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Clinical Trial Protocol Title:

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

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Brief Title: Efficacy, safety and tolerability of KLU156 in adults and children with uncomplicated P. falciparum malaria

Study Phase: III

Acronym: KALUMA

Sponsor Name: Novartis

Regulatory Agency Identifier Number(s): EudraCT 2022-002675-10

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Amendment 1 (19-May 2025)

Amendment Rationale

As of 19-May-2025, 2273 patients have been (pre)screened, and 1362 patients including approximately 40 who weigh less than 10 kg, have been randomized into the ongoing study.

The primary reason for this amendment is to revise the inclusion criteria by increasing the minimum body weight requirement for study participation from ≥ 5 kg to ≥ 10 kg. This change is based on blinded data observations indicating palatability issues in children under 10 kg as indicated by adverse events of vomiting or spitting out the study treatments within a few minutes of administration, which could affect the treatment adherence in this subgroup. CCI [redacted]

Another reason for the amendment is to revise the statistical analysis plan, specifically by excluding patients <10kg from the main analyses, in alignment with the updated inclusion criteria. CCI [redacted].

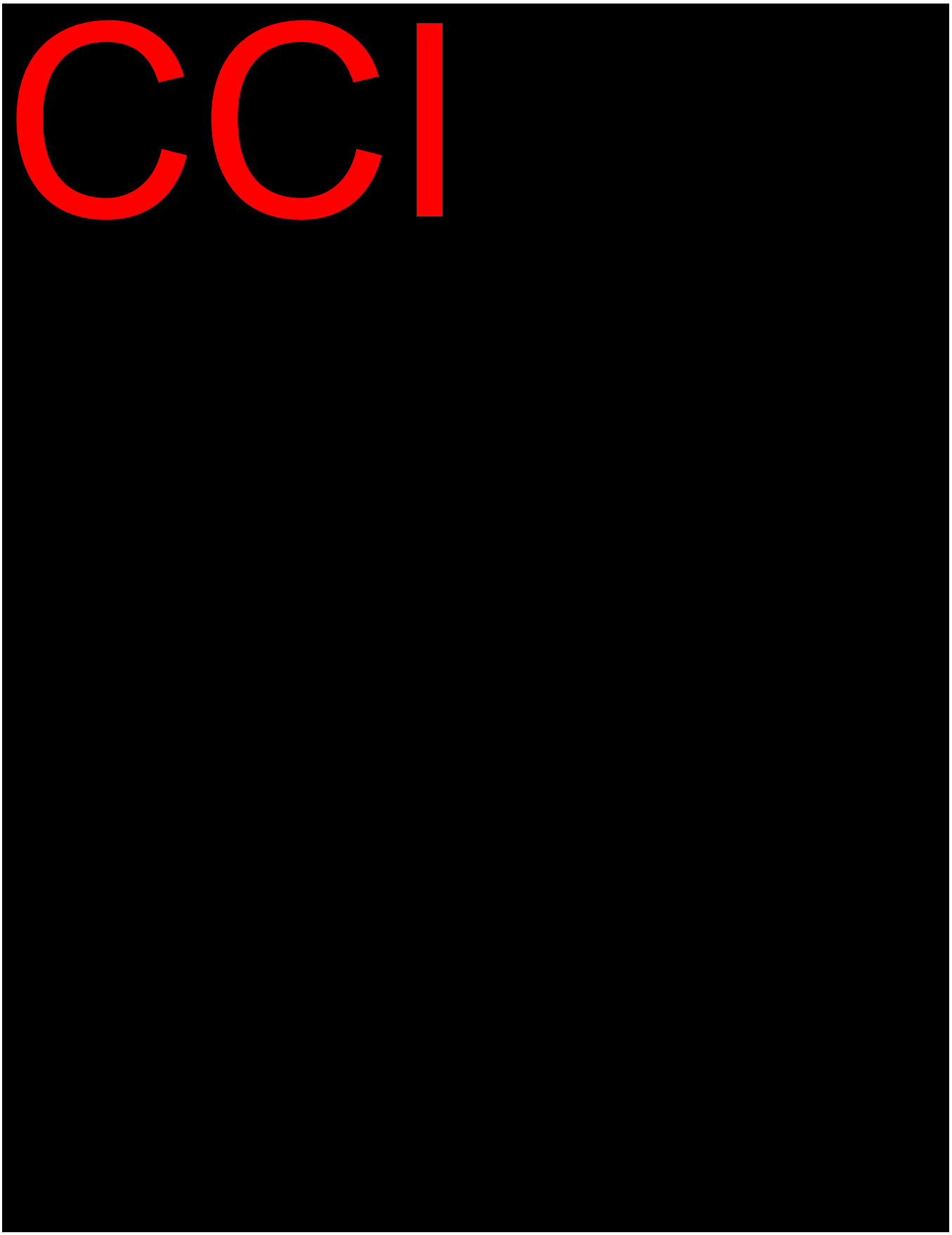
Additional protocol updates include:

- CCI [redacted]
- Clarification of the limit of the total allowable blood volume collected during the study
- Defined Hy's Law and provided guidance for potential cases to be reported as SAEs.
- CCI [redacted]
- The study sample size has been re-estimated based on blinded data review, as originally planned in the protocol. It is now documented in the present amendment.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions. Key updates include:

CCI [redacted]


CCI


CCI

CCI

In addition, some minor editorial changes have been made in the protocol to increase clarity.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC and Health Authority approval prior to implementation as per local regulations. The changes herein affect the Informed Consent. Sites are required to update and submit the revised Informed Consent that takes into account the changes described in this protocol amendment for approval to IRB/IEC as per local regulations.

1 Protocol summary

1.1 Summary

Protocol Title:

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

Brief Title:

Efficacy, safety and tolerability of KLU156 in adults and children with uncomplicated *P. falciparum* malaria

Purpose

This study aims to confirm the efficacy, safety and tolerability of KLU156, a fixed dose combination of ganaplacide (KAF156) and a solid dispersion formulation of lumefantrine (lumefantrine-SDF), when administered once daily for three days in adults and children≥ 10 kg body weight suffering from uncomplicated *P. falciparum* malaria (with or without other *Plasmodium* spp. co-infection).

In the Extension phase, the safety, tolerability and efficacy of repeated treatment with KLU156 will be assessed for a maximum of two years in patients who did not experience early treatment failure (ETF), who did not experience any study treatment-related SAE (Serious Adverse Event) previously and who gave informed consent to participate in the Extension phase.

Study Indication /Medical Condition:

Uncomplicated *Plasmodium falciparum* malaria

Treatment Type

Drug

Study Type

Interventional

Objectives, Endpoints, and Estimands:

Objectives and related endpoints and estimands are described in Table 1-1 below.

Table 1-1 Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary[1]	
Core phase: To confirm the efficacy of KLU156 in adults and children ≥ 10 kg body weight suffering from uncomplicated malaria caused by *P. falciparum* (with	● PCR-corrected ACPR at Day 29 (i.e., 28 days post-first dose administration)

Objectives	Endpoints
or without other *Plasmodium* spp. co-infection) by demonstrating that KLU156 is non-inferior to Coartem (non-inferiority (NI) margin = 5%) based on the PCR[2]-corrected Adequate Clinical and Parasitological Response (ACPR) at Day 29. **Primary clinical question of interest for the Core phase:** "What is the difference in the proportion of patients 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 patients 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 parasites (rescue treatment).	
Key secondary[1]	
Core phase: ● 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. **Secondary clinical question of interest for the Core phase:** "What is the difference in the proportion of patients 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?"	**Core phase:** ● Uncorrected ACPR at Day 29.
Secondary	
Core phase: ● 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, gametocyte carriage over time between the two treatment arms. ● To compare the safety and tolerability profile of the two treatment arms on adverse events (AEs), general laboratory, vital signs and ECG measurements. **Extension phase**: ● 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. ● 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.	**Core phase:** ● 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 (PCT,FCT, GCT). ● Proportion of patients with parasitemia at 12, 24, 48 and 72 hours after treatment. ● Disappearance or development of gametocytemia in patients with or without gametocytemia at baseline (pre-first dose administration), respectively. ● Standard safety/tolerability assessments: AE/SAE incidence and severity, laboratory and ECG (Electrocardiogram) abnormalities. **Extension phase:** ● KLU156-related AE/SAE incidence and severity by malaria episode. ● AE/SAE incidence and severity, laboratory abnormalities and ECG abnormalities by malaria episode. ● PCR-corrected and uncorrected ACPR at Day 29 by

Objectives	Endpoints
	malaria episode. ● Gametocyte carriage over time by malaria episode.

[1]Different primary and key secondary endpoints will be used for the US New Drug Application (NDA) submission, in accordance with Food and Drug Administration (FDA) requirements for demonstrating antimalarial drug efficacy

[2] PCR = Polymerase Chain Reaction

Trial Design:

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). After completion of the Core phase of the study, patients may enter in the Extension phase (single-group).

Brief Summary:

The purpose of this study is to confirm the efficacy, safety and tolerability of KLU156 in patients with uncomplicated *P. falciparum* malaria (with or without other *Plasmodium* spp. co-infection) by demonstrating that KLU156 is non-inferior to Coartem.

- The study duration will be 43 days (Core phase) plus 24 months (Extension phase).
- The treatment duration will be 3 days for each malaria episode.
- The visit frequency will be Days 1-3 (hospitalized) and 5 follow-up visits (Days 4, 8, 22, 29 and 43) in the Core phase and Days 1-3 (hospitalized) and 3 follow-up visits (Days 4, 8 and 29) in the Extension phase.

Treatment of Interest

1) KLU156 (ganaplacide/lumefantrine-SDF)

2) Coartem

Extension phase:

One treatment arm: KLU156

Number of Patients:

The study population will consist of male and female patients ≥ 10 kg of body weight with confirmed uncomplicated *P. falciparum* malaria. Only patients with malaria symptoms and a *P. falciparum* count ≥ 1,000 parasites/µL and ≤ 200,000 parasites/µL (with or without other *Plasmodium* spp. co-infection) will be included in the study.

Approximately 1,500 patients with ≥ 10 kg of body weight will be enrolled in the study (see Section 9.9 for more details on sample size determination).

Key Inclusion Criteria (Core phase)

1. Male or female patients ≥ 10 kg of body weight
2. Microscopically confirmed diagnosis of uncomplicated *P. falciparum* malaria with an asexual *P. falciparum* parasitemia ≥ 1,000 and ≤ 200,000 parasites/µL at the time of pre-screening with or without other *Plasmodium* spp. co-infection.
3. Axillary temperature ≥ 37.5 ºC or oral temperature ≥ 38.0 ºC or tympanic/rectal temperature ≥ 38.5 ºC; or history of fever during the previous 24 hours (at least documented verbally)
4. Negative pregnancy test for patients of childbearing potential
5. Signed informed consent must be obtained before any assessment is performed; for minors, signed informed consent must be obtained from parent/legal guardian. If the parent/legal guardian is unable to read and write, then a witnessed consent according to local ethical standards is permitted. Patients who are capable of providing assent, must provide it along with parent/legal guardian consent or as per local ethical standards
6. The patient and/or their parent/legal guardian is able to understand and comply with protocol requirements, instructions and protocol-stated restrictions and is likely to complete the study as planned.

Key Exclusion Criteria (Core phase)

1. Signs and symptoms of severe malaria according to WHO 2015 (World Health Organization)
2. Concurrent febrile illnesses (e.g., typhoid fever, known or suspected dengue fever, known COVID19)
3. Severe malnutrition. For patients ≥ 12 years: body mass index (BMI) < 16.0. For children < 12 years: less than 70% of median normalized WHO reference weight or very low mid-upper arm circumference (MUAC < 115 mm)
4. Repeated vomiting (defined as > 3 times in the 24 hours prior to start of screening) or severe diarrhea (defined as > 3 watery stools in the 24 hours prior to start of screening)
5. Clinically relevant abnormalities of electrolyte balance which require correction, e.g., hypokalemia, hypocalcemia or hypomagnesemia
6. Anemia (hemoglobin level <7 g/dL)
7. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs (e.g., Human immunodeficiency virus (HIV) patients on antiretroviral therapy (ART) or tuberculosis (TB) patients on treatment), or which may jeopardize the patient in case of participation in the study.
8. Any of the following:
   - Aspartate Aminotransferase/ Alanine Aminotransferase (AST/ALT) > 3 x the upper limit of normal (ULN), regardless of the level of total bilirubin
   - Total bilirubin > 3 x ULN
   - Resting QT interval corrected by Fridericia's formula (QTcF) > 450 ms at screening
9. Prior antimalarial therapy or antibiotics with antimalarial activity within minimum of their five plasma half-lives (or within 4 weeks of screening if half-life is unknown)

10. History or family history of long QT syndrome or sudden cardiac death, or any other clinical condition known to prolong the QTc interval, such as history of symptomatic cardiac arrhythmias, clinically relevant bradycardia or severe heart disease
11. Pregnant or nursing (lactating) patients.

Treatment Arms:

Core phase:

Two treatment arms (1:1 randomization):

1) KLU156 (ganaplacide/lumefantrine-SDF) 400/480 mg (full dose, i.e., this dose is for patients with a bodyweight ≥ 35kg. Patients < 35kg will take a fraction of the dose specific per weight group as shown in Table 6-4) once daily (QD) for 3 days under fed conditions (light meal).

2) Coartem twice a day (BID) for 3 days (as per product label).

Extension phase:

One treatment arm: KLU156 400/480 mg (full dose) once daily (QD) for 3 days under fed conditions.

