81	
		6-8 years < 74	
		8-12 years < 67	
		12-15 years < 62	
		≥ 15 years < 58	
Weight	High	increase from baseline <sup>3</sup> of ≥ 2 Body Mass Index (BMI)-for-age percentile categories <sup>4</sup>	Weight increase from updated baseline <sup>5</sup> of ≥ 10%
	Low	decrease from baseline <sup>3</sup> of ≥ 2 BMI-for-age percentile categories <sup>4</sup>	Weight decrease from updated baseline <sup>5</sup> of ≥ 10%

Vital sign		Patient age at visit		
		< 18 years	≥ 18 years	
Respiratory rate [breath per minute] <sup>2,6,7</sup>	High	1-6 months	>55	≥30bpm
		6-12 months	>50	
		12-18 months	> 46	
		18-24 months	> 40	
		2-3 years	> 34	
		3-4 years	> 29	
		4-6 years	> 27	
		6-8 years	> 24	
		8-12 years	> 22	
		12-15 years	> 21	
		≥ 15 years	> 20	
	Low	1-6 months	<33	≤ 10bpm
		6-12 months	< 30	
		12-18 months	<28	
		18-24 months	< 25	
		2-3 years	< 22	
		3-4 years	< 21	
		4-6 years	< 20	
		6-8 years	< 18	
		8-12 years	< 16	
		12-15 years	< 15	
		15-18 years	< 13	

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

<sup>1</sup> Blood pressure percentiles are calculated for each blood BP record using the method described in Appendix B of the following reference: The Fourth Report on Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics 2004; 114; 555.

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

<sup>3</sup> Baseline BMI-for-age weight status categories are underweight (less than the 5<sup>th</sup> percentile), healthy weight (5<sup>th</sup> percentile to less than the 85<sup>th</sup> percentile), overweight (85<sup>th</sup> to less than the 95<sup>th</sup> percentile) and obese (equal to or greater than the 95<sup>th</sup> percentile);

<sup>4</sup> BMI-for-age percentiles categories (P3, P5, P10, P25, P50, P75, P85, P90, P95, P97) are obtained from the WHO Growth Charts (<http://www.who.int/childgrowth/en/>);

Note: For patients less than 2 years old, growth charts are based on recumbent length instead of height, which is not collected in the study. As an approximation, height collected in the study is considered as equal to the recumbent length;

<sup>5</sup> Updated baseline is the last value collected before the 18<sup>th</sup> birthday.

<sup>6</sup> Eldridge L. What is a Normal Respiratory Rate?, Updated May 16, 2014;

<sup>7</sup> Kou .R., Shuei L., Bradypnea, Department of Physiology, School of Medicine, National Yang-Ming University, Taipei, Taiwan, [http://rd.springer.com/referenceworkentry/10.1007%2F978-3-540-29676-8\\_246](http://rd.springer.com/referenceworkentry/10.1007%2F978-3-540-29676-8_246)

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

**Table 16-2 Liver event and laboratory trigger definitions**

	Definition/ threshold
Liver laboratory triggers	<ul style="list-style-type: none"> <li>3 x ULN &lt; ALT / AST ≤ 5 x ULN</li> <li>1.5 x ULN &lt; TBL ≤ 2 x ULN</li> </ul>
Liver events	<ul style="list-style-type: none"> <li>ALT or AST &gt; 5 x ULN</li> <li>ALP &gt; 2 x ULN (in the absence of known bone pathology)</li> <li>TBL &gt; 2 x ULN (in the absence of known Gilbert syndrome)</li> <li>ALT or AST &gt; 3 x ULN and INR &gt; 1.5</li> <li>Potential Hy's Law cases (defined as ALT or AST &gt; 3 x ULN and TBL &gt; 2 x ULN [mainly conjugated fraction] without notable increase in ALP to &gt; 2 x ULN)</li> <li>Any clinical event of jaundice (or equivalent term)</li> <li>ALT or AST &gt; 3 x ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia</li> <li>Any adverse event potentially indicative of a liver toxicity*</li> </ul>
<p>*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</p>	

**Table 16-3 Follow-up requirements for liver events and laboratory triggers**

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case <sup>a</sup>	<ul style="list-style-type: none"> <li>Discontinue the study drug immediately</li> <li>Repeat LFTs within 24h</li> <li>Hospitalize, if clinically appropriate</li> <li>Establish causality</li> <li><b>Report to Novartis as an SAE</b></li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution <sup>c</sup> (frequency twice a week until resolution, stabilize or return to within baseline values)
<b>ALT or AST</b>		
> 8 x ULN	<ul style="list-style-type: none"> <li>Discontinue the study drug immediately</li> <li>Repeat LFTs within 24h</li> <li>Hospitalize if clinically appropriate</li> <li>Establish causality</li> <li><b>Report to Novartis as an SAE</b></li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution <sup>c</sup> (frequency twice a week until resolution, stabilize or return to within baseline values)
> 3 x ULN and INR > 1.5	<ul style="list-style-type: none"> <li>Discontinue the study drug immediately</li> <li>Repeat LFTs within 24h</li> <li>Hospitalize, if clinically appropriate</li> <li>Establish causality</li> <li><b>Report to Novartis as an SAE</b></li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution <sup>c</sup> (frequency twice a week until resolution, stabilize or return to within baseline values)
> 5 to ≤ 8 x ULN	<ul style="list-style-type: none"> <li>Repeat LFT within 24 hours</li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP

