NOVARTIS

Clinical Development

KLU156/Ganaplacide

CKLU156A12301 / NCT05842954

A randomized, open-label, multicenter study to compare efficacy, safety and tolerability of KLU156 with Coartem® in the treatment of uncomplicated Plasmodium falciparum malaria in adults and children followed by an Extension phase with repeated KLU156 treatment

Statistical Analysis Plan (SAP)-Core phase

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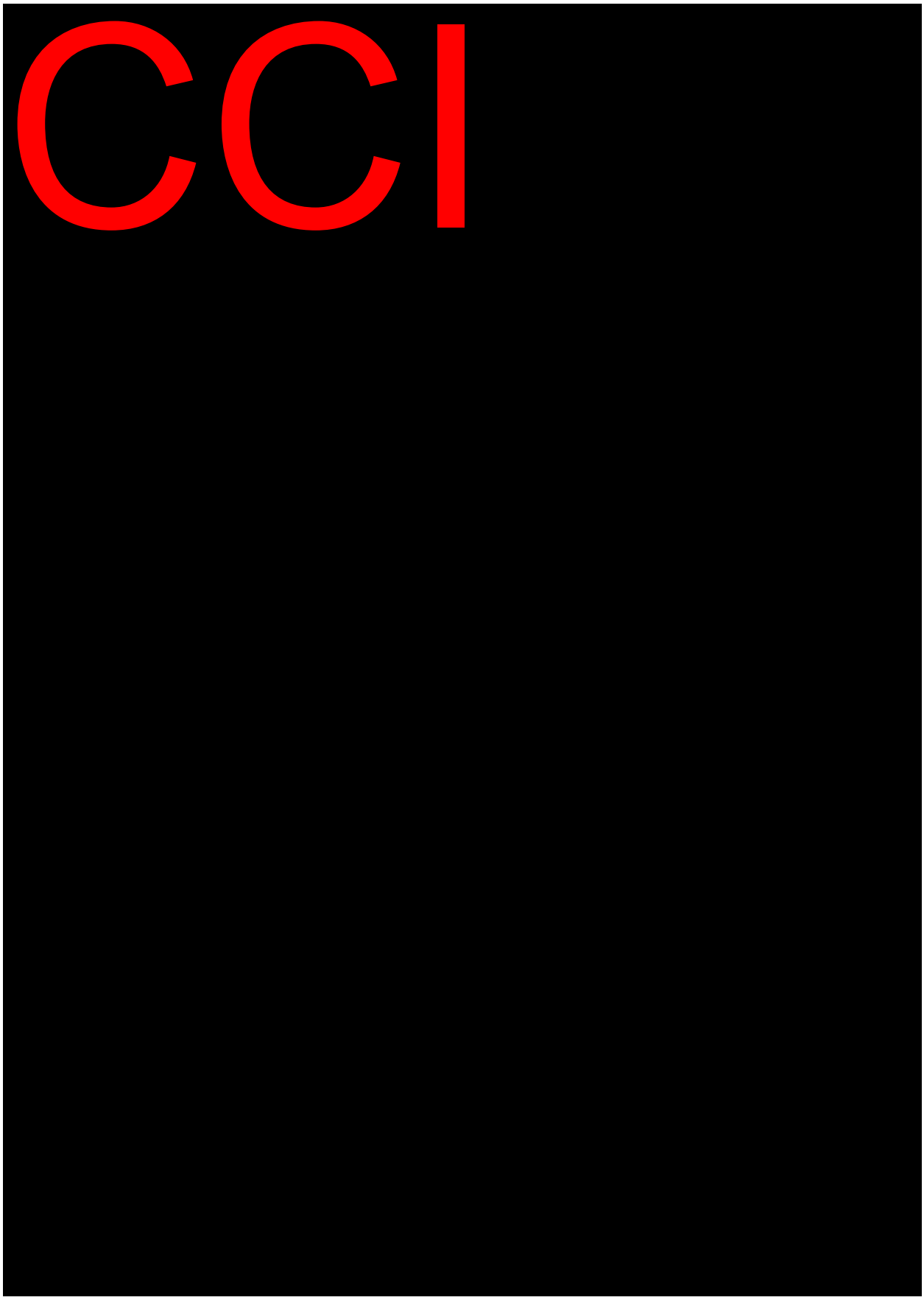
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List of abbreviations

AE	Adverse event
ACPR	Adequate clinical and parasitological response
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
Bid	bis in diem/twice a day
CDC	Centers for Disease Control and Prevention
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Data base lock
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
ETF	Early treatment failure
FAS	Full Analysis Set
FCT	Fever clearance time
GCT	Gametocyte clearance time
IMP	Investigational Medical Product
IVR	Interactive Voice Response
IWR	Interactive Web Response
LCF	Late clinical failure
L.O.S.	Level of significance
LPF	Late parasitological failure
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mRAS	Modified randomized analysis set
mFAS	Modified full analysis set
mSAF	Modified safety analysis set
mPAS	Modified PK analysis set
NCI	National Cancer Institute
o.d.	Once Daily
OP	Observed Principal Stratum
CCI	[redacted]
CCI	[redacted]
PCT	Parasite clearance time
qd	Qua'que di'e / once a day
RAS	Randomized analysis set
SAP	Statistical Analysis Plan
SAF	Safety analysis set
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analysis, which is planned in the protocol (Version 01). Two separate reports are intended to be created: 1) A report after completion of the Core phase and 2) a report after the end of Extension phase. The report after completion of the Core phase will be based on analyses using data collected during Core phase.

Mock shells for the analyses of data collected in the Core phase is based on this SAP. SAP and mock shells for the data collected in the extension phase will be prepared separately..

Statistical outputs for the analyses of data collected for the Core phase will be generated according to the mock shells and this SAP. A separate mock shell will be prepared based on this SAP and executed for DMCs.

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

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

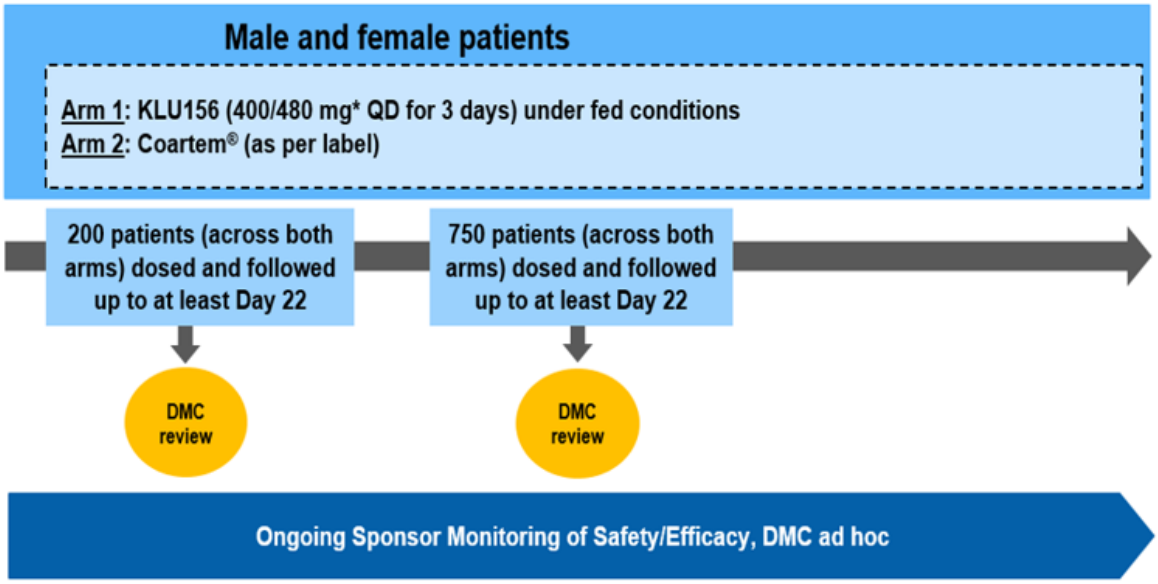
1.1 Study design

This study includes a Core phase followed by an Extension phase.

Core phase: This will be a multicenter, open-label, randomized, parallel-group, non-inferiority study in adults and children with uncomplicated *P. falciparum* malaria (*P. falciparum* with or without other *Plasmodium* spp. co-infection).

Approximately 1500 male and female participants ≥ 10 kg body weight will be randomized in the study to KLU156 or Coartem following a 1:1 ratio. Randomization will be stratified by mixed infection status (yes or no) and country. Randomization for mono-infection with *P. falciparum* will be further stratified by body weight (≥ 35, 25 to <35, 15 to < 25, and < 15 kg).

Figure 1-1 Core Phase: Study design



* KLU156 400/480mg is a fixed-dose combination containing 400 mg of ganaplacide (KLU156) and 480 mg of a solid dispersion formulation of lumefantrine (lumefantrine-SDF). This dose is for participants with a bodyweight ≥ 35kg. Participants < 35kg will take a fraction of the dose according to weight group as shown in Protocol Table 6-4. KLU156 should be administered under fed conditions (light meal). Participants will be followed up to Day 43 in the Core Phase.

The primary analysis timepoint is Day 29. There is no interim analysis planned to stop the trial early for futility or overwhelming efficacy.

Although the Core phase is open-label, the Novartis personnel responsible for conducting the trial (Novartis Clinical Trial team, CTT) will be blinded to the identity of the treatment from the time of randomization until the database lock for the analysis of the Core phase. Prior to unblinding the data of the Core phase (for the Novartis CTT), at least two DMC reviews are planned to minimize risks in this vulnerable participant population:

1. Once the first 200 participants (across both treatment arms) in the Core phase have been dosed and followed up to at least Day 22.
2. Once the first 750 participants (across both treatment arms) in the Core phase have been dosed and followed up to at least Day 22.
3. Additional DMC reviews may be conducted ad-hoc during the study, as deemed necessary.

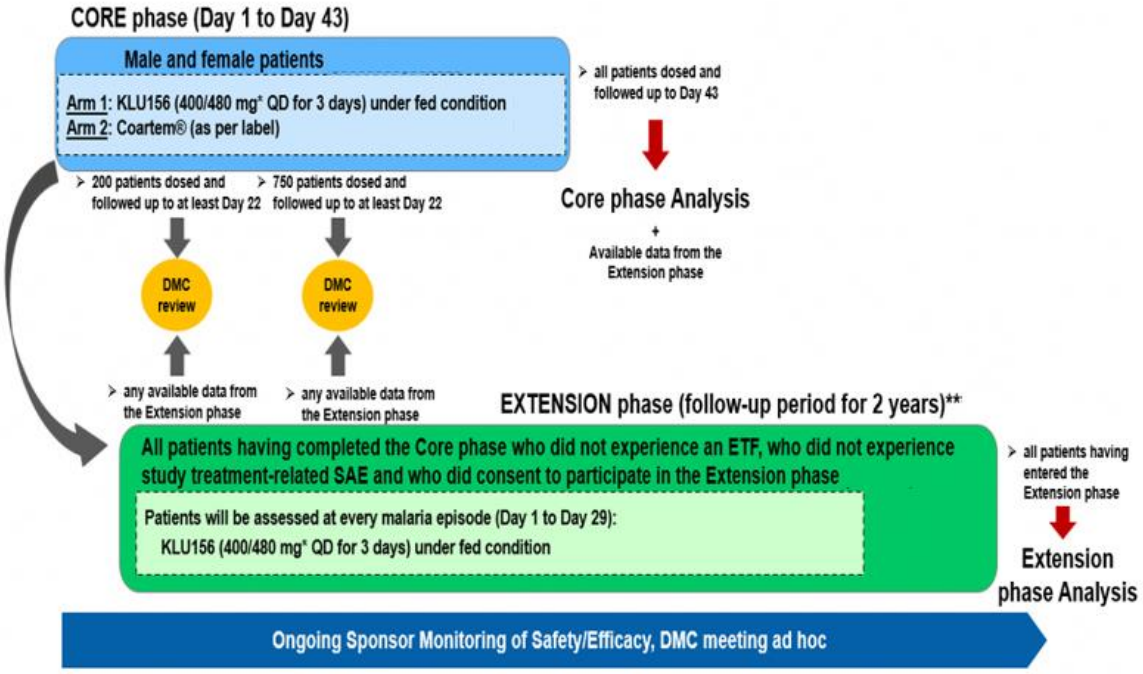
The sample size may be increased based on the outcome of the blinded sample size re-estimation after about 750 participants (across both treatment arms) in the Core phase have been randomized. Note about 200 more patients may be enrolled based on the blinded sample size review.

Extension Phase:

The Core Phase will be followed by an Extension Phase.

All participants who complete the Core Phase according to the protocol, who did not meet the criteria for ETF (see Protocol Section 10.6) and who did not experience any SAE related to KLU156 or Coartem, will be offered the opportunity to continue in the Extension Phase (N ≤ 1500) allowing them to receive study treatment for subsequent malaria episodes. A new informed consent form will be signed before proceeding into the Extension Phase. During this phase, participants should come back to the study site at any time when they develop symptoms indicative of a new malaria episode.

Figure 1-2 Core Phase and Extension Phase



* This dose is for participants with a bodyweight ≥ 35 kg. Participants < 35 kg will take a fraction of the dose according to weight group as shown in Protocol Table 6-4. KLU156 should be administered under fed conditions (light meal).

** The sample size might be reevaluated upwards (Protocol Section 9.9.3).

*** The Extension phase might be terminated early by Sponsor decision. As the main objective of the Extension phase is to assess the safety and tolerability of KLU156 repeated treatment, the number of follow-up visits is reduced to Days 4, 8 and 29 for each malaria episode.

After all participants in the Core phase have completed the Day 43 visit, the interim database will be cleaned and locked. The Novartis CTT will be unblinded to the treatment group in the Core phase. The interim locked database will be used for NDA submission. The existing database will be used to update the extension data. After the last participant has completed the last visit in the Extension phase, the database will be locked finally.

Note that a SAP and clinical study report for the Extension phase will be prepared separately.

1.2 Study objectives, endpoints and estimands

Objectives and related endpoints in the Core phase are described in Table 1-1 below. Definitions for the primary and secondary estimands that will be used for the Core Phase of the study are described respectively in Table 1-2 and Table 1-3 below.

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
To confirm the efficacy of KLU156 in adults and children ≥ 10 kg body weight suffering from uncomplicated malaria caused by *P. falciparum* (with or without other *Plasmodium* spp. co-infection) by demonstrating that KLU156 is non-inferior to Coartem (non-inferiority margin = 5%) based on the PCR-corrected ACPR at Day 29.	● PCR-corrected adequate clinical and parasitological response (ACPR) at Day 29 (i.e., 28 days post-first dose administration)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
Key secondary objective: To further confirm the efficacy of KLU156 by demonstrating non-inferiority of KLU156 to Coartem (NI margin 7.5%) based on the uncorrected ACPR at Day 29	● Uncorrected ACPR at Day 29
To confirm the efficacy of KLU156 by assessing uncorrected and PCR-corrected ACPR at additional time points, as well as fever, parasite and gametocyte clearance times (FCT, PCT and GCT), gametocyte carriage over time between the two treatment arms.	● PCR-corrected and uncorrected ACPR at Days 22 and 43 (i.e., 21 and 42 days post-first dose administration). Incidence rate of recrudescence and new infection at Days 22, 29 and 43. Parasite, Fever and Gametocyte Clearance Times. Proportion of participants with parasitemia at 12, 24, 48 and 72 h after treatment. Disappearance or development of gametocytemia in participants with or without gametocytemia at baseline (pre-first dose administration), respectively.
To compare the safety and tolerability profile of the two treatment arms on AEs, general laboratory, vital signs and ECG measurements.	● Standard safety/tolerability assessments: Adverse event (AE)/serious adverse event (SAE) incidence and severity, laboratory abnormalities and ECG abnormalities.
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
CCI	[redacted]

1.2.1 Primary estimand(s)

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g., premature discontinuation of treatment). Estimands will be used for the Core Phase of the study.