Data Monitoring/Other Committee: Yes (see Section 10.1.4)

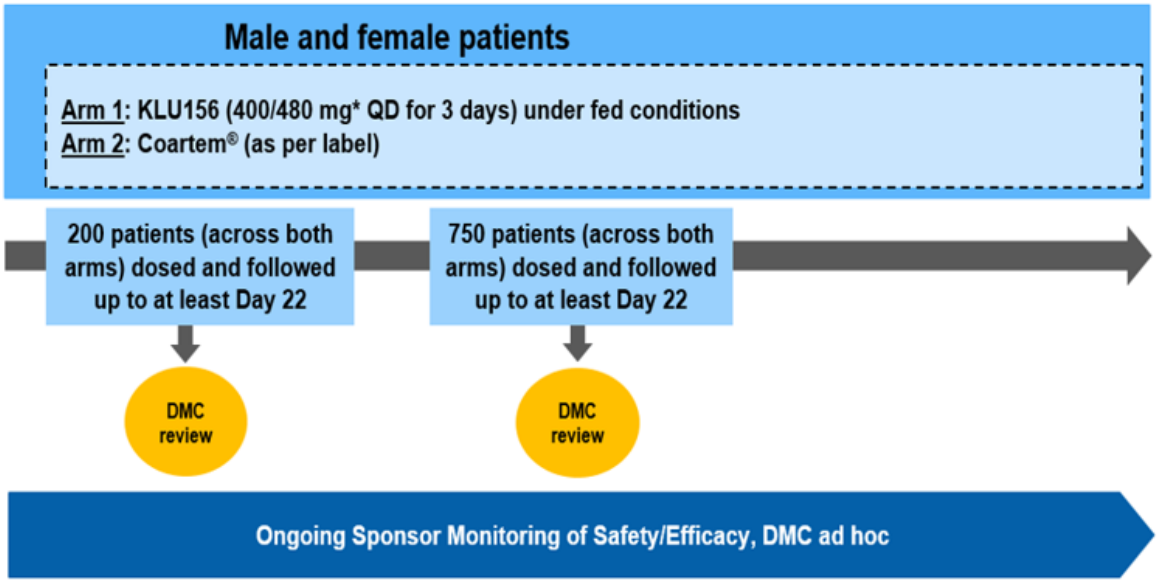
Key words

Plasmodium falciparum malaria, KLU156, ganaplacide, lumefantrine, adults, children

1.2 Schema

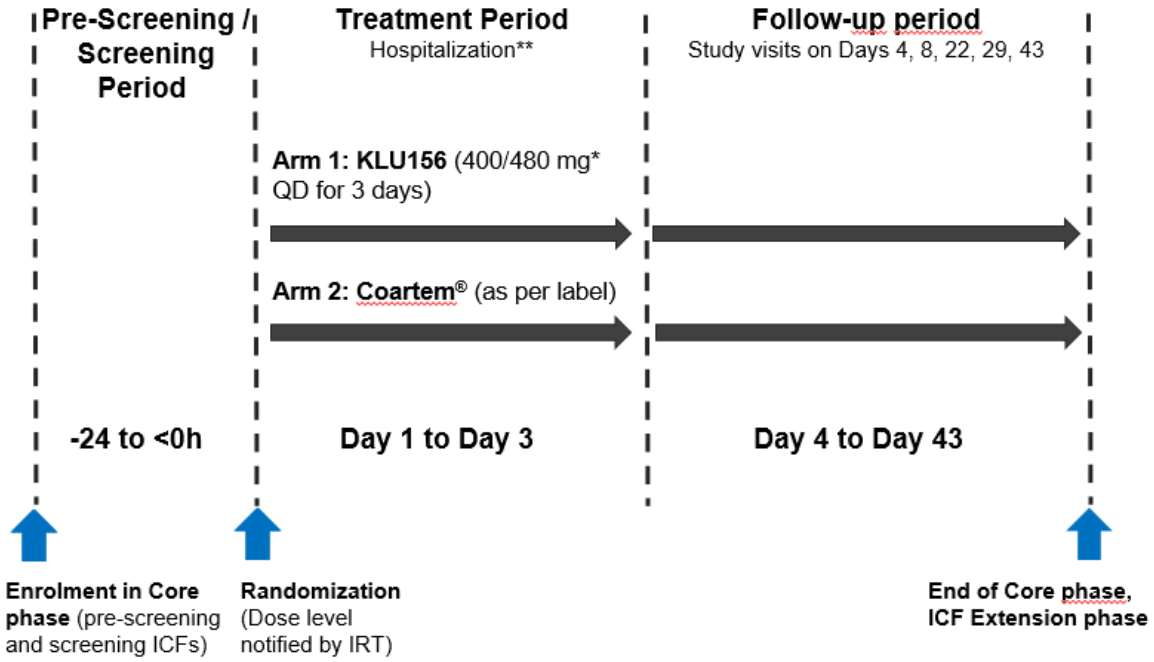
1.2.1 Core phase only

Figure 1-1 Core phase: Study design



* KLU156 400/480mg is a fixed-dose combination containing 400 mg of ganaplacide (KAF156) and 480 mg of a solid dispersion formulation of lumefantrine (lumefantrine-SDF). This dose is for patients with a bodyweight ≥ 35kg. Patients < 35kg will take a fraction of the dose according to weight group as shown in Table 6-4. KLU156 should be administered under fed conditions (light meal). Patients will be followed up to Day 43 in the Core phase.

Figure 1-2 Core phase: Patient journey

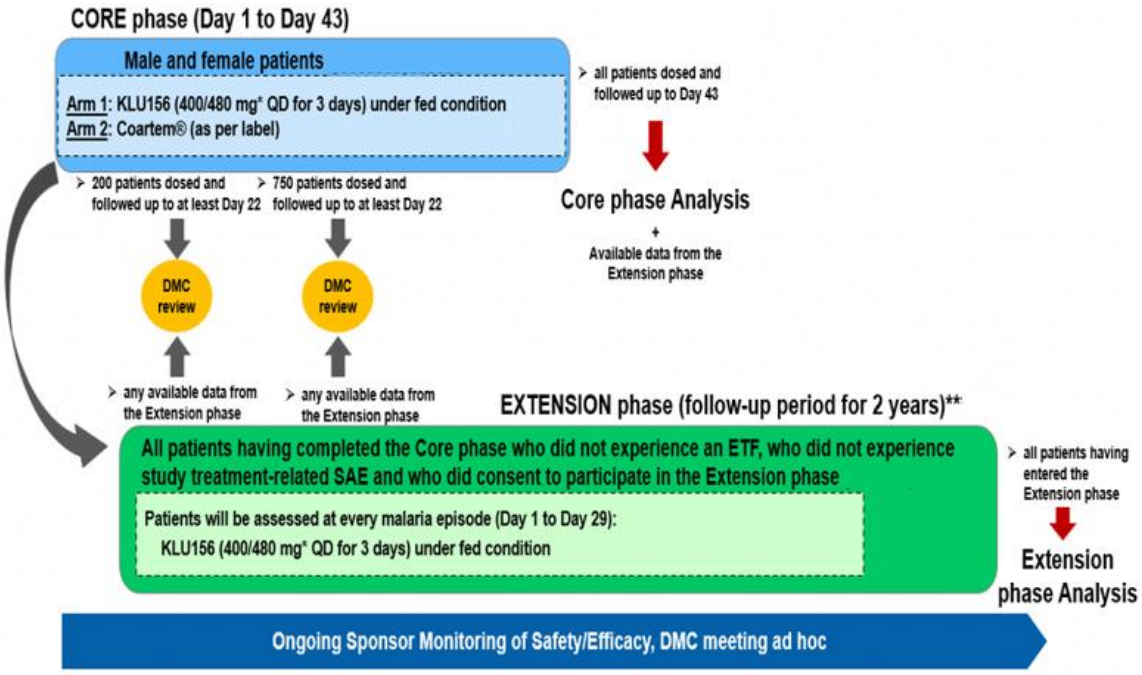


* This dose is for patients with a bodyweight ≥ 35 kg (see Table 6-4). KLU156 should be administered under fed conditions (light meal).

** Patients will be discharged after Day 4 assessments (they may stay longer at the discretion of the Investigator).

1.2.2 Core phase and Extension phase

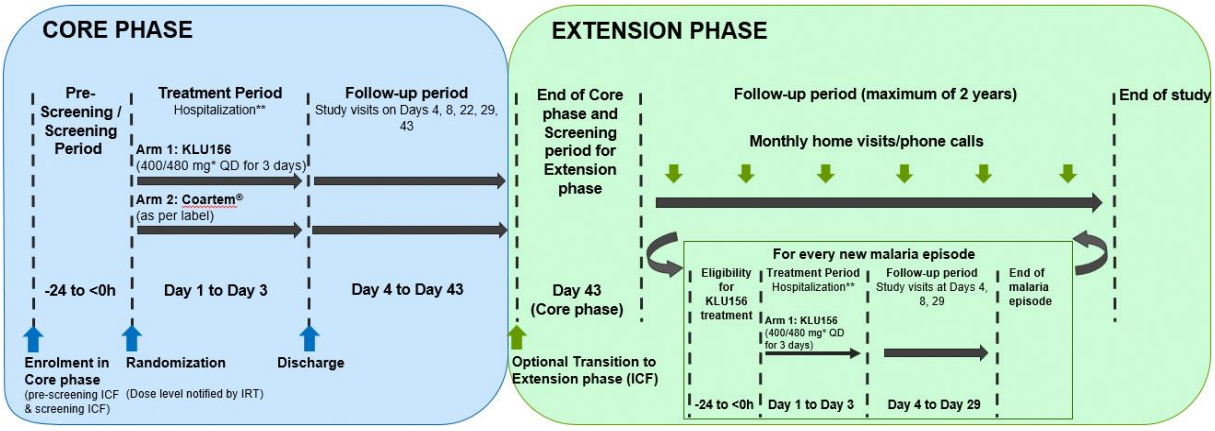
Figure 1-3 Core phase and Extension phase: Study design



* This 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. 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.

Figure 1-4 Core phase and Extension phase: Patient journey



* This dose is for patients with a bodyweight ≥ 35 kg (see Table 6-4). 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.

1.3 Schedule of activities (SoA)

The SoA lists all of the assessments and when they are performed. All data obtained from these assessments must be supported by the patient's source documentation. The "X" in the Table 1-2 and Table 1-3 denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the Table 1-2 and Table 1-3 denotes the assessments that are only in the patient's source documentation and do not need to be recorded in the clinical database.

Patients should be seen for all visits/assessments as outlined in the SoA or as close to the designated day/time as possible. Missed or rescheduled visits will not lead to automatic discontinuation.

Patients who discontinue from study treatment are to complete the remaining visits for the treatment period and attend the follow-up visits as indicated in the SoA.

Patients who discontinue from the Core phase or the Extension phase of the study should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all assessments listed for the final visit will be performed (Day 43 in the Core phase and Day 29 of the relevant malaria episode in the Extension phase). At this final visit, all dispensed investigational product should be reconciled, and the adverse events (AEs) and concomitant medications not previously reported must be recorded in the CRF (Case Report/Record Form). In order to participate in the Extension phase, patients should have completed Day 43 assessments of the Core phase and should satisfy the Extension phase's specific inclusion/exclusion criteria.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e., pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of provision of continued care may be implemented by the Investigator as the situation dictates. If allowable by a local health authority, national and local regulations and depending on operational capabilities, phone calls, virtual contacts (e.g., tele consultation) or visits by site staff/off-site healthcare professional(s) staff to the patient´s home can replace certain protocol assessments, for the duration of the disruption until it is safe for the patient to visit the site again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Table 1-2 Assessment Schedule, Core phase

Period	**Screening**	**Screening**[1]	**Treatment**[2]										**Follow-up**[2]					**UNS**[3]
Visit Name	**Pre-Screening**	**Screening**	**Day 1**				**Day 2**			**Day 3**			**Day 4**	**Day 8**	**Day 22**	**Day 29**	**Day 43/ End of Core phase**[4]	**UNS**
Days	**0**	**0**	**1**				**2**			**3**			**4**	**8**	**22**	**29**	**43**	**1 to 43**
Time (post-dose)	**-**	**-24 to <0**	**0**	**6**	**8**	**12**	**24**	**30**	**36**	**48**	**54**	**60**	**72**	**168**	**504**	**672**	**1008**	**-**
Informed consent	X[5]	X[5]															X[6]	
Inclusion / Exclusion criteria	X	X																
Demography	X																	
Malaria blood film for asexual parasite and gametocyte counts[7]	X		X	X		X	X		X	X			X[8]	X	X	X	X	X
Contact Interactive Response Technology (IRT)	X	X	X				X			X							X	
Adverse Events	continuous starting after ICF signature until end of Core phase (Day 43)																	
Medical history/current medical conditions		X																
Prior and concomitant medications		X																
Signs and symptoms of severe malaria		S	S				S			S			S	S	S	S	S	S
Physical Examination and malaria signs and symptoms[9]		S	S				S			S			S	S	S	S	S	S
Blood Pressure		X	X				X			X			X	X	X	X	X	X
Body Temperature[10]		X	X	X		X	X	X	X	X			X	X	X	X	X	X
Body Height		X															X	
Pulse rate		X	X				X			X			X	X	X	X		X
Body Weight		X	X				X			X							X	X
Mid-upper arm circumference (MUAC)		X[11]																
Clinical Chemistry[7,12]		X								X				X		X	X	X

Period	**Screening**	**Screening**[1]	**Treatment**[2]										**Follow-up**[2]					**UNS**[3]
Visit Name	**Pre-Screening**	**Screening**	**Day 1**				**Day 2**			**Day 3**			**Day 4**	**Day 8**	**Day 22**	**Day 29**	**Day 43/ End of Core phase**[4]	**UNS**
Days	**0**	**0**	**1**				**2**			**3**			**4**	**8**	**22**	**29**	**43**	**1 to 43**
Time (post-dose)	**-**	**-24 to <0**	**0**	**6**	**8**	**12**	**24**	**30**	**36**	**48**	**54**	**60**	**72**	**168**	**504**	**672**	**1008**	**-**
Hematology[7,12]		X								X				X		X	X	X
Urinalysis		X								X						X	X	X
Blood sampling for parasite PCR genotyping and resistance markers[7,13]			X			X	X			X			X	X	X	X	X	X
CCI																		
Drug administration for KLU156[16]			X				X			X								
Drug administration for Coartem[16]			X		X		X		X	X		X						
Meal record			X		X[18]		X		X[18]	X		X[18]						
Electrocardiogram (ECG)[19,20]		X								X[21]			X	X			X	
Pregnancy test (WCBP only)[22]		S															S	
Hospitalization		S	S				S			S								
CCI																		

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
[1] Screening Period has 2 parts: a Pre-Screening Part (Study Visit 1) to successfully identify the correct patients to be screened for this clinical study, and a Screening Part (Study Visit 20) in which further assessments will take place. Pre-screening, Screening and D1 visits may occur on the same day.
[2] Time windows for scheduled visits are as follows; on Days 1, 2, 3, 4: ± 0 day; on Day 8 ± 1 day; on Days 22, 29: ± 2 days; on Day 43: ± 4 days.
[3] UNS = unscheduled

Period	**Screening**	**Screening**[1]	**Treatment**[2]										**Follow-up**[2]					**UNS**[3]
Visit Name	**Pre-Screening**	**Screening**	**Day 1**				**Day 2**			**Day 3**			**Day 4**	**Day 8**	**Day 22**	**Day 29**	**Day 43/ End of Core phase**[4]	**UNS**
Days	**0**	**0**	**1**				**2**			**3**			**4**	**8**	**22**	**29**	**43**	**1 to 43**
Time (post-dose)	**-**	**-24 to <0**	**0**	**6**	**8**	**12**	**24**	**30**	**36**	**48**	**54**	**60**	**72**	**168**	**504**	**672**	**1008**	**-**

[4] Day 43 will be the last visit of the Core phase of the study. Patients who discontinue from the Core phase should be scheduled for a final evaluation visit when all assessments listed for the final visit will be performed (Day 43).
[5] Informed Consent Form (ICF) for the Core phase.
[6] ICF for the Extension phase.
[7] The total volume of blood drawn must remain under the recommended limit of 3 ml/kg (body weight at screening) over 30 days (4.2 ml/kg over the 43 days of the core phase of the study).
[8] If baseline parasites are not cleared at Day 4 as per microscopy assessment, additional daily parasite assessment should be performed until the parasites are cleared.
[9] Signs and symptoms of uncomplicated malaria to be collected at baseline and in patients showing treatment failure before standard-of-care is administered.
[10] Fever monitoring will be done every 6 h until resolution, defined as being afebrile for 24 h.
[11] At screening, mid-upper arm circumference to be assessed in patients < 12 years of age only.
[12] Laboratory tests should also be done at any time of withdrawal/discontinuation.
[13] PCR blood samples will be used for genotyping to establish malaria recrudescence/new infection and for reviewing resistance markers. Blood samples will be collected in all patients fulfilling eligibility criteria for inclusion in the study and at the time of treatment failure before standard-of-care is administered. Additional samples may be collected at selected sites following the same schedule, but they will be analyzed separately at one of those sites for capacity building purposes.