Criteria	Actions required	Follow-up monitoring
	<ul style="list-style-type: none"> <li>If elevation persists, continue follow-up monitoring</li> <li>If elevation persists for more than 2 weeks, discontinue the study drug</li> <li>Establish causality</li> <li><b>Report to Novartis as an SAE</b></li> </ul>	and GGT until resolution <sup>c</sup> (frequency twice a week until resolution, stabilize or return to within baseline values)
> 3 × ULN accompanied by symptoms <sup>b</sup>	<ul style="list-style-type: none"> <li>Discontinue the study drug immediately</li> <li>Repeat LFT within 24 hours</li> <li>Hospitalize if clinically appropriate</li> <li>Establish causality</li> <li><b>Report to Novartis as an SAE</b></li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution <sup>c</sup> (frequency twice a week until resolution, stabilize or return to within baseline values)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	<ul style="list-style-type: none"> <li>Repeat LFT within 24 hours</li> <li>If elevation is confirmed, initiate close observation of the patient</li> </ul>	Monitor LFT until resolution <sup>c</sup> (frequency twice a week until resolution, stabilize or return to within baseline values)
<b>ALP (isolated)</b>		
> 2 × ULN (in the absence of known bone pathology)	<ul style="list-style-type: none"> <li>Repeat LFT within 24 hours</li> <li>If elevation persists, establish causality</li> </ul>	Monitor LFT until resolution <sup>c</sup> (frequency twice a week until resolution, stabilize or return to within baseline values)
<b>TBL (isolated)</b>		
> 2 × ULN (in the absence of known Gilbert syndrome)	<ul style="list-style-type: none"> <li>Repeat LFT within 24 hours</li> <li>If elevation persists, discontinue the study drug immediately</li> <li>Hospitalize if clinically appropriate</li> <li>Establish causality</li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution <sup>c</sup> (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)	<ul style="list-style-type: none"> <li>Repeat LFT within the next week</li> <li>If elevation is confirmed, initiate close observation of the patient</li> </ul>	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	<ul style="list-style-type: none"> <li>Discontinue the study drug immediately</li> <li>Hospitalize the patient</li> <li>Establish causality</li> <li><b>Report to Novartis as an SAE</b></li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution <sup>c</sup> (frequency twice a week until resolution, stabilize or return to within baseline values)

Criteria	Actions required	Follow-up monitoring
Any AE potentially indicative of a liver toxicity* severe events only SMQ AE	<ul style="list-style-type: none"> <li>Consider study drug discontinuation</li> <li>Hospitalization if clinically appropriate</li> <li>Establish causality</li> <li><b>Report to Novartis as an SAE</b></li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution <sup>c</sup> (frequency twice a week until resolution, stabilize or return to within baseline values)
<p>* 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</p> <p><sup>a</sup> Elevated ALT/AST &gt; 3 × ULN and TBL &gt; 2 × ULN but without notable increase in ALP to &gt; 2 × ULN <sup>b</sup> (General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia <sup>c</sup> 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.</p>		

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

### 16.3 Appendix 3: Specific Renal Alert Criteria and Actions and Event Follow-up

**Table 16-4 Specific Renal Alert Criteria and Actions**

Renal Event	Actions
Confirmed sCR increase 25 – 49%	<ul style="list-style-type: none"> <li>Consider causes and possible interventions</li> <li>follow-up within 2-5 days</li> </ul>
sCR increase <sup>a</sup> 50 % + <b>OR if &lt;18 years old, eGFR 35 mL/min/1.73 m<sup>2</sup></b>	<ul style="list-style-type: none"> <li>Consider causes and possible interventions</li> <li>Repeat assessment within 24-48h if possible</li> <li>Consider drug interruption or discontinuation unless other causes are diagnosed and corrected</li> <li>Consider patient hospitalization and specialized treatment</li> </ul>
New onset dipstick proteinuria ≥ 3+ OR Protein-creatinine <b>ratio</b> (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	<ul style="list-style-type: none"> <li>Consider causes and possible interventions</li> <li>Assess serum albumin &amp; serum total protein</li> <li>Repeat assessment to confirm</li> <li>Consider drug interruption or discontinuation unless other causes are diagnosed and corrected</li> </ul>
New onset hematuria ≥ 3+ on urine dipstick	<ul style="list-style-type: none"> <li>Repeat assessment to confirm</li> <li>Distinguish hemoglobinuria from hematuria</li> <li>Urine sediment microscopy</li> <li>Assess sCr</li> <li>Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation</li> <li>Consider bleeding disorder</li> </ul>
* Corresponds to KDIGO criteria for Acute Kidney Injury	

Additional specialized assessments are available to assess renal function or renal pathology. (Note: In exceptional cases, when a nephrologist considers a renal biopsy, it is recommended to make slide specimen available for evaluation by the RSG to potentially identify project-wide patterns of nephrotoxicity.)