The primary estimand for the PCR-corrected ACPR at Day 29 is summarized in Table 1-2 below:

Table 1-2 Definition of Primary estimand for PCR-corrected ACPR at Day 29 (Core Phase)

Clinical question of interest	"What is the difference in the proportion of participants with uncomplicated *P. falciparum* malaria (*P. falciparum* with or without other *Plasmodium* spp. co-infection) achieving PCR-corrected ACPR at Day 29 between KLU156 and Coartem treatment arms?" This assessment is to be made in participants who would: ● take the complete course of study treatment (at least 80% of study medication) regardless of treatment assignment ● take non-study treatment with antimalarial activity prior to Day 29 only in case of recrudescence of parasite (rescue treatment) Justification for targeting this treatment effect is the need to estimate the effect of a complete course of study treatment without requirement for non-study treatment with antimalarial activity in achieving PCR-corrected ACPR at Day 29.
Population	Uncomplicated malaria in adults and children (≥ 10 kg body weight) due to *P. falciparum* (with or without other *Plasmodium* spp. co-infection): ● who would complete the full course of study treatment (at least 80% of the total dose) regardless of treatment assignment ● and who would take non-study treatment with antimalarial activity prior to Day 29 only in case of recrudescence of parasite (rescue treatment)
Primary variable	A binary outcome indicating that the participant is alive and has achieved PCR-corrected ACPR at Day 29 (see below for more detailed information).
Treatment of interest	A complete course (at least 80% of the total dose) of study treatment (KLU156 or Coartem).
Handling of remaining intercurrent events	All intercurrent events (death, treatment discontinuation or non-compliance, taking of non-study treatment with antimalarial activity) are included in the population or variable attributes. No other intercurrent event is considered.
Summary measure	Difference (and 95% confidence interval [CI]) in proportion between KLU156 and Coartem.

More information about the primary variable PCR-corrected ACPR at Day 29:

Recurrence of *P. falciparum* asexual forms on Day 8 or later is considered as failure only in the case of recrudescence confirmed by PCR genotyping i.e., if the parasite strain was already present at baseline (Day 1 is considered first day of dosing). This approach is recommended by WHO methods and techniques for clinical trials on antimalarial drug efficacy (WHO 2008) and widely used to assess drug efficacy in malaria clinical trials.

A follow-up of 28 days (corresponds to Day 29, when first day of treatment is considered as Day 1) is recommended by WHO as the minimum duration for medicines with elimination half-lives of less than 7 days (such as artemisinin derivatives, lumefantrine, ganaplacide, and others) for uncomplicated malaria studies (WHO 2022).

To distinguish between new and recrudescent infections, the WHO protocol highlights that molecular genotyping must be used in clinical trials. The PCR-corrected adequate clinical and parasitological response is the widely used endpoint for malaria drug assessment. Using this endpoint also improves the overall comparability of clinical trials, whereas the uncorrected endpoints include new infections and are heavily influenced by the level of malaria endemicity around the various study sites involved in the study. For that, the most commonly used molecular markers for genotyping *P. falciparum* will be used by the central laboratory. Blood samples collected pre-treatment (day 1) and on the day of treatment failure (day X) will be compared using three markers: genes for merozoite surface protein 1 (msp1), merozoite surface protein 2 (msp2) and glutamate-rich protein (glurp). The outcome whether a *P. falciparum* asexual parasite reappearance is recrudescence or new infection using the decision algorithm "WHO/MMV" will be provided by the central laboratory.

1.2.2 Secondary estimand

The secondary estimand for the uncorrected ACPR at Day 29 is summarized in Table 1-3 below. The estimand will be used for the Core Phase of the study.

Table 1-3 Definitions of secondary estimand of uncorrected ACPR at Day 29 (Core Phase)

Clinical question of interest	"What is the difference in the proportion of participants with uncomplicated *P. falciparum* malaria (*P. falciparum* with or without other *Plasmodium* spp. co-infection) achieving uncorrected ACPR at Day 29, without the need of non-study treatment with any antimalarial activities, between KLU156 and Coartem treatment arms?" The justification for targeting this treatment effect is to estimate the effect of study treatment in the absence of non-study treatment with any antimalarial activities in achieving uncorrected ACPR at Day 29.
Population	Uncomplicated malaria in adults and children (≥ 10 kg body weight) due to *P. falciparum* (with or without other *Plasmodium* spp. co-infection).
Variable	A binary outcome indicating that participant is alive, did not take non-study medicines with any antimalarial activities prior to Day 29, and has achieved uncorrected ACPR at Day 29.
Treatment of interest	Randomized to KLU156 or Coartem regardless of study treatment discontinuation or non-compliance.
Handling of remaining intercurrent events	All intercurrent events (death, treatment discontinuation or noncompliance, taking of non-study treatment with antimalarial activity) are included in the variable or treatment attributes of the estimand. No other intercurrent event is considered.
Summary measure	Difference (and 95% CI) in proportion between KLU156 and Coartem.

1.2.3 US NDA submission

Different primary and key secondary endpoints will be used for the Core Phase of the study for the US New Drug Application (NDA) submission, in accordance with their requirement for demonstrating antimalarial drug efficacy.

For US NDA submission, the secondary estimand based on uncorrected ACPR at Day 29 in Section 1.2.2 will become the primary estimand while the primary estimand based on PCR-corrected ACPR at Day 29 in Section 1.2.1 will become the secondary estimand. Primary analysis of PCR-corrected ACPR at Day 29 for Ex-US submission is detailed in Section 2.5 and for US submission the primary analysis of uncorrected ACPR at Day 29 is detailed in Section 2.6.

2 Statistical methods for Core Phase

Unless otherwise specified, the statistical methods discussed in this section are applicable for data collected in the Core Phase of trial.

2.1 Data analysis general information

For the primary estimand, secondary estimand, and other endpoints as applicable, the number and percentage of participants with intercurrent events will be provided by treatment arm for each intercurrent event.

Data will be analyzed by Novartis according to the data analysis presented in section 9 of the study protocol, which is also available in Appendix 16.1.1 of the CSR. Detailed information is given in the following sections.

Data analyses required for the study Data Monitoring Committee (DMC) will be analyzed by an independent CRO. The outline of the DMC analysis outputs is presented in the DMC charter and will be detailed in a separate mock shell.

Information on visit windowing, imputation rules and the methods of efficacy and safety analyses is given in the sections to follow.

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

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

Unless otherwise stated, p-values (if required) will be provided for two-sided alternative hypotheses and presented up to 4 significant digits after decimal place; confidence intervals will be presented up to 2 significant digits after decimal place. PK summaries will be presented up to 3 significant digits except CV%, which will be rounded up to 1 digit after decimal.

All post-text tables will be generated using Microsoft Word cell-based format so that they can be easily cut and pasted to create intext tables for the CSR.

2.1.1 General definitions

Study treatment: KLU156, a fixed combination of ganaplacide and Lumefantrine solid dispersion formulation (LUM-SDF) is the investigational treatment. Coartem® is used as the standard of care (SOC). They are referred to as study treatments in the document.

The following treatment group names will be used in statistical analyses and outputs:

KLU156, Coartem

Participants < 35 kg will take a fraction of that full dose according to their weight group as shown in [protocol Table 6-4]. However, they will be included under the same treatment group as with participants ≥35 kg who will be receiving full dose.

Baseline: The last measurement made prior to administration of the first dose of study treatment. Note this may include measurements taken on the day of randomization (e.g., laboratory, ECG, vitals). If a participant did not receive any dose of study treatment, then the randomization date will be used as the date of first dose of study treatment.

Study Day: Study Day will be calculated with respect to the first dose of study treatment. The first day of administration of study treatment (first dose) is defined as Day 1. Day -1 will be the day before Day 1. Day 0 does not exist. Due to the multiple assessments collected more than once for a day in the treatment phase for some variables, the study day calculation is based on the treatment start date and time.

For assessments collected prior to Day 1, Study Day = date of assessment - date of first dose of study treatment.

For assessments that are performed once for a day on or after Day 1: Study Day = date of assessment – date of first dose of study treatment + 1.

For the assessments that are performed more than once for a day on or after Day 1: Study Day = Integer [(datetime of assessment – datetime of first dose of study treatment)/(60*60*24)] + 1.

Tail of KM plots: Since participants may come to visit earlier or later than the targeted day and the tail of KM plots after the day of last planned assessment is not reliable due to small numbers of participants at risk, the time to event/censoring will be reset to Day 43 if it is greater than 43. This principle will be used for relevant tables using the KM method.

Body temperature (Axillary temperature) = (oral equivalent) – 0.5 ºC = (tympanic/rectal equivalent)- 1ºC.

Fever: Axillary equivalent temperature should be ≥ 37.5 ºC axillary or 38°C oral or 38.5°C tympanic/rectal.

2.1.1.1 Definition of treatment failures

Participants with uncomplicated P. falciparum malaria with or without other Plasmodium spp. co-infection are eligible to be enrolled in this study. Plasmodium parasite counts in Falciparum asexual forms (not gametocytes), Vivax, Ovale, Malariae, and Knowlesi will be analyzed separately in the determination of treatment failures defined below. If treatment failure is found by any of the aforementioned parasite types, the patient will be classified as the according treatment failure and the treatment failure time is the earliest occurrence day among different parasite types.

Early Treatment Failures (ETF)

Participant will be classified as ETF upon meeting any of the following criterion

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

Late Clinical Failure (LCF)

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

- Development of danger signs or severe malaria on any day from Day 5 (after Day 4) to Day 43 in the presence of parasitaemia without previously meeting any of the criteria of early treatment failure.
- Presence of parasitaemia and axillary temperature $\geq 37.5^{o}C$ on any day from Day 5 (after Day 4) to Day 43 without previously meeting any of the criteria of Early Treatment Failure.
- Missing body temperature assessment in presence of parasitemia will be classified as LCF.

  Note: Although Day 5 assessments are not planned in the assessment schedule, if baseline parasites are not cleared at Day 4 as per microscopy assessment, additional daily parasite assessment at Day 5 or later should be performed until the parasites are cleared.

Late Parasitological Failure (LPF)

Presence of parasitaemia on any day from Day 8 to Day 43 and axillary temperature $< 37.5^{o}C$ without previously meeting any of the criteria of Early Treatment Failure or Late Clinical Failure.

Note: Danger signs or severe malaria are recorded as adverse events. The adverse event start date of danger signs or severe malaria will be used in the determination of ETF and LCF. The body temperature assessment closest to the blood smear assessment date will be used. Day x means study day x. LCF or LPF at Day 43 includes assessment after Day 43 if it occurs.

Recrudescence: defined as appearance of parasites after clearance of initial infection with a genotype identical to that of parasites present at baseline. Recrudescence must be confirmed by PCR genotyping for Falciparum asexual form at baseline and at time of recurrence. For other Plasmodium spp. at baseline, appearance of parasites at post-baseline is considered as recrudescence as PCR genotyping is not considered reliable.

New infection: defined as appearance of parasites after clearance of initial infection with a genotype different from those parasites present at baseline. New infection must be confirmed by PCR genotyping for Falciparum asexual form at baseline and at time of recurrence. For other Plasmodium spp., that are not present at baseline the appearance of those parasites at post-baseline is considered as a new infection.

Whether the recurrence of Falciparum asexual parasitaemia after 7 days is recrudescence or new infection is determined and provided by the central laboratory.

Negative PCR means that no asexual parasite is detected by the central laboratory using PCR genotyping in a positive blood smear by microscope and will categorize the parasite assessment as responder for PCR corrected ACPR. In this scenario, the presence of asexual parasite by microscope will not be overwritten for uncorrected ACPR.

Time to parasite clearance (PCT): defined as time from the first dose until the first total and continued disappearance of baseline Falciparum asexual parasite forms and other spp. which remained at least a further 48 h.

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 or 38.5°C tympanic/rectal for at least a further 24 h; Fever clearance will be analyzed only in the participants with fever at baseline.

Time to gametocyte clearance (GCT): defined as time from the first dose until the first complete and sustained disappearance of gametocyte for at least a further 48h

2.1.1.2 Definition of treatment outcomes ACPRs

Uncorrected ACPR at Day X visit where X= 22, 29, or 43

- Note- once a participant is declared as non-responder at a particular visit, s/he will remain the non-responder for all subsequent visits.
- A participant is considered as non-responder at Day X if the participant experiences an ETF, LCF or LPF on or before Day X visit day.
- If the participant discontinues the study prior to Day X without ETF or LCF or LPF, the response is considered as missing
- A participant is also considered as non-responder at Day X if the parasite is not cleared by Day X visit day unless the participant discontinues the study prior to parasite clearance.
- If a participant is dead by Day X , the response is considered as non-responder.
- A participant is considered as responder at Day X if the participant is not classified as a non-responder at Day X and the participant has a malaria blood film showing absence of parasite at Day X visit day or next available visit if Day X visit day is missing.
- The response for a participant is considered as missing/undetermined at Day X if the participant is not classified as a non-responder prior to Day X visit day and the malaria blood film result for Day X is missing and not followed by a subsequent negative result.

Day X visit day is the actual visit day that is closest to the target day for Day X if there are multiple visits in a visit window (See Section 6.1.4).

Missing values will be imputed as specified in Section 2.6.4 and Section 2.6.5.

PCR-corrected ACPR at Day X visit where X=22, 29, or 43

- Note- once a participant is declared as non-responder at a particular visit, s/he will remain the non-responder for all subsequent visits.
- Response status at Day X will be derived using following rules for the participants whose response is not declared as non-responder at previous visit.
  - A participant is considered as non-responder at Day X if the participant experiences an ETF, LCF from Day 5 to Day 7 , or initial parasite is not cleared by Day X visit day. However, in case the participant discontinues the study prior to Day X without ETF or LCF or LPF, the response is considered as missing,

- A participant with recrudescence from Day 8 to Day X visit day is considered as non-responder at Day X . If the malaria blood film result at Day X is missing, a participant is considered as non-responder at Day X if the next available result indicates recrudescence.
- A participant with absence of parasite from Day 8 to Day X visit day is considered as responder at Day X if the participant is not classified as a non-responder at Day X. If the malaria blood film result at Day X is missing, a participant is considered as responder at Day X if the next available microscopic result is absence of parasite.
- If new infection/PCR negative is on or before Day X visit day and within the Day X window, the participant is considered as responder at Day X. If the malaria blood film result at Day X visit day is missing, a participant is considered as responder at Day X if the next available result indicates new infection/PCR negative.
- The response for a participant is considered as missing/undetermined if
  - The participant has parasite present from Day 8 to Day X for which the PCR genotyping of recrudescence or new infection is missing or not determined.
  - The malaria blood film result at Day X visit day is missing and the PCR genotyping of recrudescence or new infection is missing or not determined at the next available visit
  - The malaria blood film result at Day X and afterwards is missing.