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[16] On dosing days, all safety and efficacy assessments should be performed prior to study treatment administration. KLU156 should be given to patients under fed conditions (light meal).
[17] Sample to be collected in case of overdosing with KLU156 if requested by the medical monitor (determined on a case-by-case basis as per Section 6.7).
[18] Meal record to be collected in patients treated with Coartem.
[19] ECG assessment will be repeated in case of abnormalities.
[20] ECGs should be taken in triplicate within 5 minutes after resting for at least 10 minutes in the supine position to ensure a stable heart rate according to the ECG investigator manual. Also, ECGs should be taken before any other procedure at the same nominal time point is performed. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The actual time should be recorded. Time windows for scheduled timepoints, are as follows; for screening : - 3 to 0 h ; for the 48 h: within 3 h prior to Day 3 dosing; 72 h : ± 3 h; for Days 8 and 43 : ± 24 h.
[21] The ECG at 48h should be done prior to study drug administration.
[22] In women of childbearing potential (WCBP), the menstrual and contraceptive history will be recorded and a urine β-hCG pregnancy test will be performed at screening in order to exclude pregnancy, and again at end of study. The result at screening must be confirmed negative before dosing.

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Table 1-3 Assessment Schedule, Extension phase

Period	**Screening**	**Pre-Treatment**	**Treatment**			**Follow-up**			**Long term Contact/EOS**	**UNS**
Visit Name	**Screening**	**Baseline at each malaria episode**[1]	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 8**	**Day 29**[2]	**End of Extension** [3]	**UNS**
Days	**43 (Core phase)**	**-1**	**1**	**2**	**3**	**4**	**8**	**29**	**730 (of Extension)**	**1 to 29**
Time (post-dose)	**-**	**-24h to <0h**	**0h**	**24h**	**48h**	**72h**	**168h**	**672h**	**-**	**-**
Informed consent	X									
Inclusion / Exclusion criteria	X									
Eligibility / Non-eligibility criteria for KLU156 treatment at each malaria episode		X								
Malaria blood film for asexual parasite and gametocyte counts[4]		X	X		X	X	X	X		X
Contact IRT	X	X	X		X			X		
Adverse Events	X									X
Medical history/current medical conditions		X								
Prior and concomitant medications		X								X
Signs and symptoms of severe malaria		S	S		S	S	S	S		S
Physical Examination and malaria signs and symptoms[5]		S	S		S	S	S	S		S
Blood Pressure		X	X		X	X	X	X		X
Body Temperature		X	X		X	X	X	X		X
Body Height		X						X		
Pulse rate		X	X		X	X	X	X		X
Body Weight		X	X					X		X
Mid-upper arm circumference (MUAC)[6]		X								
Clinical Chemistry[4]		X				X	X	X		X

Period	**Screening**	**Pre-Treatment**	**Treatment**			**Follow-up**			**Long term Contact/EOS**	**UNS**
Visit Name	**Screening**	**Baseline at each malaria episode**[1]	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 8**	**Day 29**[2]	**End of Extension** [3]	**UNS**
Days	**43 (Core phase)**	**-1**	**1**	**2**	**3**	**4**	**8**	**29**	**730 (of Extension)**	**1 to 29**
Time (post-dose)	**-**	**-24h to <0h**	**0h**	**24h**	**48h**	**72h**	**168h**	**672h**	**-**	**-**
Hematology[4]		X				X	X	X		X
Urinalysis[4]		X					X	X		X
Blood sampling for parasite PCR genotyping and resistance markers[4,7]		X					X	X		X
CCI										
Drug administration for KLU156[8]			X	X	X					
Meal record			X	X	X					
Electrocardiogram (ECG)[9,10]		X			X[11]	X	X	X		
Pregnancy test (WCBP only)[12]		S						S		
Hospitalization		S	S	S	S					
Safety Follow-up call									X	

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
[1] Eligibility assessment will be performed at baseline for each malaria episode.
[2] Day 29 will be the last visit for that malaria episode. Patients who discontinue from the Extension phase during a malaria episode should be scheduled for a final evaluation visit when all assessments listed for the final visit of an episode will be performed (Day 29). All treated patients should have a safety follow-up contact conducted on Day 33, i.e., 30 days after last administration of study treatment (at every malaria episode). The information collected is kept as source documentation. All SAEs reported during this time period must be reported and attempts to contact the patient should be recorded in the source documentation.
[3] Telephone (or ad hoc) Contact with patient to mark the end of their participation in the Extension phase, i.e. 2 years after end of Core phase; the information collected is kept as source documentation: SAEs should only be reported to Novartis if the investigator suspects a causal relationship to study treatment. All attempts to contact the patient should be recorded in the source documentation.
[4] The total volume of blood drawn must remain under the recommended limit of 3 ml/kg (body weight at pre-treatment of each episode) over 30 days.
[5] Signs and symptoms of uncomplicated malaria to be collected at baseline and in patients showing treatment failure before standard-of-care is administered.
[6] MUAC to be assessed only in patients < 12 years of age.
[7] At baseline for each malaria episode, a blood sample will be collected in all patients fulfilling eligibility criteria. A second blood sample will be collected as per the table above in patients showing treatment failure before standard-of-care is administered.

Period	**Screening**	**Pre-Treatment**	**Treatment**			**Follow-up**			**Long term Contact/EOS**	**UNS**
Visit Name	**Screening**	**Baseline at each malaria episode**[1]	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 8**	**Day 29**[2]	**End of Extension** [3]	**UNS**
Days	**43 (Core phase)**	**-1**	**1**	**2**	**3**	**4**	**8**	**29**	**730 (of Extension)**	**1 to 29**
Time (post-dose)	**-**	**-24h to <0h**	**0h**	**24h**	**48h**	**72h**	**168h**	**672h**	**-**	**-**

[8] On dosing days, all safety and efficacy assessments should be performed before study treatment is given to the patients. KLU156 should be given to patients under fed conditions (light meal).
[9] ECG assessment will be repeated in case of abnormalities.
[10] ECGs should be taken in triplicate within 5 minutes after resting for at least 10 minutes in the supine position to ensure a stable heart rate according to the ECG investigator manual. Also, ECGs should be taken before any other procedure at the same nominal time point is performed. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. Time windows for scheduled timepoints are as follows; for baseline : - 3 h to 0 h ; for the 48 h: within 3 h prior to Day 3 dosing; 72 h : ± 3 h; for Days 8 and 29 : ± 24 h.
[11] the ECG at 48h should be done prior to drug administration
[12] In women of childbearing potential (WCBP), the menstrual and contraceptive history will be collected and a urine β-hCG pregnancy test will be performed at screening in order to exclude pregnancy and again at end of study. Result must be confirmed negative at baseline before dosing.

CCI [redacted]

2 Introduction

2.1 Study rationale

This Phase 3 study includes a Core phase and an Extension phase.

The Core phase of this study aims to confirm the efficacy, safety and tolerability of KLU156, a fixed dose combination of ganaplacide (KAF156) and a solid dispersion formulation of lumefantrine (lumefantrine-SDF), when administered once daily for 3 days in adults and children ≥ 10 kg body weight suffering from uncomplicated *P. falciparum* malaria (with or without other *Plasmodium* spp. co-infection) in order to support marketing authorization application for KLU156. There is an unmet medical need for anti-malarial combination treatment including a partner drug with a new mechanism of action to counter the emergence of resistance to artemisinin.

The Extension phase is designed to assess the safety, tolerability and efficacy of repeated treatment with KLU156 for a maximum of two years in patients who have completed the Core phase without experiencing early treatment failure (ETF) nor any study treatment-related SAE and who consent to participate in the Extension phase.

2.2 Background

Malaria is one of the leading causes of death in endemic areas. In 2020, an estimated 241 million cases of malaria and 627,000 deaths occurred worldwide: 95% of malaria cases and 96% of malaria deaths occurred in the African Region. Children under 5 years of age are the most vulnerable group affected by malaria, among them the percentage of total malaria deaths was 77% in 2020 (WHO 2021).

Human malaria is caused by one of six *Plasmodium* parasite species (or mixed *Plasmodium* infection), and two of these species – *P. falciparum* and *P. vivax* – pose the greatest threat. *P. falciparum* is the most prevalent and lethal malaria parasite on the African continent. *P. vivax* is the dominant malaria parasite in most regions outside of Sub-Saharan Africa.

Standard antimalarial drugs such as chloroquine, pyrimethamine, sulfadoxine and mefloquine have become largely ineffective in many malaria endemic regions (WHO 2021). The only exceptions are the artemisinin-based combination therapies (ACTs) such as Novartis' Coartem®/Riamet® and Eurartesim®, current standard-of-care for *P. falciparum* malaria. Partial artemisinin combination tolerance has already emerged in South East Asia, particularly the Greater Mekong Subregion (GMS), thereby posing a grave threat to global malaria control and elimination programs (Imwong et al 2017). Validated and candidate *Pfkelch13* mutations are used as artemisinin resistance markers, and several of these mutations were recently reported in Africa (WHO 2021). Despite the high (> 90%) cure rates observed with ACTs, the rising number of *Pfkelch13* mutations is alarming, as it can be a prelude to the development of resistance to artemisinins in Africa, in a similar way to what transpired in the GMS.

There is, in any case, an urgent medical need for innovative chemical entities with a new mode of action to treat this very common disease, and to alleviate the growing risk of resistance to ACTs. Additionally, once-daily treatments can improve treatment success and reduce the

probability of developing resistance via improved adherence and they could thus accelerate malaria eradication.

KLU156 is a fixed-dose combination containing ganaplacide (KAF156) and a solid dispersion formulation of lumefantrine (lumefantrine-SDF). Ganaplacide is an imidazolepiperazine, first-in-class drug, and is structurally distinct from currently marketed and experimental antimalarials. Its mechanism of action is understood to be based on inhibition of protein trafficking, blocking the establishment of new permeation pathways, and causing endoplasmic reticulum expansion (LaMonte et al 2020). Ganaplacide kills/inhibits the erythrocytic replication life cycle stages (blood stages) of *Plasmodium* species including the two main causative agents of human malaria, *P. falciparum* and *P. vivax*, both at low nanomolar EC50s (*in vitro*). CCI [redacted]. Also, ganaplacide is equally potent against drug-sensitive and a broad panel of drug resistant malaria strains (Koller et al 2018).

CCI [redacted] ganaplacide has been combined with lumefantrine-SDF, which has an improved bioavailability and lower food effect as compared to lumefantrine conventional formulation, thereby allowing a potentially curative once daily three-day regimen. Ganaplacide and lumefantrine-SDF co-administered in a loose combination were assessed in patients down to 2 years of age in a Phase 2b dose finding study (CKAF156A2202). The positive benefit-risk balance supports the evaluation of the identified effective and safe dose of the fixed-dose combination of ganaplacide and lumefantrine-SDF, i.e., KLU156 in a Phase 3 study. CCI [redacted]

2.3 Benefit/Risk assessment

Based on the preclinical and clinical evaluation to date, KLU156 is expected to be effective, generally safe and well tolerated. In a recent Phase 2 study (CKAF156A2202) in 524 malaria patients ≥ 2 years of age, the co-administration of ganaplacide and lumefantrine-SDF achieved fast parasite clearance that was maintained up to Day 29 in > 90% of patients with safety/tolerability comparable to control (artemether-lumefantrine). The most common AEs across the ganaplacide/lumefantrine-SDF treatment arms and regimens were related to the underlying disease and included malaria, upper respiratory tract infection (URTI), headache, pyrexia, vomiting, abdominal pain, electrocardiogram QT prolonged (QTcF > 60 ms from baseline), and blood bilirubin increased.

In this Phase 3 study, a fixed-dose combination of ganaplacide and lumefantrine-SDF, i.e., KLU156, will be administered to patients with uncomplicated *P. falciparum* malaria in order to confirm positive safety and efficacy results of the CKAF156A2202 Phase 2 study. KLU156 is expected to reduce the number of circulating malaria parasites in the patients' blood, consequently improve their clinical symptoms over the first 48 h, and achieve a complete cure

of their illness. Any Early Treatment Failure (ETF) (see Section 10.6), recrudescence or new infection will be managed with standard-of-care treatment. Any recrudescing parasites will be analyzed for standard markers of resistance.

The risk to patients in this trial will be minimized by compliance with the eligibility criteria and study procedures, and close clinical monitoring. In the Core and the Extension phases, patients will be hospitalized and remain under close supervision until they are discharged by the Investigator or designee on Day 4.

Appropriate patient eligibility criteria and specific stopping rules are included in the protocol (Section 5). Women of childbearing potential must be informed that taking study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and they must agree that in order to participate in the study, they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any doubt that the patient will reliably comply, they should not be enrolled at all or, if enrolled already, they should not continue in the study.

The assessment of the data will be performed through Sponsor Data Review (ongoing blinded safety/efficacy data review) and Data Monitoring Committee (DMC) Review (of the first 200 and 750 patients dosed across both treatment arms and followed-up to at least Day 22 in the Core phase and of all safety data from the Extension phase available at each of these 2 timepoints).

CCI [redacted]

As part of the protocol amendment, the minimum body weight criterion for patient inclusion has been revised from ≥ 5 kg to ≥ 10 kg. CCI [redacted].

Throughout the enrollment period in this ongoing Phase 3 study (KALUMA), it was observed that children under 10 kg experienced difficulties in swallowing the study treatments, as indicated by adverse event reports of vomiting or spitting out of the study treatments within a few minutes of administration, which affected the treatment adherence in this subgroup. CCI [redacted]

CCI [redacted].

3 Objectives, endpoints, and estimands

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

Table 3-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
● **Core phase:** 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)**
● **Core phase:** 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
● **Core phase:** 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 patients with parasitemia at 12, 24, 48 and 72 h after treatment. Disappearance or development of gametocytemia in patients with or without gametocytemia at baseline (pre-first dose administration), respectively.
● **Core phase:** 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.
● **Extension phase:** 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 malaria episode. AE/SAE incidence and severity, laboratory abnormalities and ECG abnormalities by malaria episode.
● **Extension phase:** 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 malaria episode. Gametocyte carriage over time by malaria episode.
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
CCI	

Objective(s)	Endpoint(s)
CCI	

3.1 Primary estimands

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 3-2 below:

Table 3-2 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 patients 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 patients 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 anti-malarial medicines 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 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 patient 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 study site.

3.2 Secondary estimands

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

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

Clinical question of interest	"What is the difference in the proportion of patients 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 patient 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.

3.3 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 (see Section 9.7.1), in accordance with their requirement for demonstrating antimalarial drug efficacy.

4 Study design

4.1 Overall design

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

4.1.1 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 patients ≥ 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). All efforts will be made to ensure that the proportion of patients recruited in these different body weight bands is generally reflective of the epidemiology of malaria as far as possible, considering overall constraints. To this effect, the distribution of the study population by body weight band will be evaluated on a regular basis during the course of recruitment in the study, including 4 pre-defined timepoints (i.e., when 200, 500, 750 and 1000 patients have been randomized). Ad-hoc evaluations may be performed, if required. At any one of these timepoints, if deemed appropriate, recruitment caps will be applied in the Interactive Response Technology (IRT) in order to strive to adjust the distribution ad hoc (e.g., in case one or more of the lower weight groups were under-represented).CCI [redacted]

An independent Data Monitoring Committee (DMC) will review patient safety data throughout the study. Further details will be provided in the DMC Charter.