Whenever a renal event is identified, a detailed patient history and examination are indicated to identify and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5-minute rest, with an appropriate cuff size)
- Signs and symptoms like fever, headache, shortness of breath, back or abdominal pain, dysuria or hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other diseases or causes, e.g., dehydration due to delirium, tumor lysis

**Table 16-5 Renal Event follow-up**

<b>FOLLOW-UP OF RENAL EVENTS</b>
<ul style="list-style-type: none"><li>• Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells</li><li>• Blood pressure and body weight</li><li>• sCr, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid</li><li>• Urine output</li></ul>
Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the CRF
<ul style="list-style-type: none"><li>• Event resolution: (sCr within 10% of baseline or PCR &lt; 1 g/g Cr, or ACR &lt;300 mg/g Cr) or</li><li>• Event stabilization: sCr level with <math>\pm 10\%</math> variability over last 6 months or protein-creatinine ratio stabilization at a new level with <math>\pm 50\%</math> variability over last 6 months.</li><li>• Analysis of urine markers in samples collected over the course of the DIN event</li></ul>

## **16.4 Appendix 4: Signs/symptoms of severe/complicated malaria**

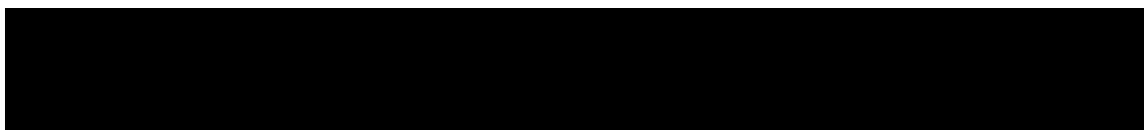
### **Danger signs:**

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:**

Outline bedside clinical classification of severe malaria in children (<12 years) in a high transmission area

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 parasitemia:



### **Group 1**

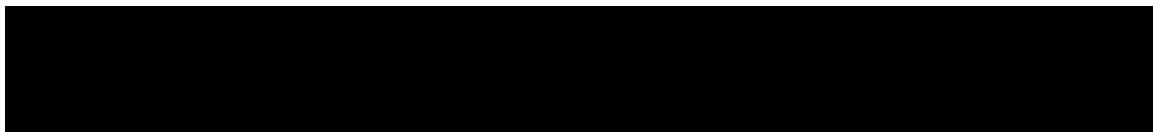
- Prostrate children (prostration is the inability to sit upright in a child normally able to do so or to drink in the case of children too young to sit). Three subgroups of increasing severity should be distinguished:
  - Prostrate but fully conscious
  - Prostrate with impaired consciousness but not in deep coma
  - Coma (the inability to localise a painful stimulus)
- Respiratory distress (acidotic breathing):
  - Mild – sustained nasal flaring and/or mild intercostal indrawing (recession)
  - Severe – the presence of either marked indrawing (recession) of the bony structure of the lower chest wall or deep (acidotic) breathing
- Shock compensated or decompensated

### **Group 2**

- Children who, although able to be treated with oral antimalarials, require supervised management because of the risk of clinical deterioration but who show none of the features of group 1 (above). These include children with any of the following:
  - Haemoglobin <5 g/dl or haematocrit < 15%
  - 2 or more convulsions within a 24-h period
  - Haemoglobinuria (blackwater)
  - Jaundice

### **Group 3**

Children who require parenteral treatment because of persistent vomiting but who lack any specific clinical or laboratory features of groups 1 or 2 (above).



## 16.5 Appendix 5: Cardiac Alert Threshold Values and Actions

**Table 16-6 Cardiac alert threshold values and actions**

	Values	Actions
QTcF	<ul style="list-style-type: none"> <li>• QTcF &gt; 500.</li> </ul>	<ul style="list-style-type: none"> <li>• If confirmed by two repeat ECG, check and correct the patient's serum potassium and magnesium immediately.</li> </ul>
Cardiac rhythm	<ul style="list-style-type: none"> <li>• Sustained ventricular tachycardia lasting 30 sec or more, or ventricular fibrillation, or any hemodynamically compromising cardiac arrhythmia</li> </ul>	<ul style="list-style-type: none"> <li>• Report as SAE to Sponsor and transmit to central vendor immediately for prompt review.</li> <li>• Discontinue patient from study therapy.</li> <li>• Monitor ECG hourly until at least 2 consecutive hourly ECGs performed are back to baseline</li> </ul>
QTcF	<ul style="list-style-type: none"> <li>• Increase from baseline <math>\geq 60</math> ms</li> </ul>	<ul style="list-style-type: none"> <li>• If confirmed by two repeat ECG, check and correct the patient's serum potassium and magnesium immediately.</li> </ul>
Resting heart rate	<ul style="list-style-type: none"> <li>• HR &lt; 50/min with &gt; 25% decrease from pretreatment baseline verified by ECG</li> </ul>	<ul style="list-style-type: none"> <li>• Report to Sponsor as AE (unless it meets the SAE criteria as described in <a href="#">Section 10.1.2</a>) and transmit to central vendor immediately for prompt review.</li> </ul>