Missing values will be imputed as specified in Section 2.5.4.

Note - In the context of derivation of ACPR status at Day X , the 'Day X ' is referred to as the Day X analysis visit. For e.g., ACPR status at Day 29 is referred to as the ACPR status at Day 29 analysis visit. Analysis visit X will be derived using the day of actual visit as defined in Table 6-5, Table 6-6, and Table 6-7. Unscheduled visits will be considered for deriving analysis visit. Assessments ‘prior to Day X' will be identified using study day of assessments prior to Day X analysis visit. The outcome of PCR-corrected ACPR and uncorrected ACPR at a given day is categorized as responder or non-responder to distinguish from failure used in early treatment failure, late clinical failure or late parasitological failure. With this notation, ACPR rate is the proportion of responders.

Missing intermediate parasite counts after baseline parasitemia has been cleared will be considered as absence of parasites if the next available parasite assessment shows absence of parasites.

Participants who do not have the baseline parasitemia cleared are, in general, considered as not achieving ACPR (irrespective of PCR correction) at all timepoints (Days 22, 29, and 43) unless the participants discontinue the study prior to parasite clearance. The above definitions of ACPRs are purely based on the malaria blood film and PCR results without consideration for taking concomitant anti-malaria drugs. In statistical analyses, some responses may be overridden for participants who take concomitant anti-malaria drugs (see Sections 2.5, Section 2.6 and Section 2.7).

See Section 6.7.4. for the various scenarios for derivation of the treatment outcomes.

2.2 Analysis sets

Randomized analysis set (RAS)

The Randomized set includes all participants who are randomized into the study. Unless otherwise specified, mis-randomized participants will be included in the randomized set. Participants will be analyzed according to the treatment arm assigned to them at randomization.

Mis-randomized participants, if identified from IRT, include participants who are screen-failures, but were mistakenly randomized by the Investigator (e.g., before final eligibility was assessed) and have not been treated.

Full analysis set (FAS)

The Full analysis set will be comprised of all participants from the Randomized set, excluding mistakenly randomized participants, whose baseline *P. falciparum* asexual parasite count is ≥ 1,000 and ≤ 200,000 parasites/ µL. Following the intent-to-treat principle, participants will be analyzed according to the treatment arm assigned to them at randomization. Participants excluded from FAS will be flagged in the data listings.

Safety analysis set (SAF)

The Safety set includes all participants who take at least one dose of study drug during the treatment period of the study. Participants will be analyzed according to the treatment received. In particular, a participant will be analyzed in the same treatment arm as randomized if they receive at least one dose of the study medication of that group. E.g., if a subject randomized to KLU and takes at least one dose of KLU (and other doses of Coartem) then the subject will be analyzed in KLU group. However, if the subject receives all the doses of Coartem then the subject will be analyzed in Coartem group.

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Modified RAS (mRAS), modified FAS (mFAS), modified SAF (mSAF) and modified PAS (mPAS)

The mRAS, mFAS, mSAF and mPAS are subsets of RAS, FAS, SAF and PAS, respectively, for patients ≥ 10 kg body weight. The analyses are primarily conducted using the modified analysis sets.

CCI [redacted]

2.2.1 Subgroup of interest

Unless otherwise mentioned, subgroup analysis will be limited to Core Phase.

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

- Age groups as per Section 2.3.2
- Baseline weight groups as per Section 2.3.2
- Sex (male vs female)
- Mono vs mixed infections at baseline (if reasonable number of participants with baseline mixed infections are randomized)
- Country
- With or without Kelch-13 mutations (if reasonable number of participants with Kelch-13 mutations are randomized; only the WHO validated or candidate/associated SNPs (F446I, N458Y, C469Y, M476I, Y493H, R539T , I543T, P553L, R561H, P574L, C580Y, R622I, A675V, P441L, G449A, C469F, A481V, R515K, P527H, N537I, N537D, G538V, V568G) will be used to define Kelch-13 mutation. Patients with Kelch-13 mutations should have at least one SNP mutation from this list; Patients without Kelch-13 mutations should have none of the validated or candidate/associated mutations. Besides, Kelch-13 status will be considered as undetermined if all Kelch-13 SNP are undetermined.

2.3 Participant disposition, demographics and other baseline characteristics

2.3.1 Participant disposition

The number of participants who screened and screening failures will be presented. In addition, the reasons for screen failures will be provided. The number and percent of participants in the randomized set who completed or discontinued the treatment and study (including the reason for discontinuation) will be presented for each treatment group and overall.

For each protocol deviation, the number and percent of participants for whom the deviation applies will be tabulated for each treatment group and overall.

The list of protocol deviation is defined in the data management's edit check specifications.

Unless otherwise specified, analyses will be based on the mRAS.

2.3.2 Demographics and other baseline characteristics

Demographic data and baseline disease characteristics will be descriptively presented and tabulated per treatment group, as well as overall, using RAS and mRAS .

The following demographic variables will be summarized if collected

- Age and age categories (< 6 months, 6 months to < 2 yrs, 2 yrs to < 6 yrs, 6 yrs to < 12 yrs, 12 yrs to < 18 yrs, < 18 yrs, ≥ 18 yrs, < 6 yrs, ≥ 6 yrs)
- Sex (male, female);
- Race (White, black, Asian, native American, pacific islander, unknown, other)

- Country
- Ethnicity
- Body weight and weight categories (5 to <10, 10 to <15, 15 to <25, 25 to <35, 35 to <70 and ≥70 kg)
- Body height (cm)
- BMI and BMI categories (<16, 16 to 25, >25) (Kg/m^2)
- Mild-upper arm circumference in <12 yrs

The following disease characteristics at baseline will be summarized.

- Body temperature and categories equivalent to axillary method (<37.5, 37.5 to <38.5, ≥38.5) (°C)
- Plasmodium falciparum species: (P. Falciparum asexual forms, P. Falciparum gametocytes, n (%))
- Mixed plasmodium infection (P. Vivax, P. Ovale, P. malariae, P. Knowlesi)
- P. falciparum density per micro ltr. and its categories (<1,000, 1,000 to <2,000, 2,000 to <5,000, 5,000 to <15,000, 15,000 to <50,000, 50,000 to <100,000, 100,000 to <150,000, ≥150,000 parasites/μL; <100,000 /μL, ≥100,000 parasites /μL)
- Gametocytes counts /μL.
- Kelch-13 mutations Medical history

Any condition entered on the Relevant medical history / current medical conditions CRF will be coded using the MedDRA dictionary. They will be summarized by system organ class (SOC) and preferred term (PT) of the MedDRA dictionary for each treatment group and overall. A summary will also be provided on medical conditions that were active at the time of screening.

Unless otherwise specified, analyses will be based on the mRAS.

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

2.4.1 Study treatment / compliance

Study treatment data will be summarized by treatment group.

The following data will be presented by treatment group:

- Number of doses taken and number of full doses taken (n and %)
- Number and percent of participants completing their dosing
- Number and percent of participants vomiting the study drug (including vomiting of IMP and spitting out of IMP)
- Number and percent of participants successfully receiving replacement dose after vomiting. A participant is considered as receiving a successful replacement dose if the participant does not vomit the replacement dose.

- Number of participants who discontinued study treatment due to vomiting
- Time to vomiting from the previous dose (hours). Only the first occurrence is considered if a subject has multiple occurrences of vomiting.
- Number and percent of participants taking at least 80% of the study drugs (Compliance). The percentage of study drug is calculated as the sum of actual drug taken from all doses divided the sum of planned study drug dose to be taken. The actual study drug taken is limited to the planned dosage, ie, over dosage part is excluded. For example, if a participant with 40 kg body weight is randomized to KLU156 and takes 4 sachets of KAF156 100mg/LUM-SDF 120 mg on Days 1 and 2 but 2 sachets on Day 3, his study drug percentage is 83% (10/12).

A dose is considered as full if it is taken without vomiting or the replacement dose is taken successfully in case of vomiting the original dose.

Meal intake (yes or no) and meal type will be summarized by treatment arm and dosing time.

Modified safety set will be used.

2.4.2 Prior, concomitant and post therapies

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

Concomitant non-study treatment with antimalarial activity will be summarized by treatment group. Please refer to Table 6-8 for the definition of non-study drugs with antimalarial activity.

Prior medications are defined as drugs taken and stopped prior to first dose of study medication. Any medication given at least once between the day of the first dose of study medication and the last day of study visit will be a concomitant medication, including those which were started pre-baseline and continued into the treatment period.

Prior and concomitant medications will be coded according to the latest version of WHO Drug Reference List dictionary which employs the ATC. The number and percentage of participants taking prior and concomitant medications will be summarized for each treatment by ATC class and preferred term (PT).

Number and percentages of the participants who received prohibited drugs prior to start of the treatment will be provided by treatment group. Likewise, number and percentages of the participants who received prohibited drugs after the start of the treatment will be summarized by treatment group. See Table 6-9 for some examples of prohibited medications. The clinical team will provide the whole list of prohibited drugs used in the study prior to the database lock.

The modified safety set will be used.

2.5 Analysis supporting primary objective for ex-US submission- PCR corrected ACPR at Day 29

The estimand for supporting primary objective for PCR-corrected ACPR at Day 29 for ex-US submission is specified in Section 1.2.1. This estimand and the analyses detailed in this section will be used to assess the key secondary objective for US submission. The estimand for uncorrected ACPR at Day 29 will be used to assess the primary objective for US submission and the analyses will be detailed in Section 2.6.

2.5.1 Primary endpoint(s)

The primary endpoint (or variable) is a binary outcome indicating that a participant is alive and has achieved PCR-corrected ACPR at Day 29, i.e., has had no early treatment failure (ETF), no late clinical failure (LCF), and no late parasitological failure (LPF) by Day 29 where presence of *P. falciparum* asexual forms on Day 8 or later is considered as failure (not ACPR) only if the same parasite strain was already present at baseline based on PCR genotyping. Please refer to Section 2.1.1 for definitions of ETF, LCF and LPF. For PCR-corrected ACPR, cases of LCF and LPF are to be categorized as non-responders only in case of recrudescence.

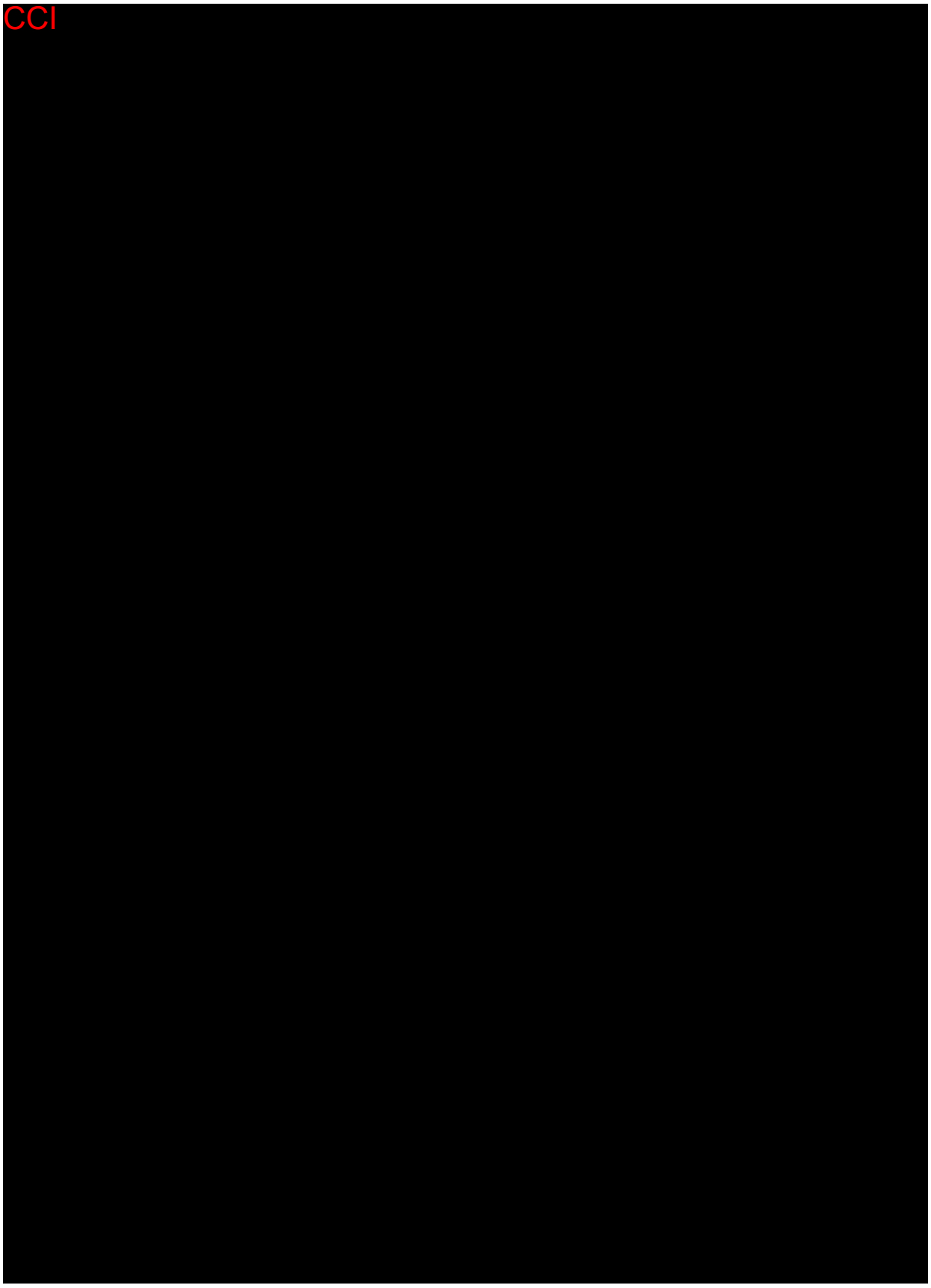
For participants with a mixed infection at baseline, any recurrence of the non-P. *falciparum* infection on Day 8 or later is considered as recrudescence of parasites (failure) as PCR genotyping is only valid for P. *falciparum*. For example, if a participant has a *P. vivax* infection in addition to *P. falciparum* infection at baseline, presence of *P. vivax* between Day 8 and Day 29 is considered as a recrudescence, therefore, a failure. On the other hand, a participant with late appearance of another species that was not present at baseline is not considered as a non-responder.

Note: the primary endpoint is binary with 2 outcomes (responder or non-responder). Beside recrudescence, a participant's outcome can be classified as non-responder due to reasons, such as missing PCR genotyping, missing assessment, etc. (Section 2.5.4).