The following Data Review timepoints are planned:

- Once the first 200 patients (approximately 100 patients from each treatment arm) have been dosed and followed up to at least Day 22.
- Once the first 750 patients (approximately 375 patients from each treatment arm) have been dosed and followed up to at least Day 22.
- Additional DMC reviews may be performed ad-hoc during the study, as deemed necessary.

The Screening Period will consist of two visits: a Pre-Screening visit and a Screening visit.

- **Pre-Screening visit**: Pre-screening is a key element aiming to identify the patients who can enter screening based on parasite count. At the pre-screening visit the following steps should be followed:

  Detection of:

  - P. falciparum asexual forms
  - P. falciparum gametocytes
  - Any other Plasmodium species (P. vivax, P. ovale, P. malariae, P knowlesi)

  Count of:

  - *P. falciparum* asexual forms. Patients should have a *P. falciparum* parasitemia of ≥ 1,000 and ≤ 200,000 parasites/µL at that time in order to proceed to the screening visit.
- **Screening visit**: Further screening assessments will take place as soon as the pre-screening *P. falciparum* parasite count has been confirmed to fall within the pre-defined range (≥ 1,000 and ≤ 200,000 parasites/µL).

At all further visits in the core phase after pre-screening visit, counts of all forms (*P. falciparum* asexual forms, *P. falciparum* gametocytes; *P. vivax, P. ovale, P. malariae, P knowlesi* asexual forms) should be performed and reflected in the microscopy CRF pages.

It is not permissible to re-screen a patient for the same malaria episode if they fail the initial pre-screening or screening. Re-screening of a previously screen failed patient may occur if the patient is returning to the study site for a new malaria episode. In this case, the patient will be assigned a new patient number.

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

At the baseline visit, eligible patients will be randomized (1:1 ratio) to one of the two treatment arms (KLU156 or Coartem):

- Treatment arm 1: KLU156 (400/480 mg) QD (once daily) for 3 days (highly recommended to be administered in patients under fed conditions (light meal) as soon as food is tolerated, see Section 6.2.3). This dose is for patients with a bodyweight ≥ 35kg. Patients < 35kg will take a fraction of the dose according to weight group as shown in Table 6-4.
- Treatment arm 2: Coartem BID (twice a day) for 3 days (highly recommended to be administered in patients under fed conditions as soon as food is tolerated). Dosing will be selected based on patient's body weight as per product (label see Table 6-4).

Patients with mixed infections involving *P. vivax or P. ovale* should be treated with non-study antimalarial medicines **after** Day 43 assessments (e.g., primaquine, tafenoquine; as per local standards and as per label at the discretion of the Investigator or designee). Patients with mixed infections involving other species (e.g., *P. malariae*) do not have this requirement.

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

Every patient will receive an insecticide-impregnated bed net (as applicable locally) and will be followed-up as an outpatient until Day 43. Visits to assess efficacy, safety and tolerability of study drugs will be scheduled during the follow-up period as described in the Assessment Schedule (see Table 1-2). If malaria symptoms re-emerge outside of the scheduled study visits, patients will be instructed to contact the Investigator.

Administration of rescue medication with a combination antimalarial product (local standard at the discretion of the Investigator or a medically qualified person) may occur after the first dose of trial drug and up to 43 days as deemed necessary by the Investigator. Lumefantrine-including treatment should preferably be avoided in patients experiencing ETF. Patients treated with at least one dose of trial medications will continue to be followed-up until Day 43 according to schedule.

Patients/patients' parents/legal guardians and Investigator or designee will not be blinded to treatment assignment. However, measures will be put in place to ensure that microscopists involved in parasite count assessments are blinded to individual subject's treatment assignment wherever feasible (Section 6.3.2). When feasible, microscopists not involved in parasite count assessments as well as all other laboratory personnel should also remain blinded to individual subject's treatment assignment. The Novartis Clinical Trial Team (CTT) will be blinded to the individual subject's treatment assignment, with a few notable exceptions.

In the event of a public health emergency, alternative methods for provision of care may be introduced as outlined in Section 4.5.

4.1.2 Extension phase

The Core phase will be followed by an Extension phase.

All patients who complete the Core phase according to the protocol, who did not meet the criteria for ETF (see 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 period, patients should come back to the study site at any time when they develop symptoms indicative of a new malaria episode.

At a particular malaria episode:

- If a patient is considered ineligible for KLU156 treatment, they will receive a combination antimalarial treatment (or treatment for severe malaria) as per local standards, and data will not be collected for that episode.
- If a patient is considered eligible for KLU156 treatment (Section 5.3), they will be treated with KLU156 400/480 mg QD for 3 days under fed conditions (light meal, see Section 6.2.3) (Patients < 35kg will take a fraction of the dose according to their weight group as shown in Table 6-4) and they will remain in the hospital under close supervision until they are discharged by the Investigator or designee on Day 4. At the discretion of the Investigator, patients may stay for a few additional days if needed. The patient will then be followed-up until Day 29. Visits to assess efficacy, safety and tolerability of study treatment will be scheduled during the follow-up period as described

in the Assessment Schedule (Table 1-3). If malaria symptoms re-emerge outside of the scheduled study visits, the patient will be instructed to contact the Investigator.

Eligibility to receive KLU156 will be assessed again at every subsequent malaria episode. If a patient is deemed ineligible at a particular malaria episode, the patient can return to the study site upon developing symptoms indicative of a new malaria episode for another eligibility assessment.

Patients with mixed infections involving *P. vivax or P. ovale* should be treated with non-study antimalarial medicines **after** Day 29 assessments (e.g., primaquine, tafenoquine; as per local standards and as per label at the discretion of the Investigator or designee). Patients with mixed infections involving other species (e.g., *P. malariae*) do not have this requirement.

Patients diagnosed with severe malaria should be treated with non-study antimalarial medicines as per local standards.

Administration of rescue medication with a combination antimalarial product (local standard at the discretion of the Investigator or a medically qualified person) may occur after the first dose of KLU156 and up to 29 days thereafter as deemed necessary by the Investigator. Lumefantrine-including treatment should preferably be avoided in patients experiencing ETF. Patients treated with at least one dose of trial medications will continue to be followed-up until Day 29 according to schedule.

Treatment will be open to patients/patients' parents/legal guardians, site staff, study monitors and to the Novartis CTT.

During the Extension phase of the study, patients will be followed up for 2 years. A monthly scheduled home visit or phone call will be performed by a designated person (e.g., a healthcare worker) to document the presence of the patient and their health status. Patients will be reminded to come to the study site for any symptoms associated with malaria. Patients will only be followed up actively at the time of a malaria episode.

Of note, the Extension phase may be terminated earlier by Sponsor decision.

In the event of a public health emergency, alternative methods for provision of care may be introduced as outlined in Section 4.5.

4.2 Scientific rationale for study design

This will be a multicenter, open-label, randomized, parallel-group, non-inferiority (NI) study in patients ≥ 10 kg body weight with uncomplicated *P. falciparum* malaria.

The use of a fixed dose combination treatment with at least two drugs for anti-malaria therapy is well established and recommended by the World Health Organization (WHO 2022). There is an unmet medical need for anti-malarial treatments with a non-artemisinin mode of action to avoid widespread treatment failure as a result of development of resistance to artemisinin combination therapies.

The primary objective of this study (Core phase) is to confirm the efficacy of KLU156 in patients ≥ 10 kg body weight by demonstrating the NI of KLU156 to Coartem, the standard of care (SoC) using PCR-corrected ACPR rate at Day 29. The NI margin has been set to 5%.

Rationale for study design is summarized in the Table 4-1 below.

Table 4-1 Rationale for study design (Core phase of the study)

Study Design Aspect	Rationale
Duration of follow-up for evaluation of primary/secondary estimands	A follow-up of 28 days (corresponds to Day 29, when first day of dosing 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)
Overall (parallel)	To ensure that the patient population is comparable between treatment arms
Randomization (strata, allocation ratio)	To reduce the risk of selection bias and also the risk of unequal distribution between 2 arms (KLU156 and Coartem)
Open-label	The risk of bias arising out of the open-label design is minimized as objective endpoints (parasite counts) have been chosen for the study
Non-inferiority (NI)	A non-inferiority setting will provide the opportunity to perform head-to-head comparison of KLU156 against Coartem. Generally, a NI margin is selected based on the placebo-adjusted treatment effect of the SoC as well as clinical judgement. However, the placebo-adjusted treatment effect for Coartem in terms of PCR-corrected ACPR at Day 29 is not available. A recent study (CLINDAQUINE) by Obonyo et al 2022 compared Coartem with quinine plus clindamycin and showed that the PCR-corrected ACPR at Day 29 is statistically significantly higher for Coartem than quinine plus clindamycin (Intent-to-treat: treatment difference 44.8%, 95% CI: 35.2% to 54.4%). The 5% NI margin in the PCR-corrected ACPR at Day 29 is only <15% of the observed treatment effect for Coartem over quinine plus clindamycin, which is much smaller than the 50% suggested by the FDA guidance for NI clinical trials to establish effectiveness (FDA 2016b). Such a small margin is considered clinically insignificant based on WHO guidance for change of treatment policy (PCR corrected efficacy ≥95% for SoC and policy of removing a drug if the effect is <90%) and a 5% NI margin was used for the approvals of previous drugs. The CLINDAQUINE trial also showed that the uncorrected ACPR at Day 29 is statistically significantly higher for Coartem than quinine plus clindamycin (Intent-to-treat: treatment difference 39.6%, 95% CI: 29.6% to 49.6%). Novartis' Coartem Study AB/MO2 showed that the uncorrected ACPR at Day 29 is statistically significant higher for Coartem than for artemether alone (Evaluable: treatment difference 45.5%, 95% CI: 30.0% to 60.0%). The 7.5% NI margin for uncorrected ACPR is only about 25% of the observed treatment effect for Coartem over quinine plus clindamycin or Coartem over artemether.
Data review check	DMC data review will occur after 200 patients and 750 (50%) patients dosed in the Core phase in order to minimize the risk for a larger group of patients.
Stratification	Randomization will be stratified by baseline mixed infection status (yes or no) and country. For mono-infection with *P. falciparum*, randomization will be further stratified by body weight group (≥ 35; 25 to <35, 15 to <25, <15kg).
Multicenter	To enroll a diverse patient population.

The Core phase of the study will be followed by an Extension phase, aiming to assess the safety and tolerability of repeated treatment with KLU156. Hence, the design of the Extension phase is similar to the one described for the Core phase (see above) with the exception of randomization, non-inferiority (one treatment arm only), and duration of follow-up.

4.3 Justification for dose

The dose and regimen of KLU156 were selected based on observed exposure, efficacy/safety outcomes of Phase 2b study CKAF156A2202 and on the CCI food effect on lumefantrine exposure in pediatric patients from Phase 2 study CKAF156A2203 (KALUMI).

The selected dose of KLU156 for patients ≥ 35 kg enrolled in this trial is 400/480 mg QD for 3 days (400 mg ganaplacide/ 480 mg lumefantrine-SDF). Treatment should be given under fed conditions (light meal), as administration under fasted conditions is not considered a preferred option for malaria patients.

CCI [redacted] The selected dose is targeted for patients with a body weight ≥ 35kg. Patients < 35kg will take a fraction of that dose according to their weight group as shown in Table 6-4.

4.4 Rationale for choice of control drugs (comparator/placebo) or combination drugs

The control treatment used is Coartem (artemether-lumefantrine), an artemisinin-based combination therapy. The dose and dose regimen in the present study are in accordance with product labeling. Coartem is widely used in *P. falciparum* malaria and it has a well-characterized safety and efficacy profile (Hamed, Grueninger 2012). In addition, Coartem contains the same partner drug (lumefantrine) as the study drug KLU156 in the current study. Hence, Coartem is considered the appropriate comparator treatment for this study.

4.5 Rationale for public health emergency mitigation procedures

In the event of a public health emergency as declared by local or regional authorities (i.e., pandemic, epidemic or natural disaster), mitigation procedures may be required to ensure patient safety and trial integrity and are listed in relevant sections of the study protocol. Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and the latter should be permitted/approved by local or regional health authorities and ethics committees as appropriate.

4.6 Purpose and timing of interim analyses/design adaptations

There will be no formal interim analysis to stop the trial early for futility or overwhelming efficacy.

Although the Core phase is open-label, the 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 (see Section 6.3.2). 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 patient population:

1. Once the first 200 patients (across both treatment arms) in the Core phase have been dosed and followed up to at least Day 22.
2. Once the first 750 patients (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.

All safety data from the Core phase as well as from the Extension phase that are available at these 2 scheduled timepoints will be included in the DMC reviews. The CTT will be unblindedafter the interim database lock for the analysis of the Core phase..

Additional safety and efficacy data analyses may be performed by Novartis in the Extension phase, in order to support the regulatory submission and the relevant safety updates.

The sample size will be increased based on the outcome of the blinded sample size re-estimation after about 750 patients (across both treatment arms) in the Core phase have been randomized (Section 9.9.3).

4.7 End of study definition

The completion of the Core phase is defined as the date when the last patient completes their last study visit of the Core phase and when any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator.

The completion of the Extension phase corresponds to the regular end of the study overall and it is defined as two years after the date when the last patient has been enrolled in the Extension phase.

5 Study population

The study population consists of male and female patients ≥ 10 kg of body weight with confirmed uncomplicated *P. falciparum* malaria. Only patients with malaria symptoms and a *P. falciparum* count ≥ 1,000 parasites/µL and ≤ 200,000 parasites/µL (*P. falciparum* with or without other *Plasmodium* spp. co-infection) will be included in the Core phase of the study.

The plan is to randomize (1:1) approximately 1500 patients ≥ 10 kg of body weight in different geographical regions with a main focus on Sub-Saharan Africa to address variations in the susceptibility of isolates, as well as to reflect differences in population host factors. The number of patients will be increased after the blinded sample size re-estimation and to account for

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5.1 Inclusion criteria

5.1.1 Core phase

Patients must meet all of the following criteria in order to be eligible for inclusion in the Core phase of this study:

1. Male or female patients ≥ 10 kg of body weight
2. Microscopically confirmed diagnosis of uncomplicated *P. falciparum* malaria with an asexual *P. falciparum* parasitemia ≥ 1,000 and ≤ 200,000 parasites/ µL at the time of pre-screening with or without other *Plasmodium* spp. co-infection.
3. Axillary temperature ≥ 37.5 ºC or oral temperature ≥ 38.0 ºC or tympanic/rectal temperature ≥ 38.5 ºC; or history of fever during the previous 24 h (at least documented verbally)
4. Negative pregnancy test for patients of childbearing potential
5. Signed informed consent (pre-screening and screening for the Core phase) must be obtained before any assessment is performed; for minors, signed informed consent must be obtained from parent/legal guardian (LAR). If the parent/LAR is unable to read and write, then a witnessed consent according to local ethical standards is permitted. Patients who are capable of providing assent, must provide it along with parental/LAR consent or as per local ethical standards
6. The patient and/or their parent/LAR is able to understand and comply with protocol requirements, instructions and protocol-stated restrictions and is likely to complete the study as planned.

5.1.2 Extension phase

Patients must meet all of the following criteria to be eligible for transition in the Extension phase of this study:

1. Patients randomized into the Core phase and having completed it.
2. Signed informed consent (for the Extension phase) must be obtained before any assessment is performed; for minors, signed informed consent must be obtained from parent/LAR. If the parent/LAR is unable to read and write, then a witnessed consent according to local ethical standards is permitted. Patients who are capable of providing assent, must provide assent with parental/legal guardian consent or as per local ethical guidelines.