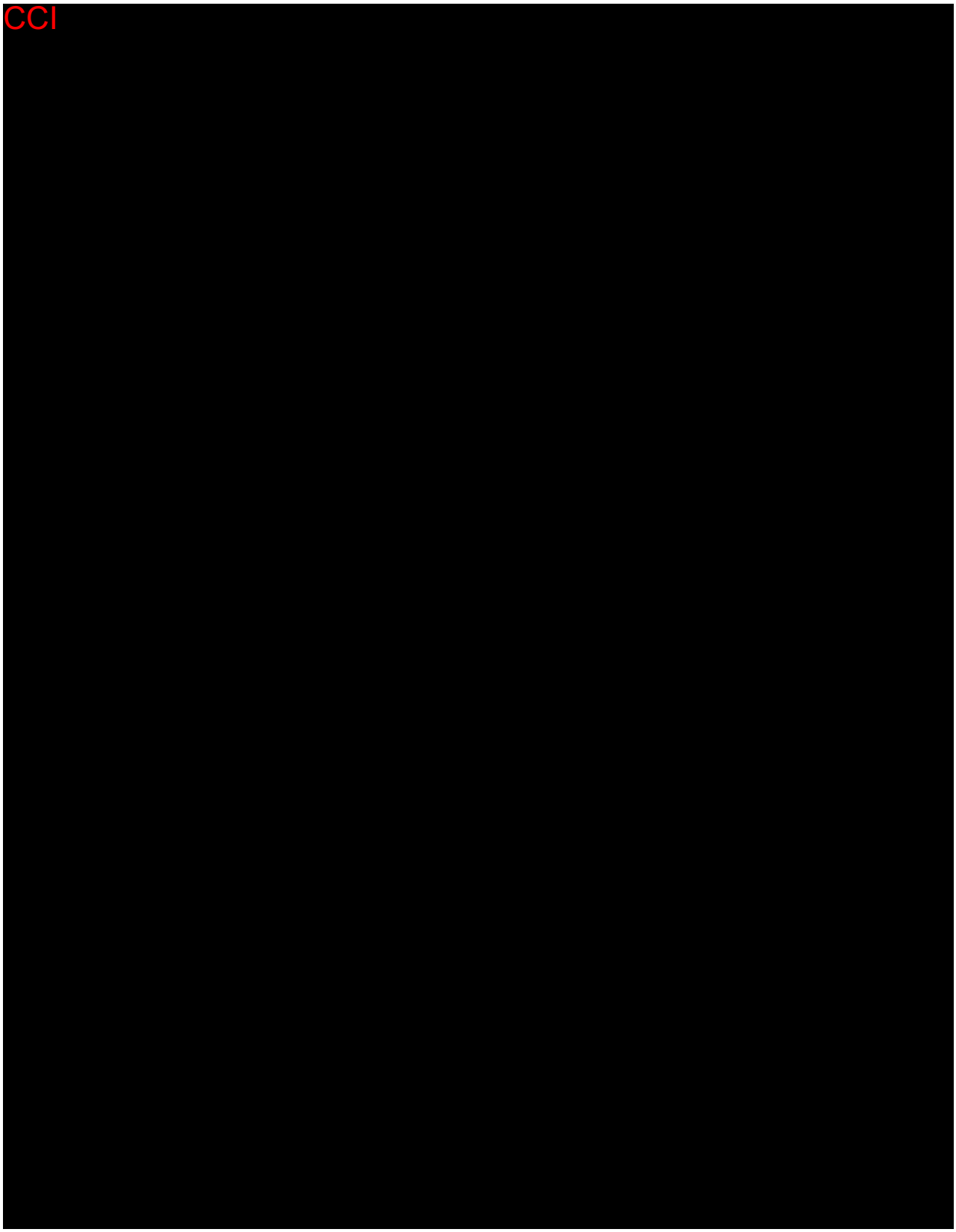
2.5.2 Statistical hypothesis, model, and method of analysis



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2.5.3 CCI

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2.5.4 CCI

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2.5.5 CCI

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2.5.6 CCI

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CCI [redacted]

2.5.6.1 CCI [redacted]

CCI [redacted]

2.5.6.2 Subgroup analyses

The primary analyses described in Section 2.5.2 will be performed by subgroups as per Section 2.2.1 using a forest plot. For a subgroup with less than 10 participants in either treatment group, number and percent for each treatment will be presented and 95% CI for treatment difference will not be provided

2.6 Analysis supporting primary objective(s) for US submission- uncorrected ACPR at Day 29

This estimand and the analyses for uncorrected ACPR at Day 29 detailed in this section will be used for US submission. These analyses will be used to assess the key secondary objective for ex-US submission.

2.6.1 Primary endpoint for US NDA submission

The endpoint is uncorrected ACPR at Day 29 (i.e., no ETF, no LCF, and no LPF by Day 29). Please refer to Section 2.1.1 for the definition.

2.6.2 Statistical hypothesis, model, and method of analysis for uncorrected ACPR at Day 29

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2.6.3 CCI

CCI

2.6.4 CCI

CCI

2.6.5 CCI

CCI

2.6.5.1 Subgroup analyses

The analyses described in Section 2.6.2 will be performed by subgroups as per Section 2.2.1 using a forest plot. For a subgroup with less than 10 participants in either treatment group, number and percent for each treatment will be presented and 95% CI for treatment difference will not be provided.

2.7 Analysis supporting secondary objectives

2.7.1 Key Secondary endpoint

CCI

2.7.2 CCI

CCI

2.7.3 CCI

CCI

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2.7.4 CCI

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2.7.5 CCI

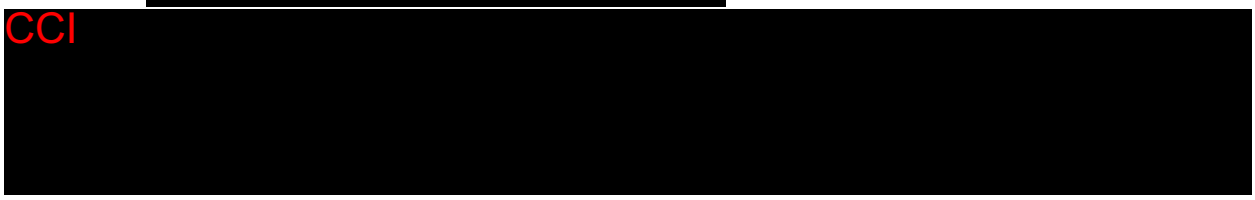
CCI

2.7.6 CCI

CCI



2.7.7 CCI



2.8 Safety analyses



2.8.1 Adverse events (AEs)

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

Adverse events and SAEs will be summarized by presenting, for each treatment group, the number and percentage of participants having at least one AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries will also be

presented for AEs by severity (Toxicity grade) and for study treatment related AEs. Treatment emergent adverse events leading to treatment discontinuation by primary system organ class and preferred term will be summarized. If a participant reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a participant reported more than one adverse event within the same primary system organ class, the participant will be counted only once with the greatest severity at the system organ class level, where applicable.

AEs will be presented also separately for up to Day 4, and after Day 4

The MedDRA version used for reporting adverse events will be described in a footnote.

The most common adverse events reported (≥ z % in any group for each preferred term in the table by SOC and PT) will be presented in the clinical study report by descending frequency according to its incidence in overall group starting from the most common event. Here threshold value z is set to 5 (%) but it may be updated following review of the dry run outputs.

Separate summaries will be provided for deaths, serious adverse events, severe malaria, and other significant adverse events leading to treatment discontinuation.

Serious adverse events in the Screening Phase will be flagged in a data listing due to rare frequency.

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

Adverse events by primary system organ class and preferred term will also be summarized for the Core phase using the mSAF. Deaths, other serious or adverse events related discontinuations will be summarized using the mSAF.

2.8.1.1 For the legal requirements of ClinicalTrials.gov and EudraCT

Two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 5 and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set.

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

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

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

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

2.8.1.2 Subgroup analysis for AEs

The adverse events and SAEs will be summarized by the following subgroups.

- Age groups as per Section 2.3.2
- Baseline weight groups as per Section 2.3.2
- Sex (male vs female)
- Infection type (mono/mixed)

Algorithms for date imputations are provided in Appendix.

2.8.1.3 Adverse events of special interest / grouping of AEs

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

-Drug code = KLU156

-the latest version of MedDRA at the time of final database lock.

-End date is null (this means this is the latest eCRS version).

The number and percentage of participants with these special AEs will be summarized. In addition, listings of related adverse events will be provided.

2.8.2 Deaths

Listing of deaths will be provided.

2.8.3 Laboratory data

Descriptive statistics will be generated for all clinical laboratory tests performed (actual values and changes from baseline) for three groups of laboratory tests (hematology, clinical chemistry and urinalysis) by laboratory test, visit and treatment group. Maximum change from baseline during study will also be reported. Change from baseline will only be summarized for participants with both baseline and post baseline values and will be calculated as:

change from baseline = post baseline value – baseline value

The following laboratory parameters will be summarized for hematology test group: hemoglobin, platelets, white blood cell count, reticulocytes, haptoglobin, hematocrit, red blood cell (RBC) count, lymphocytes, lymphocytes (%), monocytes, monocytes (%), eosinophils (%), neutrophils, neutrophils (%), basophils, and basophils (%).

The following laboratory parameters will be summarized for biochemistry test group: creatinine, total bilirubin (TBL), indirect bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glucose, blood urea nitrogen (BUN), sodium, potassium, calcium, gamma glutamyltransferase (GGT), magnesium, chloride, and total protein, albumin. Prothrombin time and INR will be listed as these parameters will only be collected for safety follow up.

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

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

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

Table 2-1 Liver-related events

Parameter	Criterion
ALT	>3xULN ; >5xULN ; >8xULN;>10xULN ; > 20XULN
AST	>3xULN ; >5xULN ; >8xULN >10xULN ; >20XULN
ALT or AST	>3xULN ; >5xULN ; >8xULN >10xULN ; >20XULN
ALT or AST and TBL	ALT or AST > 3 × ULN and TBL > 2 x ULN ALT or AST > 5 × ULN and TBL > 2 x ULN ALT or AST > 10 × ULN and TBL > 2 x ULN
TBL	>1.5xULN, >2xULN, >3XULN
ALP	>2xULN, >3xULN
ALP & TBL	ALP >3xULN & TBL >2xULN
(ALT or AST) & TBL & ALP	ALT or AST >3xULN & TBL >2xULN & ALP <2xULN **(Potential Hy's Law case**)

Listing of participants with the following liver related laboratories will be provided:

- Liver enzyme values meeting newly notable abnormalities or CTCAE grades 3/4

For urinalysis, frequency tables will be presented by treatment groups. Number and percentage of participants in each category will be presented for each visit.

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

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Average triplicate ECG measurements will be used for the summary.

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

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

To assess the dynamics of QTc, HR and body temperature, participants with notable QT, HR and fever by timepoint will be provided. Notable criteria are provided below.

To assess the temporal correlations, mean change of QTcF/QTcB over time, mean change of ECG HR over time, and mean change of temperature over time over time will be plotted with all panels aligned on the x-axis (Time after dosing).

QTc will be summarized categorically by computing the number and percentage of participants at each time point and at the maximum post baseline value with the following:

- QT, QTcF, or QTcB
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from Baseline of ≥ 30 ms to < 60ms
  - Increase from Baseline of ≥ 60 ms
- HR for age ≥18 years
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 60 bpm
  - <60 bpm
  - >100 bpm
- HR for age <18 years
  - > 90th percentile defined in Table 2-2
  - < 10th percentile defined in Table 2-2
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New value of > 120 ms

Table 2-2 Heart rate cut-offs (beats/minute) for <18 years based on centile charts

Age Range#	10th percentile	90th percentile
Birth	107	148
0 – <3m	123	164
3 – <6m	120	159
6 – <9m	114	152
9 – <12m	109	145
12 – <18m	103	140
18 – <24m	98	135
2 – <3y	92	128
3 – <4y	86	123

Age Range#	10th percentile	90th percentile
4 – <6y	81	117
6 – <8y	74	111
8 – <12y	67	103
12 – <15y	62	96
15 – <18y	58	92
# Age ranges given in years (y) and months (m). "Birth" refers to the immediate neonatal period. Reference: Lancet. 2011 March 19; 377(9770): 1011–1018. doi:10.1016/S0140-6736(10)62226-X.		

Analysis will also be performed on all parameters by age categories.

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

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

2.8.4.2 Vital signs

The following quantitative variables will be summarized: Weight (kg), temperature (°C), pulse (beats/min), systolic blood pressure (mmHg) and diastolic blood pressure (mmHg).

Analysis in vital sign measurement using descriptive summary statistics for the change from baseline for each post-baseline visit will be performed by vital sign and treatment group. Change from baseline will only be summarized for participants with both baseline and post-baseline values and will be calculated as:

Change from baseline = post-baseline value – baseline value

The number and percentage of participants with newly occurring notable vital signs will be presented. Criteria for notable vital sign abnormalities are provided for <18 years in Table 2-3 and for ≥18 years in Table 2-4 below.

Table 2-3 Criteria for notably abnormal vital signs for <18 years

Vital sign		Criteria	
Systolic blood pressure [mmHg]	High	≥ 95th percentile of the age and height group[1]	
	Low	≤ 5th percentile of the age and height group[1]	
Diastolic blood pressure [mmHg]	High	≥ 95th percentile of the age and height group[1]	
	Low	≤ 5th percentile of the age and height group[1]	
Body temperature [°C]	High	≥ 37.5°C (*axillary equivalent*)	
Pulse rate [bpm] [2]	High	1-<6 months	> 160
		6-<12 months	>150
		12-<18 months	> 140
		18-<24 months	> 135
		2-<3 years	> 128
		3-<4 years	> 123
		4-<6 years	> 117
		6-<8 years	> 111
		8-<12 years	> 103
		12-<15 years	> 96
		≥ 15 years	> 92
	Low	1-<6 months	<120

Vital sign		Criteria	
		6-<12 months	<110
		12-<18 months	< 103
		18-<24 months	< 98
		2-<3 years	< 92
		3-<4 years	< 86
		4-<6 years	< 81
		6-<8 years	< 74
		8-<12 years	< 67
		12-<15 years	< 62
		≥ 15 years	< 58
Weight	High	increase from baseline of ≥ 2 BMI-for-age percentile categories[3]	
	Low	decrease from baseline of ≥ 2 BMI-for-age percentile categories[3]	

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

[1] Fourth Report on Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics 2004; 114; 555 (see section 7.4 for detailed computation)

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

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

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

Table 2-4 Criteria for notable vital sign abnormalities for ≥18 years

Vital sign (unit)	Notable abnormalities
Systolic blood pressure (mmHg)	≥ 180 mmHg/≤ 90 mmHg with increase/decrease from baseline of ≥ 20 mmHg
Diastolic blood pressure (mmHg)	≥ 105 mmHg/≤ 50 mmHg with increase/decrease from baseline of ≥ 15 mmHg
Pulse (beats/min)	≥ 120 bpm/≤ 50 bpm with increase/decrease from baseline of ≥ 15 bpm
Temperature (°C)	>=37.5 (axillary) or >=38.0 (oral) or 38.5 (tympanic/ rectal)
Weight	decrease > 7% from Baseline increase > 7% from Baseline

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

2.9 CCI

CCI

CCI

2.10 CCI

CCI

2.11 CCI

CCI

2.12 Biomarkers

Optional Additional Research

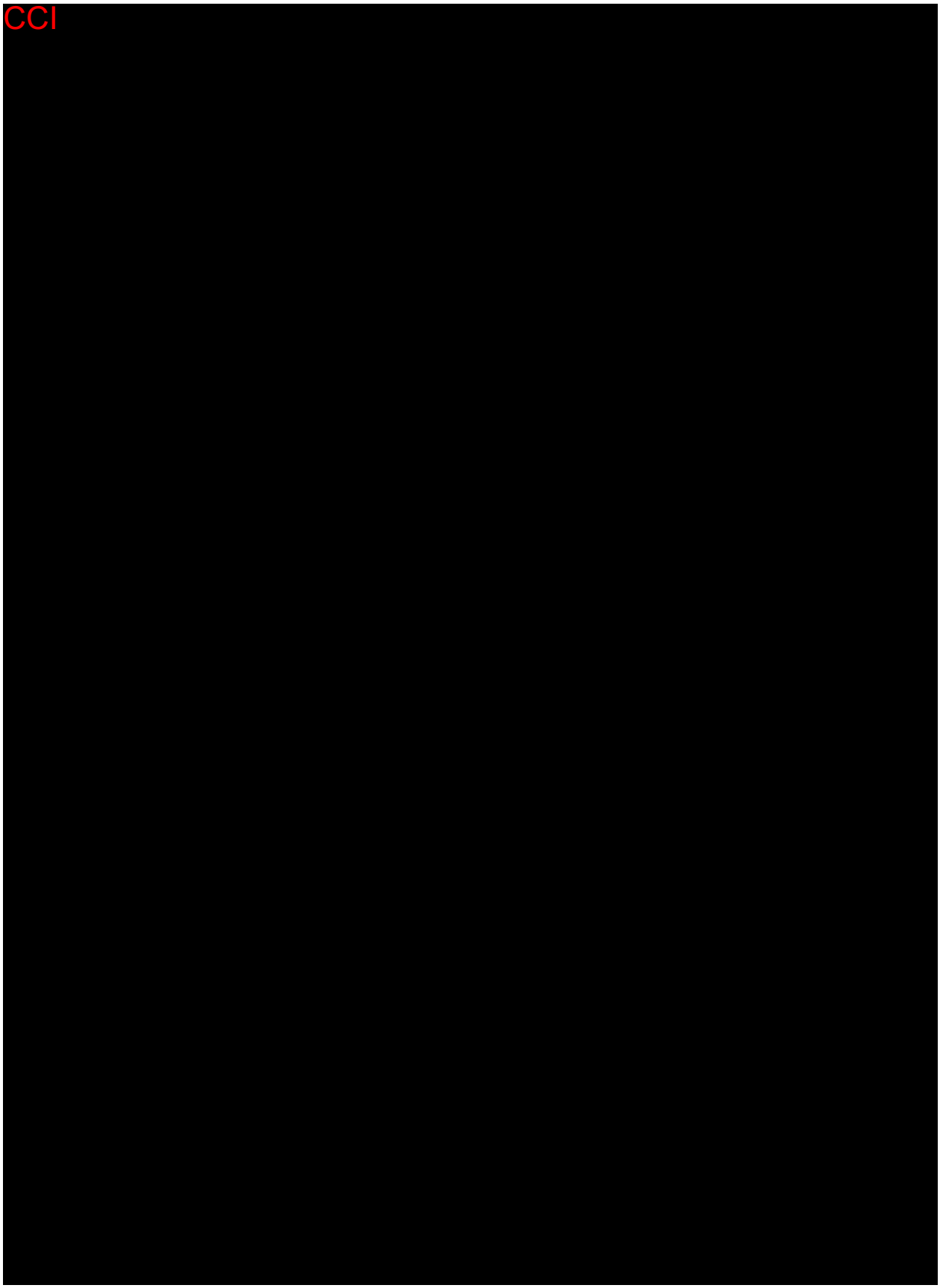
If participants agree by signing an optional consent for Additional Research, blood samples and data that remain after analysis is completed may be used for additional research to help better understand how the study treatment works, learn more about the disease, improve the way clinical studies are conducted, or to help develop ways to detect, monitor or treat human diseases. A decision to perform such exploratory research studies would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as assay availability. If such data are collected, the results will be reported outside of the CSR.

2.13 Other exploratory analyses

Exploratory objectives are

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2.14 CCI

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CCI [redacted]

3 Interim analysis

There is no formal interim analysis to stop the trial early for futility or overwhelming efficacy. There are two DMC analyses planned in the Core Phase, for the monitoring of safety data. The first DMC analysis will be performed after 200 participants have been dosed and followed up to at least Day 22 and the second DMC analysis will be performed after 750 participants have been dosed and followed up to at least Day 22. The DMC analyses will be performed by a CRO Biostatistics Team who will share the reports with the DMC committee directly.

Additional DMC reviews may be conducted ad-hoc during the study, as deemed necessary.

4 Sample size calculation

CCI [redacted]

4.1 Primary endpoint(s)

CCI [redacted]

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Table 4-1 CCI

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4.2 Secondary endpoint(s)

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Table 4-2 CCI

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4.3 CCI

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5 Change to protocol specified analyses

NA

6 Appendix

Unless otherwise mentioned, this section is applicable for Core as well as extension Phase.

6.1 Imputation rules

6.1.1 Study drug

The study drug administration date should be complete since it's taken in the hospital. In case missing or partial, the visit date will be used as the study drug administration date.

6.1.2 AE date imputation

The following missing dates will not be imputed

- Missing AE start dates
- AE start dates missing the year
- Partial/missing AE end dates

For other type of partial missing start dates, rules specified in Table 6-1 to Table 6-3 will be used

Table 6-1 AE/Treatment Date Abbreviations

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

Table 6-2 describes the possible combinations and their associated imputations. The upper text indicates the imputation (NC, A, B, C etc.) and the lower text the relationship of the AE start date to the treatment start date (TRTSTD).

Table 6-2 Imputation algorithm

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

The legend to the above table is shown in Table 6-3.

Table 6-3 Imputation algorithm legends

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

Few examples are shown in Table 6-4.

Table 6-4 Example scenarios

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

6.1.3 Concomitant medication date imputation

Missing concomitant medication start dates will be imputed similar as to AE dates. Missing concomitant medication end dates will be imputed as follows:

Missing Element	Imputation rule
Day, month and year	Completely missing end dates will be imputed by the earliest of 1) last visit date in a study phase (episode in the extension) and 2) date of death.
Day, month	If partial end date contains year only, set end date = earliest of 1) 31DecXXXX, 2) last visit date in a study phase and 3) date of death
Day	If partial end date contains month and year, set end date = earliest of 1) last date of the month, 2) last visit date in a study phase and 3) date of death

In case the imputed end date is before start date, then the end date will be imputed equal to the start date.

Partial/missing dates will be displayed as such in the data listings, and ongoing concomitant medications will be displayed as ‘ongoing’.

6.1.3.1 Other imputations

NA

6.1.4 Visit windows

When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows. E.g., if the Day 4 visit of a participant is delayed and occurs on Day 7, say, it will be re-aligned to visit window Day 8. In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a participant may fall in a particular visit window (either scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified below.

- Of note, participants are allowed to have gaps in visits. All data collected will be displayed in listings.
- Lower limit of the Day 29 visit is set to be Day 27

- Upper limit of the Day 29 visit for the core Phase is set to be Day 33 which leads to a narrow window since this is the primary analysis timepoint
- .
- Upper limit of the Day 43 visit for the core Phase is set to be the extension informed consent date for patients consented for extension, or infinity (no limit) for patients not consented for extension.
- The following rules are used to determine the window for other visits post baseline:
  - "Lower limit" = "upper limit of prior applicable visit" + 1.
  - "Upper limit" = "target day of current visit" + integer part of ("target day of next applicable visit" – "target day of current visit")/2 with the exception of Days 22, 29, and 43
  - Upper limit of Day 22 for the core Phase is one day before the lower limit of Day 29

For assessments that are scheduled to be performed only once on a day, Table 6-5 describes the analysis windows mapping to visits (not just scheduled visits) based on study days alone for the core phase. For the assessments that may be performed on multiple timepoints on a day, Table 6-6 describes the analysis windows mapping to visits based on study day and time for the core phase. Repeated and/or unscheduled visits (which will be numbered in the database according to new NCDS standards) will be mapped for analysis purposes in the same way. If there are multiple measurements within an analysis window, the conventions defined in Table 6-7 will be used to determine the appropriate measurement to be selected for analysis. As ECG is based on the average of triplicate ECG, the date of triplicate ECG will be used for determination. If there are repeated ECGs on the same date, the average of scheduled and unscheduled assessments will be calculated separately.

The mapped visits will be used in the by visit analyses. Only planned visits will be presented in summaries. However, the listings will show all collected data regardless of used in the by visit analyses. E.g. ECG is not planned at Day 2, if collected at Day 2, then it will not be presented in the summary but shown in the listing.

Table 6-5 Analysis visit windows based on study days alone for core Phase

Analysis Visit	Target Day	Analysis visit window
Baseline	1	Up to Day 1
Day 2	2	Day 2
Day 3	3	Day 3
Day 4	4	Day 4 – 6
Day 8	8	Day 7 – 15
Day 22	22	Day 16 – 26
Day 29	29	Day 27 – 33
Day 43/ End of Core Phase	43	Day 34 and above[1] Day 34 – (Day of Extension consent)[2]
[1] For the participants not entering into the extension Phase. [2] For the participants entering into the extension Phase		

Table 6-6 Analysis visit windows based on study day and time for core Phase

Analysis Visit	Analysis timepoint	Analysis visit window
Baseline	0 hrs	up to 0 hrs
Day 1	6 hrs	>0 - 9 hrs
	12 hrs	>9 - 18 hrs
Day 2	24 hrs	>18 hrs to 30 hrs
	36 hrs	>30 – 42 hrs
Day 3	48 hrs	>42 – 51 hrs
	54 hrs	>51 – 63 hrs
Day 4	Day 4 (72 hrs)	>63 hrs – Day 6
Day 8	Day 8	Day 7 – 15
Day 22	Day 22	Day 16 – 26
Day 29	Day 29	Day 27 – 33
Day 43/ End of Core Phase	Day 43	Day 34 and above[1] Day 34 – (Day of Extension informed consent)[2]
[1] For the participants not entering into the extension phase [2] For the participants entering into the extension Phase		

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

Table 6-7 Rules for flagging variables

Timing of measurement	Type of data	Rule
Baseline	All data	The last measurement made prior to administration of the first dose of study treatment – note this may include measurements taken on the day of randomization. If a participant did not receive any dose of study treatment, then the randomization date will be used.
Post-baseline efficacy	parasite count and temperature	The measurement closest to the target day/time will be used. In the event two measurements are taken equally apart, the first one will be used.
Post-baseline safety	Summary visit information (e.g., lab, ECG, etc.)	The measurement closest to the target day/time will be used. In the event two measurements are taken equally apart, the first one will be used.
Post-baseline safety	Notable abnormalities (e.g., lab, ECG, VS)	The most extreme measurement in the window will be used. Note this means a participant can have a notably high and notably low measurement within a window

6.2 Non-study drug with antimalarial activity

Table 6-8 Table of non-study drugs with antimalarial activity with respective ATC codes

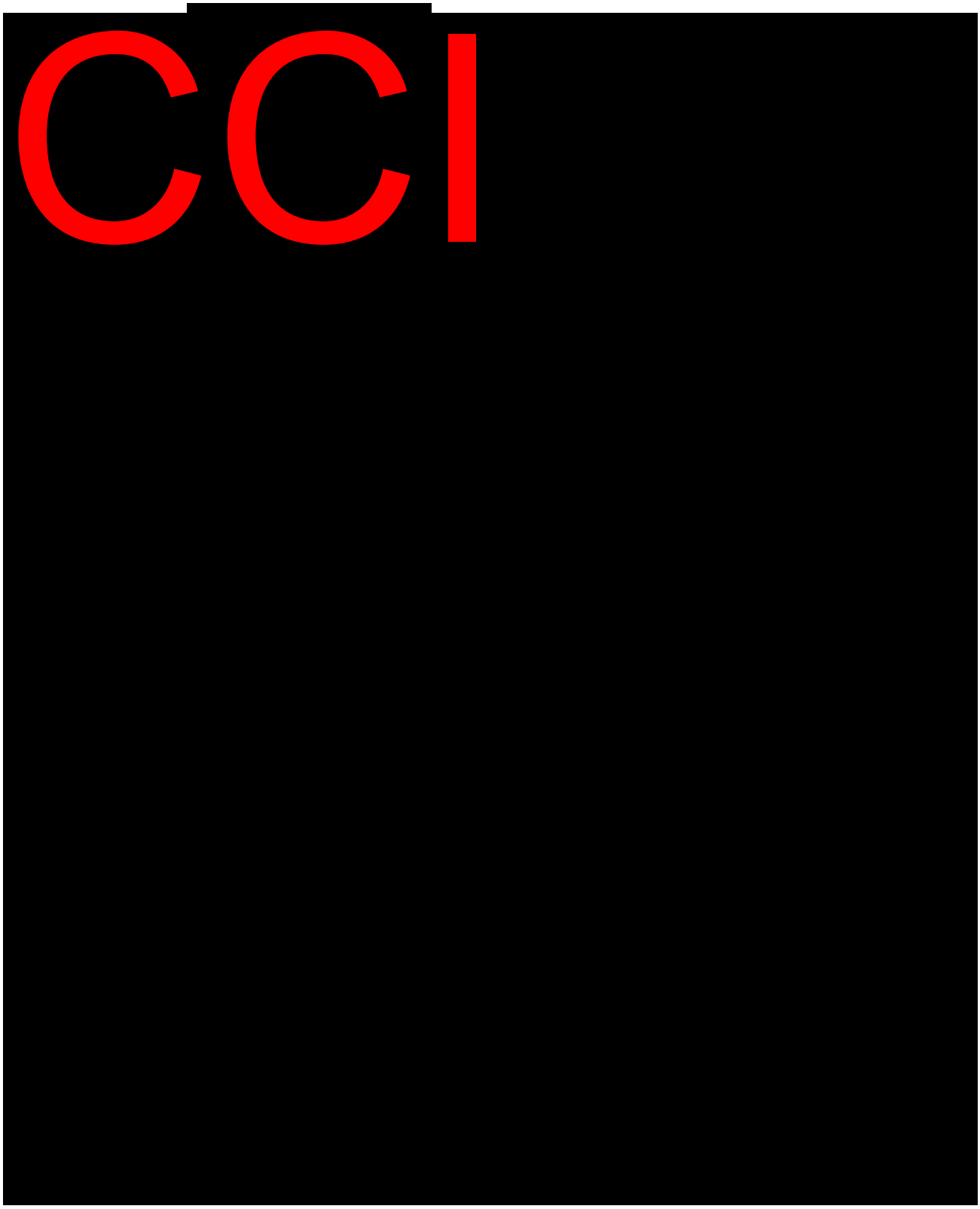
Any drug with ATC code starting with P01B and the drug listed below will be considered as non-study drugs with antimalarial activity.