5.2 Exclusion criteria

5.2.1 Core phase

Patients meeting **any** of the following criteria are **not** eligible for inclusion in the Core phase of this study.

No additional exclusions may be applied by the Investigator, in order to ensure that the study population will be representative of all eligible patients:

1. Signs and symptoms of severe malaria according to WHO 2015
2. Significant, non-plasmodial co-infections including tuberculosis
3. Concurrent febrile illnesses (e.g., typhoid fever, known or suspected dengue fever, known COVID19)
4. Severe malnutrition:
   - For patients ≥ 12 years: body mass index (BMI) < 16.0
   - For children < 12 years: less than 70% of median normalized WHO reference weight or very low mid-upper arm circumference (MUAC < 115 mm)
5. Known relevant liver disease e.g., chronic hepatitis, cirrhosis or hepatitis B or A vaccination within the past month, known gallbladder or bile duct disease, acute or chronic pancreatitis
6. Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection or family history of congenital or hereditary immunodeficiency
7. Repeated vomiting (defined as >3 times in the 24 h prior to start of screening) or severe diarrhea (defined as >3 watery stools in the 24 h prior to start of screening)
8. Clinically relevant abnormalities of electrolyte balance which require correction, e.g., hypokalemia, hypocalcemia or hypomagnesemia
9. Anemia (hemoglobin level < 7 g/dL)
10. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs (e.g., HIV patients on ART therapy or TB patients on treatment), or which may jeopardize the patient in case of participation in the study.
11. Any of the following:
    - AST/ALT > 3 x the upper limit of normal (ULN), regardless of the level of total bilirubin
    - Total bilirubin > 3 x ULN
    - Resting QT interval corrected by Fridericia's formula (QTcF) > 450 ms at screening
12. Any severe disease condition (including malignancy), known chronic underlying disease such as sickle cell disease, and severe cardiac, renal, or hepatic impairment) which might prohibit participation in this study
13. Inability to swallow oral medication (in tablet, powder and/or liquid form)
14. Prior antimalarial therapy or antibiotics with antimalarial activity within minimum of their five plasma half-lives (or within 4 weeks of screening if half-life is unknown)

15. Use of other investigational drugs within 30 days of dosing or until the expected pharmacodynamic effect has returned to baseline, whichever is longer, or longer if required by local regulations
16. Use of medications prohibited by the protocol
17. Previous participation in any malaria study or any malaria vaccine study or having received a malaria vaccine in any other circumstance within 1 month prior to start of study treatment
18. History or family history of long QT syndrome or sudden cardiac death, or any other clinical condition known to prolong the QTc interval, such as history of symptomatic cardiac arrhythmias, clinically relevant bradycardia or severe heart disease
19. Use of agents known to prolong the QT interval unless it can be permanently discontinued for the duration of the study
20. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes
21. Pregnant or nursing (lactating) patients
22. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception.

Effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps)
- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS).

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age-appropriate history of vasomotor symptoms). Women are considered not of childbearing potential if they have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks prior to screening. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential.

For further details on pregnancy testing and contraception requirements, refer to Section 8.4.6.

5.2.2 Extension phase

Patients meeting the following criteria in the Core phase are **not** eligible for transition into the Extension phase:

- Early Treatment Failure (KLU156 or Coartem treatment arm) (see Section 10.6)
- Patients with reported study treatment-related SAE (KLU156 or Coartem).

5.3 Eligibility criteria to receive KLU156 treatment in the Extension phase at each malaria episode

Patients enrolled in the Extension phase should come back to the study site at any time when they develop symptoms indicative of a new malaria episode and the following eligibility criteria must be checked before patients can receive KLU156 treatment.

A) Patients must fulfil the following conditions at every malaria episode in order to be eligible for (re-)treatment with KLU156 in the Extension phase:

1. Microscopically confirmed diagnosis of uncomplicated *P. falciparum* malaria with an asexual *P. falciparum* parasitemia ≥ 200 and ≤ 200,000 parasites/ µL with or without other *Plasmodium* spp co-infection.
2. Axillary temperature ≥ 37.5 ºC or oral temperature ≥ 38.0 ºC or tympanic/rectal temperature ≥ 38.5 ºC; or history of fever during the previous 24 h (at least documented verbally)
3. Negative pregnancy test for patients of childbearing potential.

B) Treatment should NOT be given if the subject meets any of the following criteria at the time of a new malaria episode:

1. ETF in a prior malaria episode in the Core or the Extension phase (see Section 10.6)
2. Duration < 29 days in-between two consecutive KLU156 treatment periods (end to beginning)
3. Patients with a KLU156-related SAE at any previous malaria episode in this study (Core or Extension phase)
4. Signs and symptoms of severe malaria according to WHO 2015
5. Significant, non-plasmodial co-infections including tuberculosis
6. Concurrent febrile illnesses (e.g., typhoid fever, known or suspected dengue fever, known COVID19)
7. Severe malnutrition:
   - For patients ≥ 12 years: body mass index (BMI) < 16.0.
   - For children < 12 years: less than 70% of median normalized WHO reference weight or very low mid-upper arm circumference (MUAC < 115 mm)
8. Known relevant liver disease e.g., chronic hepatitis, cirrhosis, or hepatitis B or A vaccination within the past month, known gallbladder or bile duct disease, acute or chronic pancreatitis

9. Any confirmed or suspected immunosuppressive or immunodeficient condition, including HIV infection or family history of congenital or hereditary immunodeficiency
10. Repeated vomiting (defined as more than 3 times in the 24 h prior to the visit) or severe diarrhea (defined as more than 3 watery stools in the 24 h prior to the visit)
11. Clinically relevant abnormalities of electrolyte balance which require correction, e.g., hypokalemia, hypocalcemia or hypomagnesemia
12. Anemia (hemoglobin level < 7 g/dL)
13. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs (e.g., HIV patients on ART therapy or TB patients on treatment), or which may jeopardize the patient in case of participation in the study.
14. Any of the following:
    - AST/ALT > 3 x the ULN, regardless of the level of total bilirubin
    - Total bilirubin > 3 x ULN
    - Resting QTcF > 450 ms
15. Any severe disease condition (including malignancy), Known chronic underlying disease such as sickle cell disease, and severe cardiac, renal, or hepatic impairment which might prohibit participation in this study
16. Inability to swallow oral medication (in tablet, powder and/or liquid form)
17. Prior antimalarial therapy or antibiotics with antimalarial activity within minimum of their 5plasma half-lives (or within 4 weeks of screening if half-life is unknown)
18. Use of other investigational drugs within 30 days of dosing or until the expected pharmacodynamic effect has returned to baseline, whichever is longer, or longer if required by local regulations
19. Use of medications prohibited by the protocol
20. Previous participation in any other malaria study (except the Core phase) or any malaria vaccine study or having received a malaria vaccine in any other circumstance within 1 month prior to treatment start for the current malaria episode
21. History or family history of long QT syndrome or sudden cardiac death, or any other clinical condition known to prolong the QTc interval, such as history of symptomatic cardiac arrhythmias, clinically relevant bradycardia or severe heart disease
22. Use of agents known to prolong the QT interval unless it can be permanently discontinued for the duration of study
23. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes
24. Pregnant or nursing (lactating) patients
25. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception

Effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps)
- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an IUD or IUS

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age-appropriate history of vasomotor symptoms). Women are considered not of childbearing potential if they have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment she is considered not of childbearing potential.

For further details on pregnancy testing and contraception requirements, refer to Section 8.4.6.

5.4 Screen failures

Core phase:

Patients should have a *P. falciparum* parasitemia of ≥ 1,000 and ≤ 200,000 parasites/µL at the time of pre-screening.

Patients who sign a screening informed consent form and are subsequently found to be ineligible prior to randomization will be considered as screen failures. The reason for screen failure should be recorded on the appropriate page of the CRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure patients. No other data will be entered into the clinical database for these patients, unless they experienced a SAE during the screening phase (see Section 8.6.3 for reporting details). Adverse events that are not SAEs will be followed by the Investigator and collected only as source data.

If a patient fails to be randomized (for any reason), the IRT must be notified within 2 days of the screen failure that the patient was not randomized. Data and samples collected from patients after the Core phase screening informed consent form has been signed and prior to screen failure may still be analyzed. Patients who are randomized and fail to start treatment, e.g., a patient randomized in error, will be considered an early terminator. The reason should be recorded on the appropriate Case Report Form.

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

Extension phase:

There are no screen failures expected during the Extension phase except at entry into the Extension phase, in case of patient/Investigator decision or if a patient had either ETF or a study treatment-related SAE reported in the Core phase.

Patients not meeting eligibility criteria for KLU156 treatment at a particular malaria episode will receive an antimalarial treatment as per local standards and will not be considered as a screen failure, but as an eligibility failure. They should come back to the study site at their next malaria episode and be then re-assessed for eligibility.

5.4.1 Replacement policy

Not applicable.

5.4.2 Participant numbering

Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient is first enrolled in pre-screening, and is retained as the primary identifier for the patient throughout their participation in the trial. The Patient No. consists of the Center Number (assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each patient is numbered uniquely across the entire database. Upon signing the pre-screening informed consent form, the patient is assigned the next sequential Patient No. available. Once assigned to a patient, the Patient No. will not be reused.

If the patient fails to be randomized in the Core phase for any reason, the IRT must be notified of it within 2 days. The reason for it will be entered on the Pre-screening or the Screening Phase Study Disposition CRF.

Once a patient is randomized in the Core phase, the same Patient No. will be used throughout the study, including the Extension phase.

6 Study treatment(s) and concomitant therapy

6.1 Study treatment(s)

Novartis will supply the following Investigational products as open-label patient-specific supplies. Coartem will be used according to the Prescribing Information.

Table 6-1 Core phase: Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Treatment Form or Pharmaceutical Dosage Form	Route of Administrat-ion	Presentation	Sponsor (global or local)
KLU156 100/120 mg	Powder	Oral use	Open label; stick pack	Sponsor (global)
KLU156 400/480 mg	Powder	Oral use	Open label; stick pack	Sponsor (global)
Coartem 20/120 mg	Dispersible Tablet	Oral use	Open label; blister packs	Sponsor (global)
Coartem 80/480 mg	Tablet	Oral use	Open label; blister packs	Sponsor (global)

Table 6-2 Extension phase: Investigational drug

Investigational Drug (Name and Strength)	Treatment Form or Pharmaceutical Dosage Form	Route of Administrat-ion	Presentation	Sponsor (global or local)
KLU156 100/120 mg	Powder	Oral use	Open label; stick pack	Sponsor (global)
KLU156 400/480 mg	Powder	Oral use	Open label; stick pack	Sponsor (global)

6.1.1 Additional study treatments

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

6.1.2 Treatment arms/group

Core phase:

Two treatment arms (Patients will be assigned to one of them in a ratio of 1:1):

1) KLU156 (400/480 mg is the full dose, i.e., this dose is for patients with a bodyweight ≥ 35kg. Patients < 35kg will take a fraction of the dose specific per weight group as shown in Table 6-4) once daily (QD) for 3 days under fed conditions (light meal).

2) Coartem twice a day for 3 days (as per product label).

Extension phase:

One treatment arm: KLU156 (400/480 mg is the full dose, i.e., this dose is for patients with a bodyweight ≥ 35kg. Patients < 35kg will take a fraction of the dose according to weight group as shown in Table 6-4) once daily (QD) for 3 days under fed conditions (light meal).

Table 6-3 Treatment Arm(s)

Arm	Treatment	Dosing Regimen	Core phase	Extension phase
1	KLU156	QD 3 Days	X	X
2	Coartem	BID 3 Days	X	Not applicable

Table 6-4 KLU156 and Coartem dosing per weight

Weight Band	KLU156	Coartem
≥35 kg	full dose QD (i.e., 400/480 mg)	80/480 mg BID
25 to < 35 kg	0.75 of the full dose QD	60/360 mg BID
15 to < 25 kg	0.50 of the full dose QD	40/240 mg BID
< 15 kg	0.25 of the full dose QD	20/120 mg BID

Based on the outcome of CKAF156A2203 (KALUMI), the pediatric weight bands and/or dose multiplier and/or food condition for KLU156 may be adjusted before they are enrolled in the present study, in order to achieve the target exposures for optimal safety and efficacy.

6.1.3 Treatment duration

Core and Extension phases

The duration of the treatment with KLU156 is 3 days QD for an individual patient. Patients may be discontinued from treatment earlier due to unacceptable toxicity or disease progression,

and/or at the discretion of the Investigator or the patient. See Section 6.6 for information on continued access to study treatment after the end of the study.

Core phase only

Coartem will be given twice a day (BID) for 3 days as per product label.

6.2 Preparation, handling, storage, and accountability

Each study site will be supplied with study treatment in packaging as described under Table 6-1 Investigational and control drugs section.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the patient by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document. Coartem, which is supplied as commercial form, will not have a 2-part label.

If a patient vomits study drugs within 1 hour of intake, the Investigator or designee will notify IRT and a replacement dose will be given to the patient. If the second dose is vomited within 1 hour of intake the patient has to be given rescue treatment in accordance with local regulations and standard of care.

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

6.2.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the Investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified in the Investigator's Brochure (IB) for KLU156 and on the labels for Coartem.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization Quality Assurance.

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

The Investigator or designated site staff (unblinded) must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by field monitors during site or remote monitoring visits, and at the completion of the trial.

The study treatment will be administered to patients under hospital supervision. The site may destroy and document destruction of unused study treatment, drug labels and packaging, as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the Investigator will return all unused study treatment,

packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the Investigator folder at each site.

6.2.2 Handling of other treatment

Patients with mixed infections involving *P. vivax or P. ovale* should be treated with non-study antimalarial medicines after Day 43 assessments in the Core phase and after Day 29 assessments at every malaria episode in the Extension phase.

6.2.3 Instruction for prescribing and taking study treatment

KLU156 (ganaplacide/lumefantrine-SDF)

Patients will take KLU156 QD for 3 days according to their body weight (Table 6-4). Medication should be taken in fed conditions. Patients should take a light meal or a drink with some fat content, including breast milk (as soon as food is tolerated).

KLU156 will be administered as a powder. More detailed instructions for KLU156 treatment administration will be provided to the sites.

CCI [redacted]

Coartem

Patients receiving Coartem will be dosed BID for 3 days (at 0, 8, 24, 36, 48, and 60 h). Medication should be followed whenever possible by a normal diet or a drink rich in fat (including breast milk, broth, sweetened condensed milk, etc), as per label. Dosages will be administered according to weight group as described in Table 6-4.

The dispersible tablet is to be dissolved in 10 mL of water in a small cup, and subsequently administered orally under hospital supervision; thereafter the cup will be rinsed with an additional 10 mL of water and the content is to be swallowed again. This procedure will be repeated as necessary in order to administer the amount of doses indicated. Each patient's mouth must be examined to verify that the medication was swallowed.

Procedure in case of vomiting of the study drugs

In the case that the patient vomits within 1 hour of intake, a replacement dose will be given to the patient and the Investigator or designee will notify IRT. If the second dose is vomited the patient has to be given alternative treatment preferably not containing lumefantrine.

Patients treated with at least one dose of trial medications will continue to be followed-up until Day 43 (Core phase) or Day 29 (Extension phase) according to schedule.