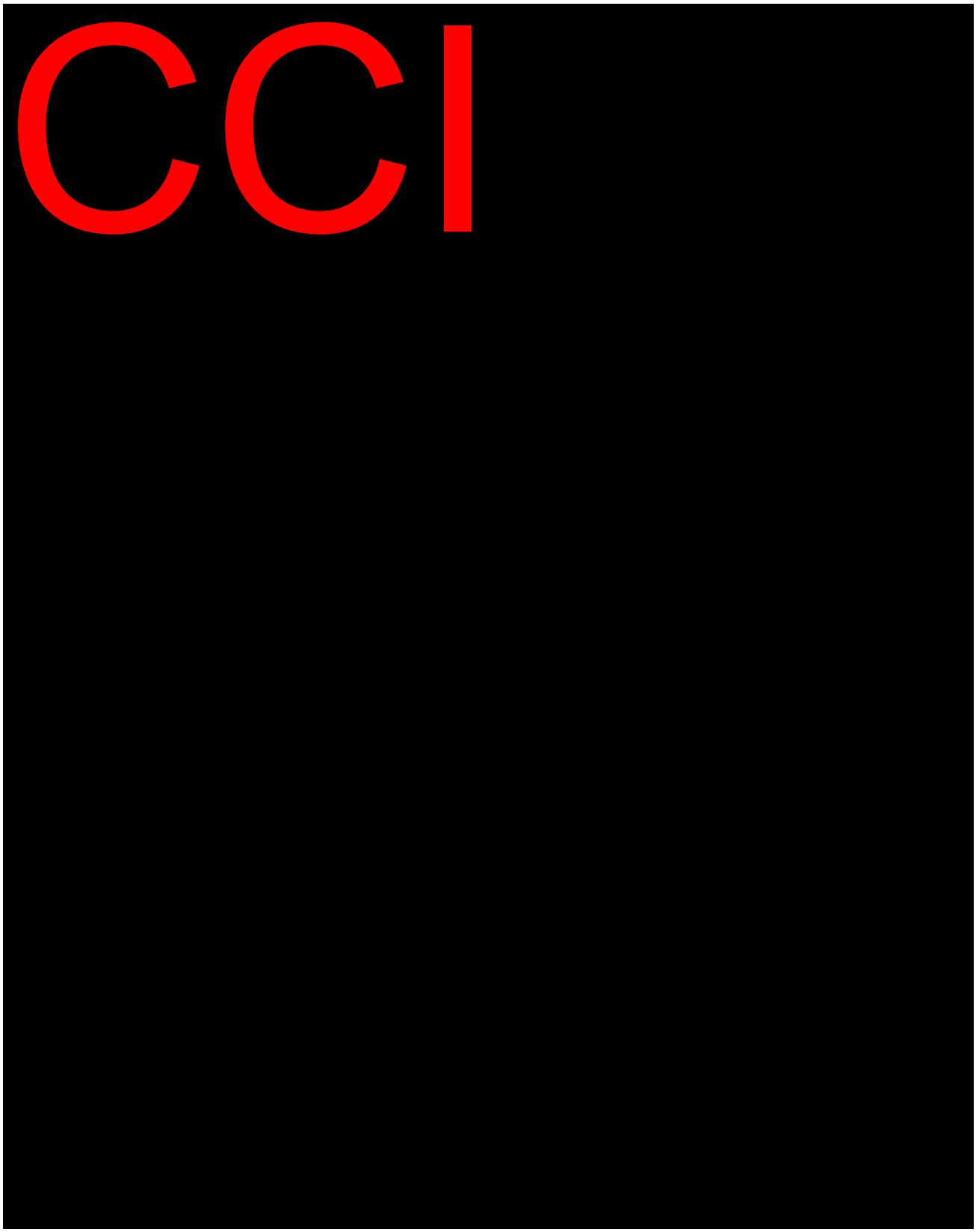
Other drugs with possible antimalarial activity	ATC code	ATC name
	P02CA03	Albendazole
	P02CA01	Mebendazole
	P02BA01	Praziquantel
	J01XD01	Metronidazole
	J01AA02	doxycycline
	J01AA08	minocycline
	J04AB02	rifampicin
	J04BA02	dapsone
	J01EE01	sulfamethoxazole and trimethoprim
	J01FF01	clindamycin
	J01MA02	ciprofloxacin
	J01MA14	moxifloxacin
	P01AB01	metronidazole
	J01RA14	norfloxacin and metronidazole
	P01AB02	tinidazole

*In case used by participants receiving KLU156/Lum-SDF

6.3 Prohibited medications

Table 6-9 CCI




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6.4 AEs coding/grading

AEs will be coded using the most recent MedDRA version.

6.5 Laboratory parameters derivations

Normal ranges provided from the laboratory will be used.

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

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

- To compute the systolic blood pressure (SBP) percentile of a boy whose age is y years and height =h inches with SBP = x mmHg:
  - Convert the height of *h* inches to a height Z-score relative to boys of the same age (as per data tables provided Table 6-11 and Table 6-12; this is denoted by Z_{ht}. For age < 2 years, age is recorded in the CRF with month as the unit and will be converted into year with 1 decimal, the corresponding height Z score can be calculated using months (see Table 6-11).
  - Compute the expected SBP (μ) for boys of age *y* years and height *h* inches given by

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

    where, regression coefficients are given in the 3rd column of Table 6-10.

  - Then convert the boy's observed SBP (x) to a Z-score (Z_{BP}) given by

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

    where, σ is given in the 3rd column for standard deviation row of Table 6-10.

  - To convert the bp Z-score to a percentile (P), compute P = $\phi(Z_{BP})$ x 100%
    where $\phi(Z)$ = area under a standard normal distribution to the left of Z.
- Likewise, to compute percentiles for SBP for girls, diastolic blood pressure (DBP) (K5) for boys, and DBP (K5) for girls, use the regression coefficients from the 4th, 5th, and 6th columns of Table 6-10.

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

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

Table 6-10 Regression coefficients from Blood Pressure Regression Models

Regression Coefficients From Blood Pressure Regression Models*

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

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

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

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

Computation of Z-score for height:

As per the recommendation from Centers for Disease Control and Prevention (CDC) use WHO growth charts for 0 to < 2 years of age and CDC growth charts for age ≥2 years. Accordingly, convert the given height into corresponding Z-score as per Table 6-11 and Table 6-12 given for the growth standards using the following formula.

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

where median, L, S (i.e., CV) are provided in the Table 6-11 for age up to 2 years and in Table 6-12 for age 2-20 years; height in centimeters.

Table 6-11 Table for WHO standard Length-for-age growth chart for age 0 to < 2 years

		Boy		Girl	
Month	L	Median (cm)	S (CV)	Median (cm	S (CV)
0	1	49.8842	0.03795	49.1477	0.0379

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

Reference:

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

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

Note – Table 6-11 to be accessed from the GPS II growth_data (where TEST='Body Length', YEAR_CHG='WHO2006' and VER_NO='V2')

Table 6-12 Table for CDC growth standard height-for-age growth charts for age 2 -20 years

	Boy			Girl		
Age(year)	L	Median (cm)	S (CV)	L	Median (cm)	S (CV)
2	0.941524	86.4522	0.040322	1.072449	84.97556	0.040791
3	-0.39092	95.27359	0.040534	0.541981	94.21336	0.042018
4	0.827637	102.5105	0.041344	0.225706	101.0339	0.04326
5	1.266367	109.1751	0.042593	-0.05773	107.9566	0.044277
6	1.137443	115.6609	0.043673	-0.21907	115.0055	0.044964
7	0.753244	122.0305	0.044403	-0.21021	121.7617	0.045461
8	0.455268	128.1237	0.045127	-0.07928	127.8263	0.045968
9	0.415687	133.7345	0.046217	0.084148	133.1304	0.046884

	Boy			Girl		
Age(year)	**L**	**Median (cm)**	**S (CV)**	**L**	**Median (cm)**	**S (CV)**
10	0.505564	138.8234	0.04761	0.284749	138.2112	0.048705
11	0.487939	143.7304	0.048938	0.74429	144.2609	0.050524
12	0.420919	149.3088	0.049948	1.303045	151.4866	0.048599
13	0.81624	156.4099	0.050333	1.242968	157.3437	0.043859
14	1.670433	164.1418	0.048945	0.956572	160.4777	0.041022
15	2.20518	170.1393	0.04589	0.89557	161.898	0.040084
16	2.113023	173.6101	0.043086	0.941146	162.569	0.039821
17	1.724738	175.341	0.041408	0.999506	162.9238	0.039732
18	1.399999	176.185	0.040644	1.047571	163.1308	0.039687
19	1.229163	176.6179	0.040391	1.083315	163.259	0.039657
20	1.167279	176.8492	0.04037	1.108046	163.3383	0.039636

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

Note – Table 6-12 to be accessed from the GPS II growth_data (where TEST='Height', YEAR_CHG='CDC2000' and VER_NO='V2')

6.7 Statistical models

6.7.1 Analysis supporting primary objective(s)





6.7.2 Analysis supporting secondary objective(s)



6.7.3 Other secondary/exploratory analysis

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6.7.4 Summary of treatment outcome assignment

The below table provides treatment outcome assignments for both uncorrected and PCR-corrected ACPR at a given Day, say X where X can be 22, 29, or 43, for various specific scenarios.

Table 6-13 Derivation Criteria of uncorrected ACPR and PCR- corrected ACPR

Criteria	Principal Stratum (OP)		Full Analysis Set (FAS)	
	Treatment Outcome uncorrected ACPR	Treatment Outcome PCR-corrected ACPR	Treatment Outcome uncorrected ACPR	Treatment Outcome PCR-corrected ACPR
1. Completed up to Day (X) without re-emergence (new infection/ recrudescence) of parasites after initial clearance	Responder	Responder	Responder	Responder
2. Missing assessment on Day (X), but parasite free on subsequent visit after Day (X).	Responder	Responder	Responder	Responder
3. Missing assessment on Day (X), new infection at first assessment after Day (X).	Non-responder	Responder	Non-responder	Responder
4. Early treatment failure from Day 2 to Day 4.	Non-responder	Non-responder	Non-responder	Non-responder
5. Late clinical failure from Day 5 to Day 7.	Non-responder	Non-responder	Non-responder	Non-responder
6a. Receive non-study treatment with antimalarial activity without ETF/LCF day 5-day 7/recrudescence prior to Day (X)	Excluded from OP	Excluded from OP	Non-responder/KM-censoring	Non-responder/KM-censoring
6b Compliance <80% and not received non-study treatment with antimalarial activity	Excluded from OP	Excluded from OP	Treatment policy	Treatment policy
7. Recrudescence on or before Day (X) (thus on or after Day 8 to X)	Non-responder	Non-responder	Non-responder	Non-responder
8. New infection/PCR negative on Day (X)	Non-responder	Responder	Non-responder	Responder
9. New infection/PCR negative before Day (X) (thus on or after Day 8 to Day X).	Non-responder	Excluded from OP	Non-responder	Non-responder/ KM-censoring
10a. Re-emergence on Day (X) but PCR result is indeterminate or missing.	Non-responder	imputed as	Non-responder	imputed as

		Non-responder/ KM Censoring		Non-responder/ KM Censoring
10b. Re-emergence before Day (X) but PCR result is indeterminate or missing.	Non-responder	Non-responder/ KM-censoring	Non-responder	Non-responder/ KM-censoring
11. Missing assessment on Day (X), recrudescence at first assessment after Day (X).	Non-responder	Non-responder	Non-responder	Non-responder
12. Prematurely study discontinued from the study without parasite re-emergence before Day (X) and received antimalarials.	Excluded from OP	Excluded from OP	Non-responder/KM-censoring	Non-responder/KM-censoring
13. Missing assessment on Day (X), no more assessments thereafter.	Non-responder/KM-censoring	Non-responder/KM-censoring	Non-responder/KM-censoring	Non-responder/KM-censoring

Note: '/' indicates separate analysis, e.g., 'non-response/KM-censoring' indicates one analysis considering outcome as non-responder and another analysis using KM method considering outcome as censored.

Derivation criteria are defined for mono as well as mixed infection. For the definitions of recrudescence/ new infection for P. Falciparum and other species, refer to Section 2.1.1.

Censoring means exclusion from analysis after the censoring time (KM approach).

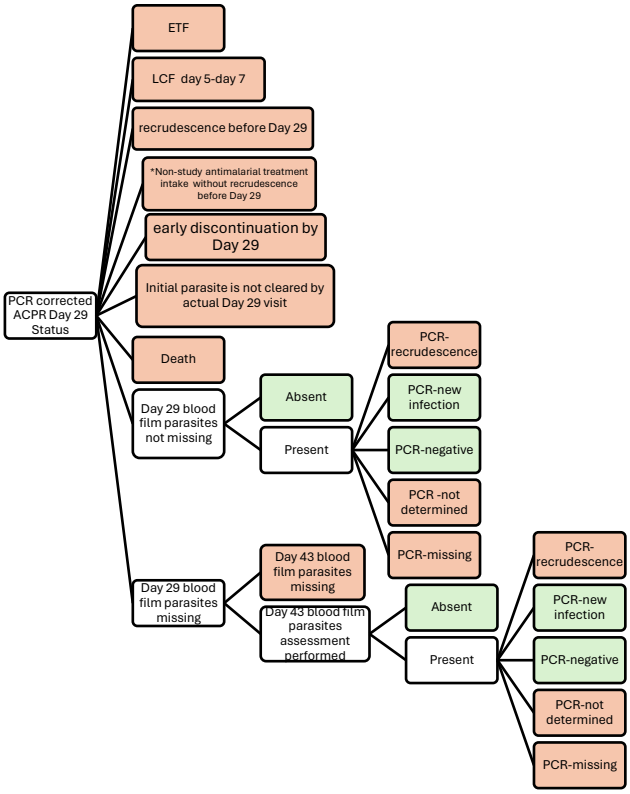
6.7.4.1 Uncorrected/PCR-corrected ACPR definition tree

Figure 6-1 Uncorrected ACPR at Day 29 definition tree



Legend: non-responder, responder

Figure 6-2 PCR corrected ACPR at Day 29 definition tree



Legend: non-responder, responder

*: in the principal stratum analysis, non-study antimalarial treatment intake before visit without recrudescence is treated as intercurrent event and patient with this event will be excluded from the principal stratum.

Once the patient is a non-responder at a visit, the patient will be a non-responder at following visits. When defining the outcome at Day 22, if the microscopy parasite counts at Day 22 and Day 29 are missing, use the parasites data at Day 43 to impute. Outcome at Day 43 is similar to outcome at Day 29 with the exception of no tree for Day 43 parasite assessment missing

6.8 Rule of exclusion criteria of analysis sets

Participants meeting any criteria in Table 6-14 will be excluded from the given Analysis set

Table 6-14 Criteria leading to exclusion from analysis sets

Analysis Set	PD Criteria that cause participants to be excluded (PD ID)	Non-PD criteria
RAS	No written inform consent	Not randomized
FAS	Baseline *P. falciparum* asexual parasite count is < 1,000 or > 200,000 parasites/ μL	Not in RAS; Mistakenly randomized;

Analysis Set	PD Criteria that cause participants to be excluded (PD ID)	Non-PD criteria
PAS	Received Prohibited conmeds impacting study drug exposure (M_COMD01B_Nonmalaria drug impact PK Exp)	No study drug taken; No evaluable PK data; Non-compliance with study medication;
SAF		No study drug taken

7 Reference

Chiba, Y., & VanderWeele, T. J. (2011). A simple method for principal strata effects when the outcome has been truncated due to death. American journal of epidemiology, 173(7), 745-751.