6.3 Measures to minimize bias: randomization and blinding

6.3.1 Treatment assignment, randomization

Core phase:

All eligible patients will be randomized in the Core phase via IRT to one of the 2 treatment arms (KLU156 or Coartem) on Day 1. The investigator or their delegate will contact the IRT

again after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and it will specify (a) medication kit number(s) and the appropriate dose for that medication. Both the medication kit number(s) and the dose will be communicated to the caller so that the corresponding investigational drug(s) can be properly administered to the patient.

The randomization numbers will be generated using the following procedure in order to ensure that treatment assignment is unbiased and concealed from the Novartis Clinical Trial Team. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of the Novartis Global Clinical Supply team using a validated system that automates the random assignment of medication numbers to kits containing the investigational drug. Randomization will be stratified by baseline mixed infection status (yes/no) and country. For mono-infection with *P. falciparum*, randomization will be further stratified by body weight (≥ 35; 25 to <35, 15 to <25, <15kg). All efforts will be made to ensure that the proportions of patients recruited in these different body weight groups are generally reflective of the epidemiology of malaria as far as possible, considering overall constraints (See Section 4.1.1).

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

Extension phase:

All eligible patients who give informed consent for the Extension phase will be assigned to the KLU156 (ganaplacide/lumefantrine-SDF) treatment arm.

6.3.2 Treatment blinding

This study is randomized and open label. Treatment will be open to patients/patients' parents/legal guardians and Investigator or designee. Measures will be put in place to ensure microscopists (involved in parasite count assessments) are blinded to individual subject's treatment assignment wherever feasible. In addition, other laboratory personnel, when feasible, should also remain blinded to individual subject's treatment assignment. The Novartis 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 (Table 6-5). The randomization list will be kept strictly confidential. In the clinical data system, dosing information, CCI [redacted], and other data that may reveal individual treatment information will be blinded to the Novartis CTT during the Core phase. These data will be reviewed and cleaned by an independent data manager and an independent clinician who are not involved in the conduct of the trial. An independent biostatistics team (statistician and programmer) who is not involved in the conduct of the trial will be responsible to generate unblinded Data Monitoring Committee (DMC) reports and send the unblinded reports to DMC using secure file transfer system. Further details on data handling are documented in the appropriate data handling plan (DHP)/data management plan (DMP).

Table 6-5 Blinding and unblinding plan during the Core phase

	Time and Event			
Role	**Randomization list generated**	**Treatment allocation & dosing**	**Safety event (single patient unblinded)**	**DMC review**
Patients	B	UI	UI	B
Site staff (PI, Sub PI, study nurse)	B	UI	UI	B
Microscopists[1]	B	B	B	B
Randomization Office	UI	B	B	B
Clinical Trial Team[1]	B	B	B	B
SL,CPMs, TVM, CTSM and CQA[2]	B	UI	UI	B
Independent Trial Data Manager	B	UI	UI	B
Safety team[2]	B	B	UI	B
CRA[2]	B	UI	UI	B
Independent team (Stats, clinical, programming)	UG/UI	UG/UI	UG/UI	UG
DMC	B	UI	UI	UG/UI

[1] Microscopists involved in parasite count assessments should remain blinded to individual subject's treatment assignment; in addition, other laboratory personnel should, when feasible, also remain blinded to individual subject's treatment assignment
[2] see exceptions: Safety team, Study Lead, Clinical Project Managers, Trial Vendor Managers, Clinical Trial Supply Manager; Clinical Quality Assurance Lead), Clinical Research Associate(s)

B: Completely blinded
UG: Unblinded at the group level (i.e., has access to unblinded group level summary results, but not to the individual patient treatment codes)
UI: Unblinded to individual patient treatment codes

6.3.3 Emergency breaking of assigned treatment code

Not applicable since this is an open-label study.

6.4 Study treatment compliance

Patients will be treated with study drugs at the study site under close supervision.

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

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

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

6.5 Dose modification

Investigational or other study treatment dose adjustments and/or interruptions are not permitted. Specifically, no intra-patient dose modification is allowed.

In case of vomiting of a dose, see Section 6.5.3.

6.5.1 Definitions of dose limiting toxicities (DLTs)

Not applicable.

6.5.2 Follow-up for toxicities

Not applicable.

6.5.3 Retreatment criteria

In the Core phase of the study, patients will be treated with KLU156 or Coartem on Days 1 to 3. Re-treatment is not allowed except if a patient vomits within 1 hour of study drug administration. If the replacement dose is also vomited, the patient must be given alternative treatment preferably not containing lumefantrine.

In the Extension phase of the study, re-dosing with KLU156 is permitted at each new malaria episode if the patient meets eligibility criteria. Re-dosing is not allowed within a malaria episode except if the patient vomits within 1 hour of dosing.

A Patient who vomits within 1 hour of trial drug administration will be given a replacement dose, and the IRT must be notified. If the second dose is vomited the patient must be given alternative treatment preferably not containing lumefantrine (Section 6.8.3).

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

6.6 Continued access to study treatment after the end of the study

Since malaria is an acute illness which requires only short-term treatment (up to 3 days), there is no need for continued access to treatment with KLU156 or Coartem after resolution of the malaria episode(s) followed up during the course of the study (Core or Extension phase). For further malaria episodes experienced by a patient after the end of the study, well established and efficacious treatments are already available in the participating countries.

6.6.1 Post trial access

Not applicable.

6.7 Treatment of overdose

In the event of an overdose, the principal Investigator or designee should:

- Contact the medical monitor immediately.
- Evaluate the patient to determine, in consultation with the medical monitor, whether study treatment should be interrupted.
- Closely monitor the patient for any AE/SAE, ECG and laboratory abnormalities.
- Obtain a plasma sample for PK analysis as soon as possible if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose.

6.7.1 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE. Study treatment errors and uses outside of what is foreseen in the protocol, misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 h of Investigator's awareness. For more information on AE and SAE definition and reporting requirements, please see Section 8.6.1 and Section 8.6.2 respectively.

6.8 Concomitant and other therapy

6.8.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded on the appropriate Case Report Forms.

Each concomitant drug must be individually assessed against all exclusion criteria and prohibited medication. If in doubt, the Investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started. If the patient is already enrolled, the Investigator should contact Novartis to determine if the patient should continue participation in the study.

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

Concomitant medication is defined as any medication, other than the Investigational Medicinal Product (IMP), here KLU156, or the comparator product (Coartem), which is given at least once between the day of first dose of study medication and the last day of study visit (including those which were started pre-baseline and continued into the treatment period or follow-up period), including prescription and over-the-counter medicines, and any traditional or herbal remedies.

For mixed infections (only those including *P. vivax* or *P. ovale*), another antimalarial treatment is allowed to eradicate the parasite's dormant stage in the liver (hypnozoites) after completion of the Core phase (Day 43) and every malaria episode of the Extension phase (Day 29). This treatment will be administered as per local standards.

Paracetamol as an antipyretic, and metopimazine for repeated vomiting (or if not available, any other antiemetic which is not known to prolong QT and/or cause torsade de pointes) will be

allowed. If paracetamol or equivalent drug is given as an antipyretic up to 72 h prior to the first dose of study medication, it has to be reported as prior medication.

Metoclopramide is contraindicated from the period prior to the first dose of study medication (Day 1) to Day 5 post-first dose (120 h).

Beta-lactam antibiotics can be given in case of a bacterial infection appearing after enrollment. All antibiotics, new-quinolones included, with anti-malarial activity should be prohibited (e.g., clindamycin, rifampin, dapsone and all sulphones, all sulfonamides (sulphonamides) or sulfonamide containing preparations including co-trimoxazole (trimethoprim-sulfamethoxazole), all tetracycline class antibiotics including minocycline and doxycycline).

De-worming agents with a possible anti-malarial activity, such as metronidazole, albendazole and praziquantel, should not be given to the patients from inclusion to Day 29 (in the Core phase and for every treatment cycle in the Extension phase). Patients that have used these drugs within 2 weeks prior to be enrolled should not be included. In case the situation of a patient requires immediate treatment with these agents, this treatment should occur, and such patient should not be included in the study.

The Investigator must instruct the patient (or their parent/legal guardian) to notify the study site about any new medications they take after they were enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the concomitant medication eCRF.

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

6.8.2 Prohibited medication

Drug with potential impact on efficacy & safety:

- **Drugs with antimalarial activity:** Drugs/supplements which are known to have antimalarial effects are NOT allowed within minimum of their five (5) plasma half-lives (or minimum of 4 weeks if half-life is unknown) prior to enrollment and during the entire study period. They may be used in the course of managing a patient who has developed ETF or LTF or failed to respond to standard-of-care. Lumefantrine- including treatments should be avoided as therapy for ETF, unless there is no alternative.
- **Drugs with QTc Potential:** Drugs/supplements which have potential to increase QTc interval such as but not limited to antiarrhythmic drugs, neuroleptics and antidepressant agents, metoclopramide, macrolides and fluoroquinolones antibiotics, imidazole and triazole antifungal agents, certain non-sedating antihistamines (terfenadine, astemizole), and cisapride, should be avoided during the study and within minimum of their five (5) plasma half-lives of last dose (or minimum of 14 days if unknown) prior to dosing. Furthermore, drugs that slow the heart rate (HR), like digitalis and beta blockers should be avoided.

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

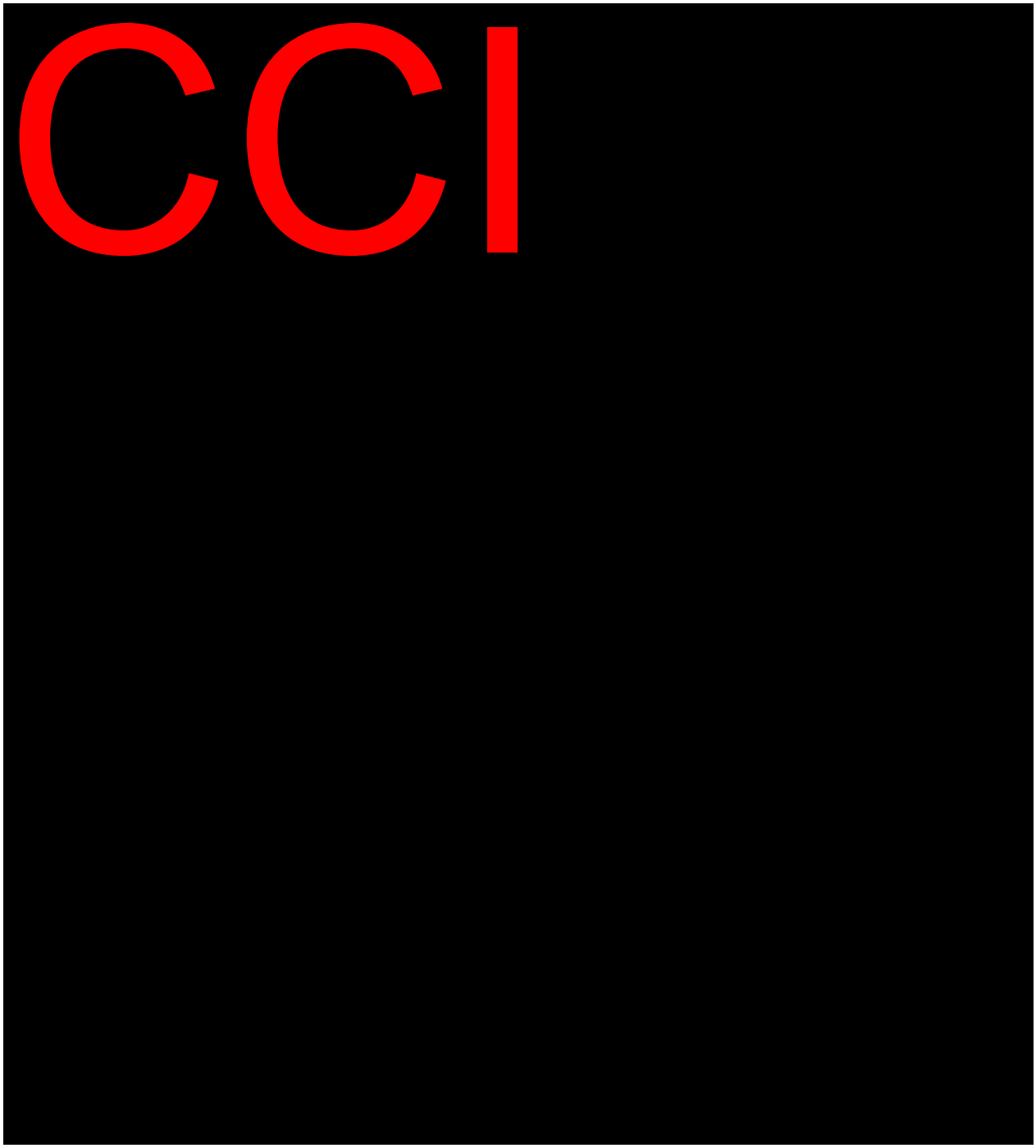
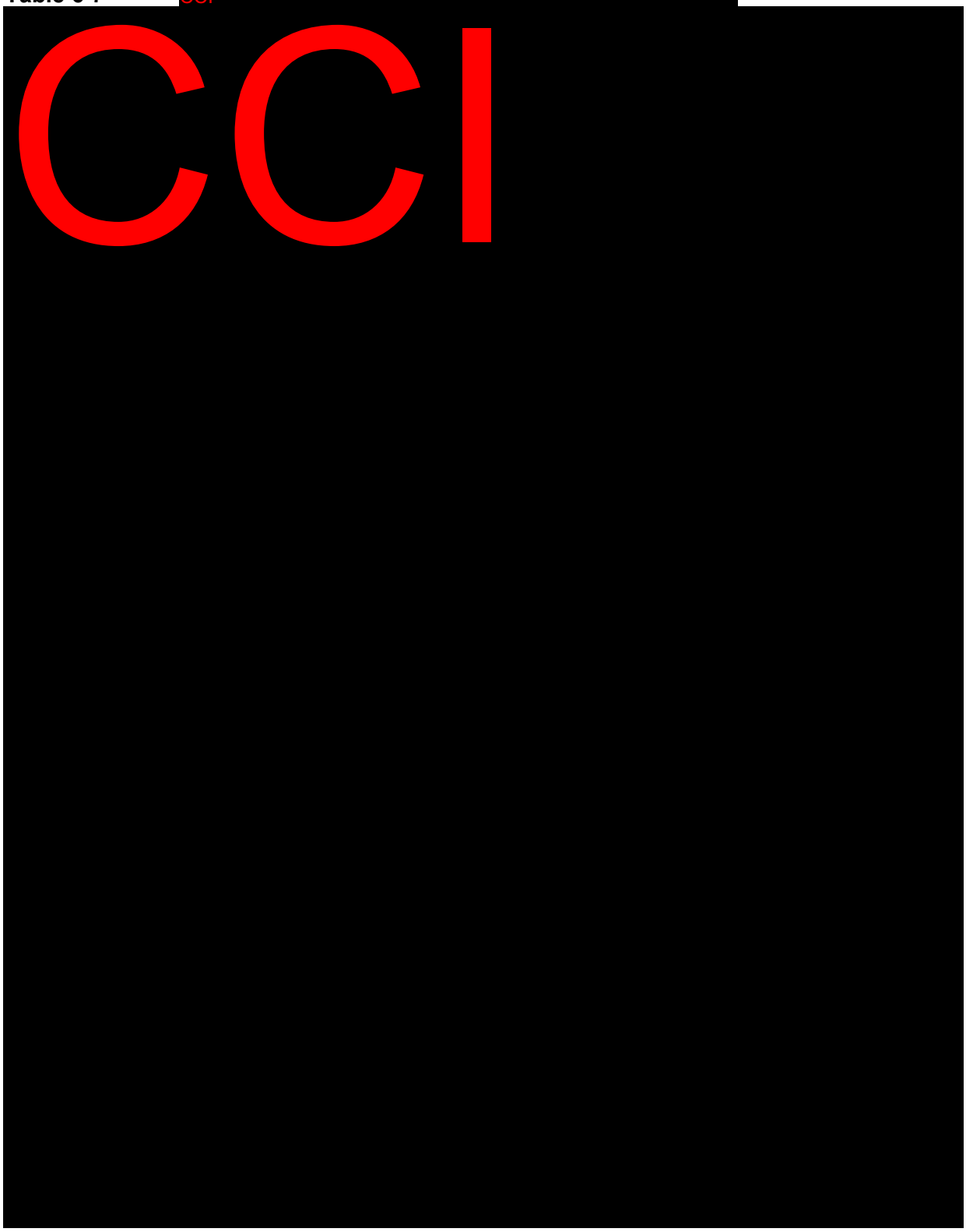


Table 6-7 CCI



6.8.3 Rescue medicine

6.8.3.1 Core phase

The following circumstances warrant discontinuation of study treatment and the implementation of rescue medication (see Section 10.6):

Early Treatment Failure (ETF)

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

Late Clinical Failure (LCF)

- Development of danger signs or severe malaria in the presence of parasitemia on any day between Day 5 and Day 43 in patients who did not previously meet any of the criteria of early treatment failure;
- presence of parasitemia on any day between Day 5 and Day 43 with axillary temperature ≥ 37.5°C in patients who did not previously meet any of the criteria of early treatment failure.

Late Parasitological Failure (LPF)

- Presence of parasitemia on any day between Day 8 and Day 43 with axillary temperature < 37.5°C in patients who did not previously meet any of the criteria of early treatment failure or late clinical failure.

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

Administration of rescue medication with a combination antimalarial product (local standard at the discretion of the Investigator or a medically qualified person) may occur after the start of trial medications and up to Day 43 as deemed necessary by the Investigator. An antimalarial combination containing Lumefantrine should preferably be avoided in patients experiencing ETF. **Patients will be monitored at clinic, by telephone, or via home visits for 3 days following the start of treatment to ensure adherence to the rescue medication therapy**. These patients will not be replaced and will not discontinue the study (i.e., all the examinations as per the assessment schedule and all CRF pages for these patients will need to be completed). However, patients meeting ETF will not be transitioned into the Extension phase and will have their final visit on Day 43 of the Core phase.

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

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

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

6.8.3.2 Extension phase

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

Early Treatment Failure (ETF)

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

Late Clinical Failure (LCF)

- Development of danger signs or severe malaria in the presence of parasitemia on any day between Day 5 and Day 29 in patients 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 with axillary temperature ≥ 37.5ºC in patients who did not previously meet any of the criteria of early treatment failure.

Late Parasitological Failure (LPF)

- presence of parasitemia on any day between Day 8 and Day 29 with axillary temperature < 37.5ºC in patients who did not previously meet any of the criteria of early treatment failure or late clinical failure.

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

Administration of rescue medication with a combination antimalarial product (local standard at the discretion of the Investigator or a medically qualified person) may occur after the start of trial medications and up to Day 29 as deemed necessary by the Investigator. Lumefantrine-including treatment should preferably be avoided in patients experiencing ETF. **Patients will be monitored, either in the clinic, by telephone, or via home visits for 3 days to ensure adherence to the rescue medication therapy**. These patients will not be replaced and will not discontinue the study (i.e., all the examinations as per the assessment schedule and all CRF pages for these patients will need to be completed). However, patients meeting ETF will have their final visit on Day 29 of the concerned malaria episode and will then be discontinued from the Extension phase.

Safety blood tests (full blood count (FBC) and blood chemistry) and an ECG will be collected on the initial day of rescue medication dosing. Blood films and blood sampling for parasite count and genotyping must be taken before giving the established anti-malarial treatment.

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

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

7 Discontinuation of study treatment and participant discontinuation/withdrawal

7.1 Discontinuation of study treatment

Patients will be treated for 3 days under hospital supervision during the Core phase and each episode of the Extension phase. Discontinuation of study treatment for a patient occurs when study drug is stopped earlier than the protocol planned duration, and discontinuation can be initiated by either the patient or the Investigator.

The Investigator must discontinue study treatment for a given patient if, he/she believes that continuation would negatively impact the patient's well-being.

Discontinuation from study treatment is required under the following circumstances:

- Patient/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations (in Section 6.8.2)
- Any situation in which study participation might result in a safety risk to the patient and/or any adverse events that in the judgment of the investigator, taking into account the patient’s overall status, prevent the patient from continuing participation in the study
- Unsatisfactory therapeutic effect
- Emergence of the following adverse events: severe nausea/vomiting, severe pruritus, increases in QTcF to > 500 ms (mean of triplicate ECGs), development of ventricular arrhythmia or clinically significant (symptomatic) bradycardia,(please refer to Table 10-4).
- Any laboratory abnormalities that in the judgement of the investigator, taking into consideration the patient’s overall status, prevent the patient from continuing participation in the study (please refer to Section 10.5.1).
- Deviation from the planned dose regimen for the study drug (e.g., vomiting of the replacement dose within 1 h of intake).

Patients who discontinue study drug for any of the above reasons may be given rescue medication at the discretion of the Investigator and will be followed up to Day 43 in the Core phase and up to Day 29 in the Extension phase.

If discontinuation from study treatment occurs, the Investigator should make a reasonable effort to understand the primary reason for the patient’s discontinuation from study treatment and record this information.

Patients who discontinue from study treatment agree to return for the end of treatment and follow-up visits indicated in Section 1.3.

Patients who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 7.3). Where possible, they should return for the assessments indicated in the Assessment Schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g., telephone, e-mail, and letter) should be made to contact the patient/pre-designated contact as specified in the lost to follow-up section (Section 7.4). This contact should preferably be done according to the study visit schedule.

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

After discontinuation from study treatment, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

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

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

7.2 Participant discontinuation from the study

Discontinuation from study is when the patient permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the patient agrees, a final evaluation (EOS) at the time of the patient’s study discontinuation should be made as detailed in Section 1.3.

7.3 Withdrawal of informed consent and exercise of participants’ data privacy rights

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a patient:

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be as per local regulations (e.g., in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the patient, collect follow-up data (e.g., to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the Investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw their consent/exercise data privacy rights and record this information. The Investigator shall clearly document if the patient has withdrawn their consent for the use of data in addition to a study discontinuation.

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

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

If the patient agrees, a final evaluation at the time of the patient's withdrawal of consent/exercise data privacy rights should be made as detailed in Section 1.3.

Further details on withdrawal of consent or the exercise of patients' data privacy rights are included in the corresponding informed consent form.

7.4 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other patients' data privacy rights), the Investigator must show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the timepoint of the following scheduled visit has passed (Day 43 in the Core phase or Day 29 of the concerned malaria episode in the Extension phase).

7.5 Early study termination by the Sponsor

The study overall or its extension phase in particular can be terminated by Novartis at any time and any reason.

Reasons for early termination (but not limited to):

- Unexpected, significant, or unacceptable safety risk to patients enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Sponsor decision
- Discontinuation of study treatment development in this indication

In taking the decision to terminate, Novartis will always consider patient welfare and safety. Should early termination be necessary, patients must be seen as soon as possible and treated as a patient who discontinued from study treatment. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The Investigator or Novartis, depending on local

regulations, will be responsible for informing the Institutional Review Board(s)/Independent Ethics Committee(s) (IRBs/IECs) of the early termination of the trial.

8 Study Assessments and Procedures

8.1 Screening

Core phase:

Patients should have a *P. falciparum* parasitemia ≥ 1,000 and ≤ 200,000 parasites/μL at the time of pre-screening.

It is not permissible to re-screen a patient for the same malaria episode if they fail the initial pre-screening or screening. Re-screening of a previously screen failed patient may occur in case the patient is returning to the study site for a new malaria episode. A new patient number will be issued to them.

Extension phase:

Patients should have completed the Core phase without experiencing ETF or any study treatment-related SAE at the time of screening for the Extension phase. They will keep the same patient number as assigned in the Core phase.

8.2 Participant demographics/other baseline characteristics

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

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

- Age
- Sex
- Childbearing potential for females (post first menarche)
- Body weight
- Body height
- Mild-upper arm circumference (MUAC; in patients < 12 years of age)
- Body temperature
- Initial medical and treatment history
- Signs and symptoms of severe malaria
- Vital signs
- Physical exam
- Prior and concomitant medications
- Blood chemistry and hematology as specified above
- Urinalysis
- Pregnancy test (in women of childbearing potential)
- Malaria blood film for asexual parasite and gametocyte counts and species differentiation
- Blood sampling for parasite genotyping

- Medical history/current medical conditions
- Triplicate 12-lead ECG

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

8.3 Efficacy assessments

Planned time points for all efficacy assessments are provided in Section 1.3 Schedule of Activities.

Core phase:

Efficacy assessments will be based on the PCR-corrected and uncorrected ACPR at Days 22, 29 and 43, the incidence rate of recrudescence and new infection at Days 22, 29 and 43, and the PCT, FCT, GCT and gametocyte carriage over time.

Extension phase:

Efficacy assessments will be based on the PCR-corrected and uncorrected ACPR at Day 29, PCT, the incidence rate of recrudescence and new infection at Day 29, and gametocyte carriage over time.

8.3.1 Parasitemia assessment

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

Parasite counts:

- Giemsa stained thick (and thin) films will be examined. Thin films will be examined only if identification of species is needed after malaria (*Plasmodium*) parasite is detected in a thick film
- Examination with binocular microscope and with oil immersion lens at 1000 magnification
- A total of 200 thick films fields (or 800 thin film fields) are examined before a slide can be pronounced negative
- If asexual forms of *P. falciparum* are found, a total of 200 thick film fields are to be screened for *Plasmodium* species other than *P. falciparum* before a final identification of species is made (and it is recommended to have observed at least 10 to 20 parasites).
- If there is no malaria *P. falciparum* parasite during the **pre-screening examination (Core phase)**, the patient is excluded from the study.
- If *Plasmodium* species other than *P. falciparum* are found, note the species and perform a parasite count (**not needed at pre-screening examination - Core phase**).
- When it has been ascertained that *P. falciparum* is present, a count is made of the asexual forms and gametocytes against leukocytes, using a tally counter.

- If *P. falciparum* **gametocytes** are seen, perform a gametocyte count against 1000 leukocytes
- Counting needs to be done based on at least 200 leukocytes according to the WHO standards.
- If less than 100 parasites are counted, counting will be extended to 500 leukocytes.
- If the actual leukocytes (white blood cells, WBC) count is not available, the assumed WBC count (by WHO) of 8000 WBC/µL will be used.
- The previous actual leukocytes (WBC) count (from the previous timepoint) can also be used, and is highly recommended in case of major observed deviation from the assumed WHO WBC count.
- The parasite density will be calculated according to the formula:

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

The count should be made for **each species** and for ***P. falciparum* gametocytes** (White et al 2014). Thick blood films will be used for gametocyte count and may be potentially confirmed by PCR. Thick (and thin) blood films will be prepared as specified in the assessment schedule Table 1-2 and Table 1-3 and evaluated by standard techniques (Giemsa stain and light microscopy). This will be the definitive test for a positive *P. falciparum* infection. The parasite counts can also be quantified in percentage (per 1,000) of red cells on the thin film.

CCI [redacted]

CCI [redacted]

8.3.2 Parasite genotyping

Blood will be sampled for parasite genotyping as indicated in the assessment schedules (Table 1-2 and Table 1-3).

At baseline, a blood sample will be collected from all patients fulfilling eligibility criteria for inclusion in the study. A second blood sample will be analyzed in patients showing parasite recurrence. This will be used to distinguish between recrudescence and new infection. Molecular analysis will be performed for all sites by a pre-selected specialized central laboratory.

Microscopic species identification will be confirmed and determined with PCR- based methods from aliquots of samples collected at the time of withdrawal/Late Parasitological Failure (LPF).

All blood samples collected for genotyping at the timepoints indicated in the assessment schedule for the Core phase will be analyzed to explore the impact of PCR methods on efficacy estimates, and also be screened for specific genes/single-nucleotide polymorphisms (SNPs) that are known as markers of *P. falciparum* resistance. For each malaria episode of the Extension phase, blood samples at Baseline and at the time of recurrence will be screened for specific genes/SNPs that are known as markers of *P. falciparum* resistance.

8.3.3 CCI



8.3.4 CCI





8.4 Safety assessments

Clinical AEs will be monitored throughout the study to confirm the general safety and tolerability of the study treatments.

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

For details on AE collection and reporting, refer to Section 8.6.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e., pandemic, epidemic, political and/or conflict situation or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (weekly or more frequently if needed) for safety monitoring and discussion of the patient´s health status until it is safe for the patient to visit the site again.

8.4.1 Physical examinations

A **complete** physical examination will be performed by the investigational staff at screening in the Core phase and for every new malaria episode in the Extension phase. It will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen including splenomegaly, back, lymph nodes, extremities, vascular and neurological. In addition, body height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in the schedule of assessment (Section 1.3). Mid-upper arm circumference (MUAC) will be measured at screening in patients < 12 years of age.

A **short** physical exam will be performed at the other visits starting from Day 1 including the examination of general appearance and vital signs (blood pressure [systolic blood pressure (SBP) and diastolic blood pressure (DBP)] and pulse). Body Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured at study end only (or earlier in case of premature patient withdrawal from study participation).

A full assessment of **malaria signs and symptoms** will be made alongside the physical examinations at time points described in the assessment schedule for all patients. Pediatric patients in particular need to be examined for signs of dehydration.

Information from all physical examinations must be included in the source documentation at the study site. Body height and body weight must be recorded in the clinical database. Clinically relevant findings that are present prior to signing informed consent must be included in the Medical History part of the eCRF. Significant findings made after signing informed consent

which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the eCRF.

8.4.2 Vital signs

Vital signs will include the collection blood pressure (BP) and pulse measurements.

After the patient has been sitting for 3 minutes, with back supported and both feet placed on the floor (whenever possible), systolic and diastolic BP will be measured using an automated validated device, e.g. OMRON with an appropriately sized cuff. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

If vital signs are out-of-range at screening and/or baseline (see Exclusion Criteria Section 5.2 of the protocol for details), two additional readings can be obtained, so that three consecutive assessments are made, with the patient seated quietly for approximately five minutes preceding each repeat assessment. The last reading must be within the ranges provided in the eligibility criteria in order for the patient to qualify.

In case of repeated vital assessments, the eCRF should contain the collection blood pressure (BP) and pulse measurements.

8.4.3 Body temperature

Body temperature will be monitored as indicated in the study assessment schedule Table 1-2 and Table 1-3 and recorded on the clinical database.

Fever monitoring will be done every 6 h until resolution of fever, defined as being afebrile for 24 h.