Lott A & Reiter JP (2018). Wilson Confidence Intervals for Binomial Proportions with Multiple Imputation for Missing Data, The American Statistician, DOI:

10.1080/00031305.2018.1473796

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NOVARTIS

Clinical Development

KLU156/Ganaplacide

CKLU156A12301 / NCT05842954

A randomized, open-label, multicenter study to compare efficacy, safety and tolerability of KLU156 with Coartem® in the treatment of uncomplicated Plasmodium falciparum malaria in adults and children followed by an Extension phase with repeated KLU156 treatment

Statistical Analysis Plan (SAP) – Extension Phase

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List of abbreviations

AE	Adverse event
ACPR	Adequate clinical and parasitological response
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
Bid	bis in diem/twice a day
CDC	Centers for Disease Control and Prevention
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Data base lock
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
ETF	Early treatment failure
FAS	Full Analysis Set
mkluFAS	Modified KLU156 Full Analysis Set
FCT	Fever clearance time
GCT	Gametocyte clearance time
IMP	Investigational Medical Product
IVR	Interactive Voice Response
IWR	Interactive Web Response
LCF	Late clinical failure
L.O.S.	Level of significance
LPF	Late parasitological failure
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
o.d.	Once Daily
OP	Observed Principal Stratum
CCI	[redacted]
CCI	[redacted]
PCT	Parasite clearance time
qd	Qua'que di'e / once a day
RAS	Randomized analysis set
SAP	Statistical Analysis Plan
SAF	Safety analysis set
mkluSAF	Modified KLU156 Safety Analysis Set
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analysis for the Extension phase, which is planned in the protocol (Version 01).

A CSR report will be created after the end of the Extension phase. The report will be based on analyses using key efficacy and safety data from the Core Phase and data collected during the Extension phase.

Mock shells, and consequently, statistical outputs for the analysis report after the end of the Extension phase will be prepared according to the analysis plan specified in this SAP.

A separate SAP and mock shells were prepared and executed for DMCs. Likewise, a separate SAP and mock shells were prepared and executed for the analysis of the Core phase data.

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

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

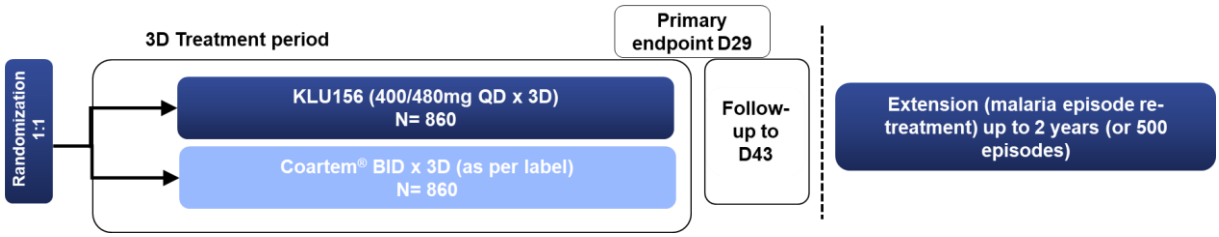
1.1 Study design

This study includes a Core phase followed by an Extension phase (Figure 1-1).

Core phase: This will be a multicenter, open-label, randomized, parallel-group, non-inferiority study in adults and children with uncomplicated *P. falciparum* malaria (*P. falciparum* with or without other *Plasmodium* spp. co-infection).

Approximately 1500 male and female participants ≥ 10 kg body weight will be randomized in the study to KLU156 or Coartem following a 1:1 ratio. Randomization will be stratified by mixed infection status (yes or no) and country. Randomization for mono-infection with *P. falciparum* will be further stratified by body weight (≥ 35, 25 to <35, 15 to < 25, and < 15 kg).

Figure 1-1 Core Phase and Extension phase: Study design



KLU156 400/480mg dose is for patients with a bodyweight ≥ 35 kg. Patients < 35 kg will take a fraction of the dose according to weight group as shown in Table 6-4 in the protocol. KLU156 should be administered under fed conditions (light meal).

The Extension phase may be terminated early by Sponsor decision. As the main objective of the Extension phase is to assess the safety and tolerability of KLU156 repeated treatment, the number of follow-up visits is reduced to Days 4, 8 and 29 for each malaria episode.

The primary analysis timepoint is Day 29. There is no interim analysis planned to stop the trial early for futility or overwhelming efficacy.

Although the Core phase is open-label, the Novartis personnel responsible for conducting the trial (Novartis Clinical Trial team, CTT) will be blinded to the identity of the treatment from the time of randomization until the database lock for the analysis of the Core phase. Prior to unblinding the data of the Core phase (for the Novartis CTT), at least two DMC reviews are planned to minimize risks in this vulnerable participant population:

1. Once the first 200 participants (across both treatment arms) in the Core phase have been dosed and followed up to at least Day 22.
2. Once the first 750 participants (across both treatment arms) in the Core phase have been dosed and followed up to at least Day 22.
3. Additional DMC reviews may be conducted ad-hoc during the study, as deemed necessary.

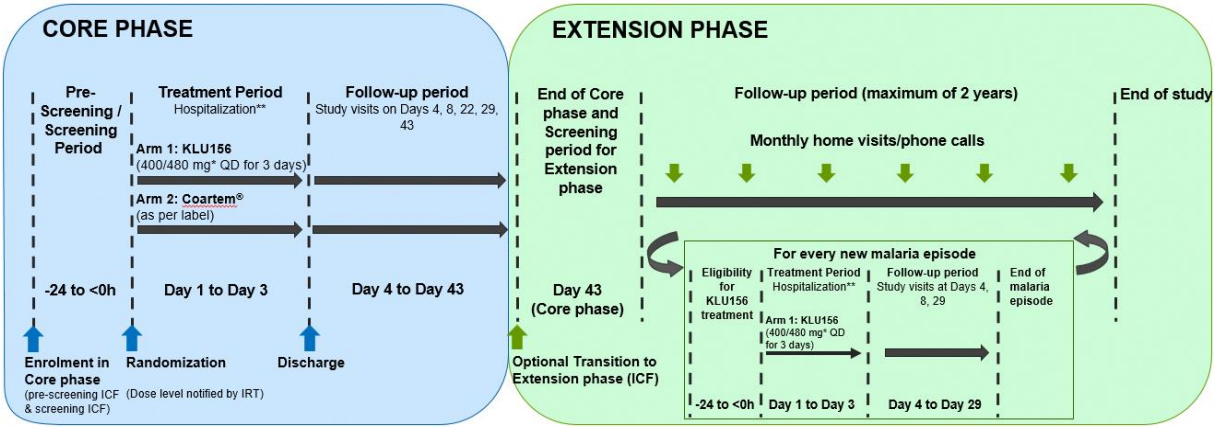
The sample size may be increased based on the outcome of the blinded sample size re-estimation after about 750 participants (across both treatment arms) in the Core phase have been randomized. Note about 200 more patients may be enrolled based on the blinded sample size review.

Extension Phase:

The Core Phase will be followed by an Extension Phase. See Figure 1-2 for the patient journey.

All participants who completed the Core Phase according to the protocol, who did not meet the criteria for ETF (see Protocol Section 10.6) and who did not experience any SAE related to KLU156 or Coartem, will be offered the opportunity to continue in the Extension Phase allowing them to receive study treatment for subsequent malaria episodes. A new informed consent form will be signed before proceeding into the Extension Phase. During this phase, participants should come back to the study site at any time when they develop symptoms indicative of a new malaria episode.

Figure 1-2 Core Phase and Extension Phase: Patient journey



* This dose is for patients with a bodyweight ≥ 35 kg (see Table 6-4 in the protocol). KLU156 should be administered under fed conditions (light meal).

** Patients will be hospitalized and discharged after Day 4 assessments in the Core and Extension phases.

After all participants in the Core phase have completed the Day 43 visit, the interim database will be cleaned and locked. The Novartis CTT will be unblinded to the treatment group in the Core phase. The interim locked database will be used for NDA submission. The existing database will be used to update the extension data. After the last participant has completed the last visit in the Extension phase, the database will be locked finally.

1.2 Study objectives and endpoints

Objectives and related endpoints for the Extension phase are described in Table 1-1 below. Handling of intercurrent events for the primary and secondary estimand in the core phase will be used for the efficacy in the Extension phase. However, no estimand is defined for the Extension phase..

Table 1-1 Objectives and related endpoints for the Extension phase

Objective(s)	Endpoint(s)
● To assess the safety and tolerability over repeated treatment with KLU156 in adults and children ≥ 10 kg body weight suffering from uncomplicated malaria caused by *P. falciparum* (with or without other *Plasmodium* spp. co-infection) for a maximum of 2 years.	● KLU156-related AE/SAE incidence and severity by KLU156 treatment sequence. AE/SAE incidence and severity, laboratory abnormalities and ECG abnormalities by KLU156 treatment sequence.
● To evaluate efficacy over repeated treatment with KLU156 in adults and children ≥ 10 kg body weight suffering from uncomplicated malaria caused by *P. falciparum* (with or without other *Plasmodium* spp. co-infection) for a maximum of 2 years.	● PCR-corrected and uncorrected ACPR at Day 29 by KLU156 treatment sequence. Gametocyte carriage over time by KLU156 treatment sequence.
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
CCI	

2 Statistical methods for Extension Phase

2.1 General definitions

Study treatment: The investigational treatment is KLU156, a fixed combination of ganaplacide and Lumefantrine solid dispersion formulation (LUM-SDF).

Baseline for Extension Phase: Baseline during Extension Phase will be re-derived for each new malaria episode. It is the last measurement made prior to administration of the first dose of study treatment for a malaria episode during Extension Phase. If the measurement was done more than 24 hours before the first dose of study treatment for a malaria episode, consider baseline missing.

For baseline for a current episode, data from the previous episodes should not be used.

Study day for Extension Phase: Study Day will be re-calculated with respect to the first dose of study treatment for each new malaria episode in Extension Phase using the formula given for Core Phase as follows:

The first day of administration of study treatment (first dose) is defined as Day 1. Day -1 will be the day before Day 1. Day 0 does not exist. Due to multiple assessments collected more than once for a day in the treatment phase for some variables, study day calculation is based on the treatment start date and time.

For assessments collected prior to Day 1,

Study Day = date of assessment – date of first dose of study treatment

For assessments that are performed once for a day on or after Day 1,

Study Day = date of assessment – date of first dose of study treatment + 1

For assessments that are performed more than once for a day on or after Day 1,

Study Day = integer[(datetime of assessment – datetime of first dose of study treatment)/(60*60*24)] + 1.

Body temperature: Axillary temperature = (oral equivalent) – 0.5°C = (tympanic/rectal equivalent) - 1°C.

Fever: Same as Core Phase, axillary equivalent temperature should be ≥ 37.5°C axillary or 38°C oral or 38.5°C tympanic/rectal.

Early discontinuation: episode disposition is not recorded as "completed"; early discontinuation date is the time of last parasite assessment;

2.1.1 Definition of treatment failures

Plasmodium parasite counts in Falciparum asexual forms (not gametocytes), Vivax, Ovale, Malariae, and Knowlesi will be analyzed separately in the determination of treatment failures defined below. If treatment failure is found by any of the aforementioned parasite types, the patient will be classified as the according treatment failure, and the treatment failure time is the earliest occurrence day among different parasite types.

Early Treatment Failure (ETF) for each malaria episode

For each malaria episode, participants will be classified as ETF upon meeting any of the following criteria:

- Development of danger signs or severe malaria on Days 2, 3 or 4, in the presence of parasitemia;
- Parasitemia on Day 3 higher than Day 1 baseline, irrespective of axillary temperature;
- Parasitemia on Day 4 with axillary temperature ≥ 37.5°C;
- Parasitemia on Day 4 ≥ 25% of count on Day 1 baseline.

Late Clinical Failure (LCF) for each malaria episode

For each malaria episode, participants will be classified as LCF upon meeting any of the following criteria:

- Development of danger signs or severe malaria in the presence of parasitemia on any day between study Day 5 and Day 29 (up to study day 42) in participants who did not previously meet any of the criteria of early treatment failure;
- Presence of parasitemia on any day between Day 5 and Day 29 (up to study day 42) with axillary temperature ≥ 37.5ºC in participants who did not previously meet any of the criteria of early treatment failure.

Note: Although Day 5 assessments are not planned in the assessment schedule, if baseline parasites are not cleared at Day 4 as per microscopy assessment, additional daily parasite assessment at Day 5 or later should be performed until the parasites are cleared.

Late Parasitological Failure (LPF) for each malaria episode

- Presence of parasitemia on any day between Day 8 and Day 29 (up to study day 42) with axillary temperature < 37.5ºC in participants who did not previously meet any of the criteria of early treatment failure or late clinical failure.

Note: Danger signs or severe malaria are recorded as adverse events. The adverse event start date of danger signs or severe malaria will be used in the determination of ETF and LCF. The body temperature assessment closest to the blood smear assessment date will be used.

Recrudescence: Same as Core Phase, recrudescence is defined as appearance of parasites after clearance of initial infection with a genotype identical to that of parasites present at baseline for each episode. It must be confirmed by PCR genotyping for *P. falciparum* asexual form at baseline and at time of recurrence. For other *Plasmodium spp*. at baseline, appearance of parasites at post-baseline is considered as recrudescence as PCR genotyping is not considered reliable.

New infection: Same as Core Phase, new infection is defined as appearance of parasites after clearance of initial infection with a genotype different from those parasites present at baseline for each episode. New infection must be confirmed by PCR genotyping for *P. falciparum* asexual form at baseline and at time of recurrence. For other *Plasmodium spp.* that are not present at baseline, the appearance of those parasites at post-baseline is considered as a new infection.

Whether the recurrence of *P. falciparum* asexual parasitemia after 7 days is recrudescence or new infection is determined and provided by the central laboratory.

Negative PCR means that no asexual parasite is detected by the central laboratory using PCR genotyping in a positive blood smear by microscope and will categorize the parasite assessment as responder for PCR corrected ACPR. In this scenario, the presence of asexual parasite by microscope will not be overwritten for uncorrected ACPR.

2.2 Analysis sets

Extension enrolled set: Patients who have consented to participate in the Extension Phase and are treated with KLU156 at least once in the extension.

Modified KLU156 analysis set:

It is based on patients with body weight >= 10 kg (at core phase and first episode in the extension phase) in the extension enrolled set:

- For patients >= 10 kg treated with KLU156 in the Core phase, core phase data (up to Day 33) and extension data will be included,
- For patients >=10 kg treated with Coartem in the Core Phase, extension data will be used

As the objective is to evaluate the safety, tolerability and efficacy over repeated treatment, analysis will be performed by KLU156 treatment sequence (1st KLU156 treatment, 2nd KLU156 treatment, i-th KLU156 treatment…).

1st KLU156 treatment: patients who receive KLU156 for the first time, including all Core Phase KLU156 patients who entered the extension phase, and Core Phase Coartem patients who receive KLU156 for the first time in the Extension Phase.

2nd KLU156 treatment: patients who receive KLU156 for the second time, including Core Phase KLU156 patients who receive KLU156 again in the Extension Phase and Core Phase Coartem patients who receive KLU156 for the second time in the Extension Phase.

i-th KLU156 treatment: patients who receive KLU156 for the i-th time, including Core Phase KLU156 patients who receive KLU156 for the (i-1)-th time in the Extension Phase and Core Phase Coartem patients who receive KLU156 for the i-th time in the Extension Phase.

Modified KLU156 full analysis set (mkluFAS): all patients in the modified KLU156 analysis set whose episode baseline *P. falciparum* asexual parasite count is >= 200 and <= 200,000 parasites/ µL and who are treated with the KLU156 treatment sequence; patients who are treated with KLU156 in the Core phase mFAS (modified FAS) and enter the extension phase. Note that if the same patient has a baseline *P. falciparum* asexual parasite count outside the acceptable range at one episode, but within the acceptable range at another episode, that patient will be included in the mkluFAS.

Modified KLU156 safety analysis set (mkluSAF): all patients in the modified KLU156 analysis set >=10kg in the Extension phase who are treated with the KLU156 treatment sequence and patients who treated with KLU156 in the Core phase mSAF and enter the extension phase

Unless otherwise specified, treatment sequence (i>=3) will be combined as a group (3rd +KLU156) and the three treatment sequence groups (1st KLU156, 2nd KLU156, 3rd +KLU156) will be used for subsequent analyses.

The same patient with multiple extension episodes will be counted repeatedly in each different treatment sequence. For example, Patient A from the Core phase Coartem group with 5 treated episodes in the extension will be counted in the 1st KLU156, 2nd KLU156, 3rd KLU156 , 4th KLU156 and 5th KLU156. In the 3rd +KLU156 group , this patient will be counted three times (from the 3rd, 4th, and 5th KLU156 treatment sequence) and the data for each treatment sequence will be analyzed separately. The patient count in the 3rd +KLU156 group will be the sum of the patients in 3rd, 4th, and i-th (i>=5) KLU156 treatment sequence.

The total number of patients in each treated episode will be used to derive N count for the treatment sequence group. In particular, for 3rd +KLU156, if there are 47 patients in the 3rd time KLU156 episode, 11 in the 4th time KLU156 episode, 4 in the 5th time KLU156 episode and 2 in the 6th time KLU156 episode, the N count in the "3rd+ KLU156" will be 47 + 11 + 4 + 2 = 64.

2.2.1 Subgroup of interest

Subgroup analysis may be performed if sufficient data are available for selected endpoints.

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

- Age groups as per Section 2.3.2 of the Core Phase SAP Amendment 2
- Baseline weight groups as per Section 2.3.2 of the Core Phase SAP Amendment 2

2.3 Participant disposition, demographics and other baseline characteristics

2.3.1 Current medical conditions

Summary will be provided on medical conditions that were active at the time of treatment for the specified KLU156 treatment sequence. They will be summarized by system organ class (SOC) and preferred term (PT) of the MedDRA dictionary using mkluFAS modified KLU156 analysis set for each KLU156 treatment sequence group.

2.3.2 Participant disposition

The number of participants who were assessed for eligibility and eligibility failures for the whole extension enrolled set will be presented. In addition, the reasons for eligibility failures will be provided.

The number and percent of participants who completed or discontinued the treatment (and follow up, if collected) for each KLU156 treatment sequence group and study (including the

reason for discontinuation) will be presented using the modified KLU156 analysis set for each KLU156 treatment sequence group.

The number of patients in each extension episode by the core phase treatment group will be summarized based on the Extension enrolled set.

The number of patients in each treatment sequence by the core phase treatment group will be summarized based on the modified KLU156 analysis set.

For each protocol deviation, the number and percentage of participants for whom the deviation applies will be tabulated based on the mkluFAS.

The list of protocol deviations is defined in the data management's edit check specifications.

2.3.3 Demographics and other baseline characteristics

Demographic data will be summarized for each KLU156 treatment sequence group. Disease characteristics will be presented for each KLU156 treatment sequence group. See Section 2.3.2 of the Core Phase SAP Amendment 2 for the list of variables. The modified KLU156 analysis set will be used. These variables including age, will be based on the time of screening for the Extension episode. The age of patients is collected only in the Core phase at screening, but not in the Extension phase.

The age of patients at the Extension screening at each malaria episode will be derived as follows:

- If the age at screening in the Core phase is < 2 years, convert the number of days from date of Core screening to date of Extension screening into months by dividing the number of days by 30.4375 (knowing that 1 month is 365.25/12 = 30.4375 days). Add the integer part of the result to the age at Core screening (in months). If the result is ≥ 24 months, further convert to years and take the integer part of the result.

For example, if age at Core screening is 13 months and there are 241 days from Core screening to Extension screening, then age at Extension is 13 + integer(241/30.4375) = 20 months.

If age at Core screening is 23 months and there are 241 days from Core screening to Extension screening, then age at Extension is 23 + integer(241/30.4375) = 30 months, which gives 2 years.

- If the age at screening in the Core phase is >=2 years, convert the number of days from date of Core screening to date of Extension screening into years using a year=365.25 days with truncation and then add to the Core screening age.

For example, age at core=5 years, 240 days from date of Core screening to date of Extension screening, the extension age is 5 years + integer(240/365.25) = 5 years.

Example 2, age at core=5 years, 380 days from date of Core screening to date of Extension screening, the extension age is 5 years + integer(380/365.25) = 6 years.

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

2.4.1 Study treatment / compliance

Study treatment data will be summarized for each KLU156 treatment sequence group :

- Number of doses taken and number of full doses taken (n and %)
- Number and percentage of participants completing their dosing
- Number and percentage of participants vomiting the study drug (including vomiting of IMP and spitting out of IMP)
- Number and percentage of participants successfully receiving replacement dose after vomiting
- Number of participants who discontinued study treatment due to vomiting
- Time to vomiting from the previous dose (mins). Only the first occurrence is considered if a subject has multiple occurrences of vomiting.

As in the Core Phase, a dose is considered as full if it is taken without vomiting or the replacement dose is taken successfully in case of vomiting the original dose.

Meal intake (yes or no) and meal type will be summarized by the KLU156 treatment sequence group and dosing time.

The mkluSAF will be used.

2.4.2 Concomitant and post therapies

Concomitant medications will be summarized in separate tables for each KLU156 treatment sequence group.

Concomitant rescue and other anti-malarial medications will also be summarized for each KLU156 treatment sequence group. Please refer to Table 6-8 of the Core Phase SAP Amendment 2 for the definition of non-study drugs with antimalarial activity.

Any medication given at least once between the day of first dose of study medication and the last day of study visit for each malaria episode will be a concomitant medication, including those which were started pre-baseline and continued into the treatment period.

Concomitant medications will be coded according to the latest version of WHO Drug Reference List dictionary which employs the ATC. The number and percentage of participants taking concomitant medications will be summarized for each KLU156 treatment sequence group by ATC class and preferred term (PT).

Number and percentages of the participants who received prohibited drugs after the start of the treatment will be summarized by each treatment sequence group. The clinical team will provide the whole list of prohibited drugs used in the study prior to the database lock.

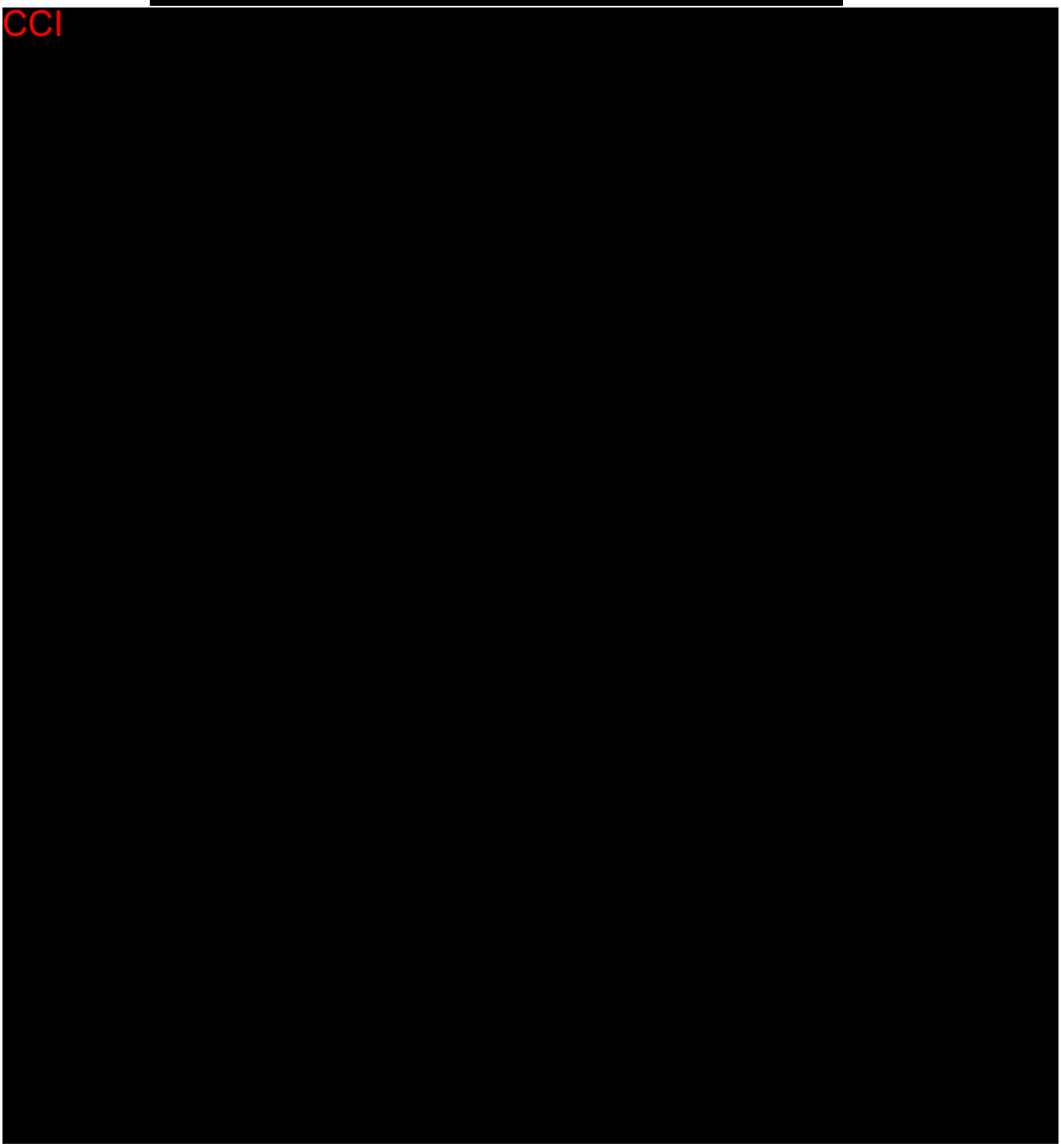
The mkluSAF will be used.

2.5 Primary endpoint(s)

There is no primary endpoint planned for the Extension Phase.

2.6 Secondary endpoint

2.6.1 CCI



CCI

2.6.2 CCI

CCI

2.6.3 CCI

CCI

2.7 CCI

CCI

2.7.1 Adverse events (AEs)

The number and percent of participants with treatment emergent adverse events will be presented by primary System Organ Class (SOC) and Preferred Term (PT) for each KLU156 treatment sequence

The treatment emergent adverse events are the events that started on or after the first dose of study medication for each malaria episode or events present prior to the first dose of study medication for each malaria episode but increased in severity based on preferred term on or after the first dose of study medication. Since the 1st KLU156 group includes the Core Phase data for Core Phase KLU156 patients and Extension Phase data for the Core Phase Coartem patients who receive the first KLU156 in the extension, only the AEs in the Core phase that started after the first dose of study medication and by the study day 33will be considered.

Adverse events will be summarized by presenting the number and percentage of participants having at least one AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries will also be presented for study treatment related AEs. If a participant reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a participant reported more than one adverse event within the same primary system organ class, the participant will be counted only once with the greatest severity at the system organ class level, where applicable.

AEs will be presented also separately for up to Day 4, and after Day 4.

The MedDRA version used for reporting adverse events will be described in a footnote.

The most common adverse events reported (≥ z % in any group for each preferred term in the table by SOC and PT) will be presented in the clinical study report by descending frequency according to its incidence in overall group starting from the most common event. Here threshold value z is set to 5 (%) but it may be updated following review of the dry run outputs.

Separate summaries will be provided for deaths, serious adverse events, severe malaria, and other significant adverse events leading to treatment discontinuation.

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

The above analyses will be provided for each KLU156 treatment sequence group using the corresponding mkluSAF for the treatment sequence group.

2.7.1.1 For the legal requirements of ClinicalTrials.gov and EudraCT

The below analyses will be provided by KLU156 treatment sequence group using the mkluSAF for the treatment sequence group.

Two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 5% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set.

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

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

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

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

2.7.1.2 Subgroup analysis for AEs

Selected AEs may be summarized by the subgroups as defined in Section 2.2.1.

2.7.1.3 Adverse events of special interest / grouping of AEs

The number and percentage of participants with these special AEs as identified from the eCRS will be summarized for each KLU156 treatment sequence group. In addition, listings of related adverse events will be provided.

2.7.2 Deaths

Listing of deaths will be provided. Laboratory data

Descriptive statistics will be generated for each KLU156 treatment sequence group as described in Section 2.8.3 of the Core Phase SAP, using the mkluSAF for the treatment sequence group.

2.7.2.1 ECG and cardiac imaging data

Descriptive statistics will be generated for each KLU156 treatment sequence group as described in Section 2.8.4.1 of the Core Phase SAP, using the mkluSAF for the treatment sequence group.

2.7.3 Vital signs

Descriptive statistics will be generated for each KLU156 treatment sequence group as described in Section 2.8.4.2 of the Core Phase SAP using the mkluSAF for the treatment sequence group. The following quantitative variables will be summarized: temperature (^{o}C) , pulse(beats/min), systolic blood pressure (mmHg) and diastolic blood pressure (mmHg).

2.7.4 CCI

CCI

2.7.5 CCI

CCI

2.8 Other exploratory analysis

3 Change to protocol specified analyses

The protocol specifies that data from the Extension phase will be listed and summarized by episode and by Core phase treatment arm. During SAP Amendment 2, the Extension phase analysis plan in the protocol was re-evaluated and found not to directly address the Extension objective—assessing the safety and tolerability of repeated treatment with KLU156. Therefore, the analysis plan has been revised so that analyses will be conducted by treatment sequence.

4 Appendix

Unless otherwise mentioned, Section 6 of the Core Phase SAP Amendment 2 also applies to Extension Phase.

Table 4-1 Analysis visit windows for each malaria episode in extension Phase

Analysis Visit	Target Day	Analysis visit window
Baseline at each malaria episode	1	Up to Day 1
Day 3	3	Day 2- 3
Day 4	4	Day 4- 6
Day 8	8	Day 7- 15
Day 22	22	Day 15-26
Day 29	29	Day 27-Day 42

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