Fever clearance, assessed in the Core phase, is defined (in patients with an increased temperature at baseline) as the time of the first measurement of axillary temperature of < 37.5°C (or < 38.0°C for oral temperature or < 38.5°C for tympanic/rectal temperature). Fever clearance will be confirmed by subsequent measurements of an axillary temperature < 37.5°C (or < 38.0°C for oral temperature or < 38.5°C for tympanic/rectal temperature) for a period of at least 24 h. Within the patients the same route of measurement should be used throughout the study.

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

8.4.4 Electrocardiograms

8.4.4.1 Core and Extension phases

Electrocardiograms (ECGs) will be centrally evaluated and must be recorded after 10 minutes' rest in the supine position if feasible to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, blood sampling, and any remaining assessments for that visit (refer to flow diagram below).

Figure 8-1 Timing of study procedures



The Fridericia QT correction formula (QTcF) must be used for clinical decisions, e.g., at the Screening visit to assess eligibility. The Investigator must calculate QTcF if it is not auto-calculated by the ECG machine.

In all patients and at all timepoints, triplicate 12-lead ECGs are to be collected with ECG machines supplied by the central laboratory and recorded approximately 2 minutes apart. The mean QTcF value for each visit will be calculated from the triplicate ECGs for each patient.

An initial manual readout will be done locally in order to detect significant safety findings and to allow for immediate response if needed. Local readout will be used for inclusion/exclusion purposes as central readout is not available within 24 h. Additional, unscheduled safety ECGs may be repeated at the discretion of the Investigator at any time during the study as clinically indicated.

In the event that a clinically significant ECG abnormality is identified at the site (e.g., severe arrhythmia, conduction abnormality of QTcF > 500 ms), the patient should be assessed at the site and appropriate safety procedures initiated without delay, if required (please see Section 10.8 for ECG alert values and actions) and ECGs should be repeated as clinically indicated. If the patient is hemodynamically compromised, the Investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example, cardioversion).

All ECGs, including unscheduled safety ECGs with clinically relevant findings collected during the study, need to be transmitted to the central ECG laboratory for review.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the Investigator at any time during the study as clinically indicated. For any ECG resulting in patient safety concerns, triplicate ECGs must be performed to confirm the safety finding. ECG safety monitoring, or a review process, should be in place for clinically significant ECG findings at baseline before administration of study treatment and during the study.

Clinically significant abnormalities present at screening should be reported on the appropriate CRF, medical history/current medical condition. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

Any patient with a post-dose average QTcF > 500 ms must not receive any further dose of study drug and will be discontinued from treatment if any subsequent treatment was planned.

Assessments will be performed as indicated in the study assessment schedule (Table 1-2, Table 1-3). All ECGs will be assessed centrally by an independent cardiologist blinded to treatment but not to patient age.

Cardiac alert threshold values are defined in Section 10.8.

8.4.5 Clinical safety laboratory tests

A local laboratory that has the capability to collect and analyze micro-samples should be used for analysis of safety variables (hematology, blood chemistry, and urinalysis). The total volume of blood drawn must comply with the guidelines for pediatric population (Howie 2011) with a recommended limit of 3 ml/kg (body weight at screening) drawn over 30 days, and a maximum of 4.2 ml/kg over the duration of the core phase (43 days). Assessments will be done as indicated in the study assessment schedules Table 1-2 and Table 1-3.

As per Section 4.5, during a public health emergency declared by local or regional authorities, i.e., a pandemic, epidemic or natural disaster, which limit or prevent on-site study visits, so that patients cannot visit the site for protocol-specified safety lab assessments, an alternative lab (local) collection site may be used to this effect.

Liver events and laboratory triggers are defined in Section 10.5.1.

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

Table 8-1 Clinical safety laboratory tests per category

Test Category	Test Name
Hematology	Erythrocytes, Hematocrit, Hemoglobin, Leukocytes, Platelets, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Reticulocytes (absolute value and/or %s)). Haptoglobin levels will be analyzed in case of clinically significant hemoglobin drop (> 2g/dL) or hemoglobin levels ≤ 5g/dL, and if technically feasible, based on the availability of relevant equipment at the study site.
Chemistry	Albumin, Alkaline phosphatase (ALP), ALT, AST, Calcium, Chloride, Creatinine, Gamma-glutamyl-transferase (GGT), Glucose (non-fasting), Indirect Bilirubin, Magnesium, Potassium, Sodium, Total Bilirubin, Total Protein, Urea Nitrogen
Urinalysis	Macroscopic Panel (Dipstick) (Specific Gravity, Glucose, Blood, Protein)
Liver Event Testing and Liver Follow-Up Testing	These tests are in addition to routine testing, to be performed only in follow-up to safety events when indicated in Section 10.5 Liver safety monitoring: Albumin, ALP, ALT, AST, Total Bilirubin (TBL), Prothrombin time/ International Normalized Ratio (PT/INR), and GGT until resolution
Pregnancy Test and Assessments of Fertility	Urine β-hCG pregnancy test (refer to Section 8.4.6)

8.4.6 Pregnancy testing

Pregnancy testing

A pregnancy test in urine will be performed as per the assessment schedules (Table 1-2 and Table 1-3) in all women of childbearing potential (in children < 12 years of age, the pregnancy test should be done at the discretion of the Investigator).

A woman of child-bearing potential is defined as female physiologically capable of becoming pregnant, i.e., from menarche and until becoming post-menopausal unless permanently sterile.

This includes female pediatric patients who have achieved menarche or who become menarchal during the study.

Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. A post-menopausal state is defined as no menses for 12 months without an alternative medical cause and an appropriate clinical profile. In absence of the medical documentation confirming permanent sterilization, or if the post-menopausal status is not clear, the Investigator should use his medical judgment to appropriately evaluate the fertility state of the woman and document it in the source document.

A urine β-hCG pregnancy test will be performed for all females of childbearing potential according to the protocol assessment schedule (See Table 1-2,Table 1-3).

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

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

Contraception requirements

The contraception requirements differ between the treatment arms:

- If the female patient is randomized to the investigational drug (KLU156), effective contraception is required during the 3-day treatment period.
- If the female patient is randomized to the control drug (Coartem), effective contraception is required until the start of the next menstruation after treatment, while women using an oral transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non hormonal methods of birth control, as per product label.

Effective contraception is described in Section 5.2.

As per Section 4.5, during a public health emergency as declared by local or regional authorities' i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if patients cannot visit the site to have urine pregnancy tests, urine pregnancy test kits may be used at home. Relevant patients can perform the urine pregnancy test at home and report the result to the site. It is important that patients are instructed to perform the urine pregnancy test. A communication

process should be established with the patient so that the site is informed and can verify the pregnancy test results (e.g., following country specific measures).

8.4.7 Appropriateness of safety measurements

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

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

8.5.1.1 CCI



8.5.1.2 CCI



8.5.2 Other assessments



CCI

8.6 Adverse events (AEs), serious adverse events (SAEs), and other safety reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Section 8.6.1 and Section 8.6.2 respectively.

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's LAR).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 8.6.3.

8.6.1 Adverse events

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

The Investigator has the responsibility for managing the safety of an individual patient and for identifying AEs.

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

For patients who sign the pre-screening ICF of the Core phase, AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in Section 8.6.2 and are reported as causally related with study procedures (e.g. blood sampling for microscopy).

Patients whose pre-screening *P. falciparum* parasite count falls within the pre-defined thresholds will be asked if they agree to sign the Screening ICF for the Core phase.

For a patient who signs:

- the Core phase screening ICF, all AEs as described below will be captured until Day 43
- the Extension phase ICF: at each treatment cycle, AEs occurring after the patient started study treatment (KLU156) and until Day 29 will be captured.

The occurrence of AEs must be sought by non-directive questioning of the patient (or caregiver, surrogate, or the patient's LAR) at each visit during the study. AEs also may be detected when they are volunteered by the patient (or caregiver, surrogate, or the patient's LAR) during or

between visits or through physical examination findings, laboratory test findings, or other assessments.

AEs must be recorded in the Adverse Event CRF under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 8.6.2):

1. The Common Terminology Criteria for Adverse Events (CTCAE) grade (version 5.0).
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e., progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single patient
3. Its duration (start and end dates or ongoing) and the outcome
4. Whether it constitutes a SAE (see Section 8.6.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding study treatment, which may include one or more of the following:
   - Dose not changed
   - Drug interrupted/ permanently discontinued
6. Any treatment used to treat the AE
7. Its outcome

Conditions that were already present at the time of the Core phase screening informed consent should be recorded in the patient's medical history CRF.

AEs (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

AE monitoring should be continued at least until the last visit of the Core phase (Day 43) and in each treatment cycle, after KLU156 treatment initiation and until Day 29 in the Extension phase.

Once an AE is detected, it must be followed until its resolution or until it is judged to be not recovered/not resolved (e.g., continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug KLU156 (ganaplacide/lumefantrine-SDF) can be found in the IB. The safety profile of Coartem is described in the product label.

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 10.3.1.

8.6.2 Serious adverse events

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

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) -E2D Guidelines).

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

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2A Guidelines).

Potential Hy's Law cases: Treatment-emergent elevations in AST or ALT (>3xULN for patients with normal baseline or >2x baseline for patient with elevated baseline) in combination with

direct bilirubin >2xULN,. in the absence of cholestasis (defined as ALP <2xULN) or other causes of hyperbilirubinemia can be an indicator of severe drug induced liver injury (Hy's Law). A potential Hy's law case will be managed as a serious adverse event associated with the use of the study treatment (assessing it as medically significant event in the absence of any other seriousness criteria). It must be reported as an SAE to the sponsor promptly (i.e., even before all other possible causes of liver injury have been excluded and even if abnormal transaminases values at baseline). Reporting should include all available information, especially that are needed for evaluating the diagnosis, severity and likelihood that the study treatment caused the reaction. For patient monitoring and investigation of potential etiologies, the investigator must initiate a close follow-up until complete resolution of the problem and make all attempts to obtain necessary supplementary information.

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

All reports of intentional misuse and abuse of the product are also considered SAEs irrespective of whether a clinical event has occurred.

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

8.6.3 SAE reporting

Core phase

For patients who sign the pre-screening ICF of the Core phase, SAEs which occur after signature of this consent will only be captured if reported to be causally related with study procedures (e.g., blood sampling for microscopy). Once the Core phase screening ICF has been signed, all SAEs will be captured as described below.

For randomized patients, to ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided Core phase screening informed consent and until Day 43 must be reported to Novartis immediately, without undue delay, but under no circumstances later than within 24 h of obtaining knowledge of the events.

SAEs experienced after Day 43 of the Core phase should only be reported to Novartis safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

For screen failures, SAEs occurring after a patient has provided Core phase screening informed consent until the time the patient is deemed a screen Failure must be reported to Novartis.

Extension phase

To ensure patient safety, at each treatment cycle, every SAE, regardless of causality, occurring after the patient started study treatment (KLU156) and until Day 33 (i.e., 30 days after the last administration of study treatment) must be reported to Novartis immediately, without undue delay, but under no circumstances later than within 24 h of obtaining knowledge of the event.

Any SAEs experienced by a patient after Day 33 (i.e., the 30-day period following last administration of study treatment, KLU156) should only be reported to Novartis safety if the

investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/ regulations, and this until the start of their next treatment cycle for a malaria episode or until the end of the Extension phase for that patient.

Both Core and Extension phases

Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site. Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 h of the Investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety (CMO & PS) Department associate may urgently require further information from the Investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees as per national regulatory requirements in participating countries.

8.6.4 Pregnancy

- Details of all pregnancies in female patients will be collected after the start of study treatment and until Day 43 in the Core phase and within each treatment cycle (i.e., after start of treatment until Day 29) in the Extension phase.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- Any post study pregnancy-related SAE considered reasonably related to study treatment by the Investigator will be reported to Novartis as described in Section 8.6.3. The Investigator is not obligated to actively seek this information in former study patients, but they may learn of an SAE through spontaneous reporting.

To ensure patient safety, each pregnancy occurring after signing the Core phase screening informed consent form and after starting treatment cycles in the Extension phase, must be reported to Novartis within 24 h of learning of its occurrence. If a female patient becomes

pregnant during the treatment period, it should be stopped (if applicable), and the pregnancy consent form should be presented to the patient. They must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy. The pregnant women and her newborn must be followed up to one year after the estimated date of delivery, to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the Investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment of any pregnancy outcome.

After pregnancy consent is provided, the pregnancy reporting will continue up to one year after the estimated date of delivery.

8.6.5 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not applicable.

8.7 CCI



8.8 Biomarkers

Optional Additional Research

If patients 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.

8.9 Immunogenicity assessments

Immunogenicity is not evaluated in this study.

8.10 Health economics OR Medical resource utilization and health economics

Health economics OR Medical resource utilization and health economics parameters are not evaluated in this study.

9 Statistical considerations

9.1 Analysis sets

Randomized analysis set (RAS)

The Randomized set includes all patients who are randomized into the study. Unless otherwise specified, mis-randomized patients will be included in the randomized set.

Mis-randomized patients, if identified from IRT, include patients who are screen-failures, but were mistakenly randomized by the Investigator (e.g., before final eligibility was assessed) and have not been treated. If patients were re-screened and successfully randomized, they will be included in the randomized set according to the treatment assigned at the last randomization.

Full analysis set (FAS)

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

Safety analysis set (SAF)

The Safety set includes all patients who take at least one dose of study drug during the treatment period of the Core phase of the study. Patients will be analyzed according to treatment received in the Core phase of the study. In particular, a patient will be analyzed in the same treatment arm as randomized if they receive at least one dose of the study medication of that 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]

9.2 Statistical analyses

9.2.1 General considerations

For the Extension phase, the first dose is defined for each episode separately.

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

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. Note: patients 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).

Data in the Extension phase will be listed and summarized by episode and also by Core phase treatment arm. Extension data will be summarized overall by episode.

As the primary study population consists of patients ≥ 10 kg body weight, all analyses will be based on the modified analysis sets as defined in Section 9.1 unless otherwise specified.

CCI [redacted]

9.2.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment arm and overall for the RAS, mRAS and mFAS.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by treatment arm, using the mFAS.

9.2.3 Treatments

The modified Safety set will be used for the analyses below.

The duration of exposure in number of doses of KLU156 or Coartem will be summarized by means of descriptive statistics. The percentage of patients with study drug vomiting and dose replacement will be presented. Average daily dosage and total dosage (in mg) of each of the 2 drugs (KLU156 and Coartem) will be summarized. Meal intake and meal type will be summarized by treatment arm and day.

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

9.3 Primary endpoint(s)/estimand(s) analysis

The primary objective is to show that KLU156 is non-inferior (NI margin 5%) to Coartem in achieving PCR-corrected ACPR at Day 29 for the treatment of uncomplicated malaria caused by *P. falciparum* (with or without other *Plasmodium* spp co-infection) in adults and children ≥ 10 kg of body weight.

9.3.1 Definition of primary endpoint(s)

The primary endpoint is that a patient 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 parasite strain observed was already present at baseline based on PCR genotyping. Please refer to Section 10.6 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 patients 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 patient 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 patient 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 (ACPR or not ACPR). Beside recrudescence, a patient's outcome can be classified as not ACPR due to reasons, such as missing PCR genotyping, missing assessment, etc. (Section 9.3.4).

9.3.2 Statistical model, hypothesis, and method of analysis




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9.3.3 CCI



9.3.4 CCI



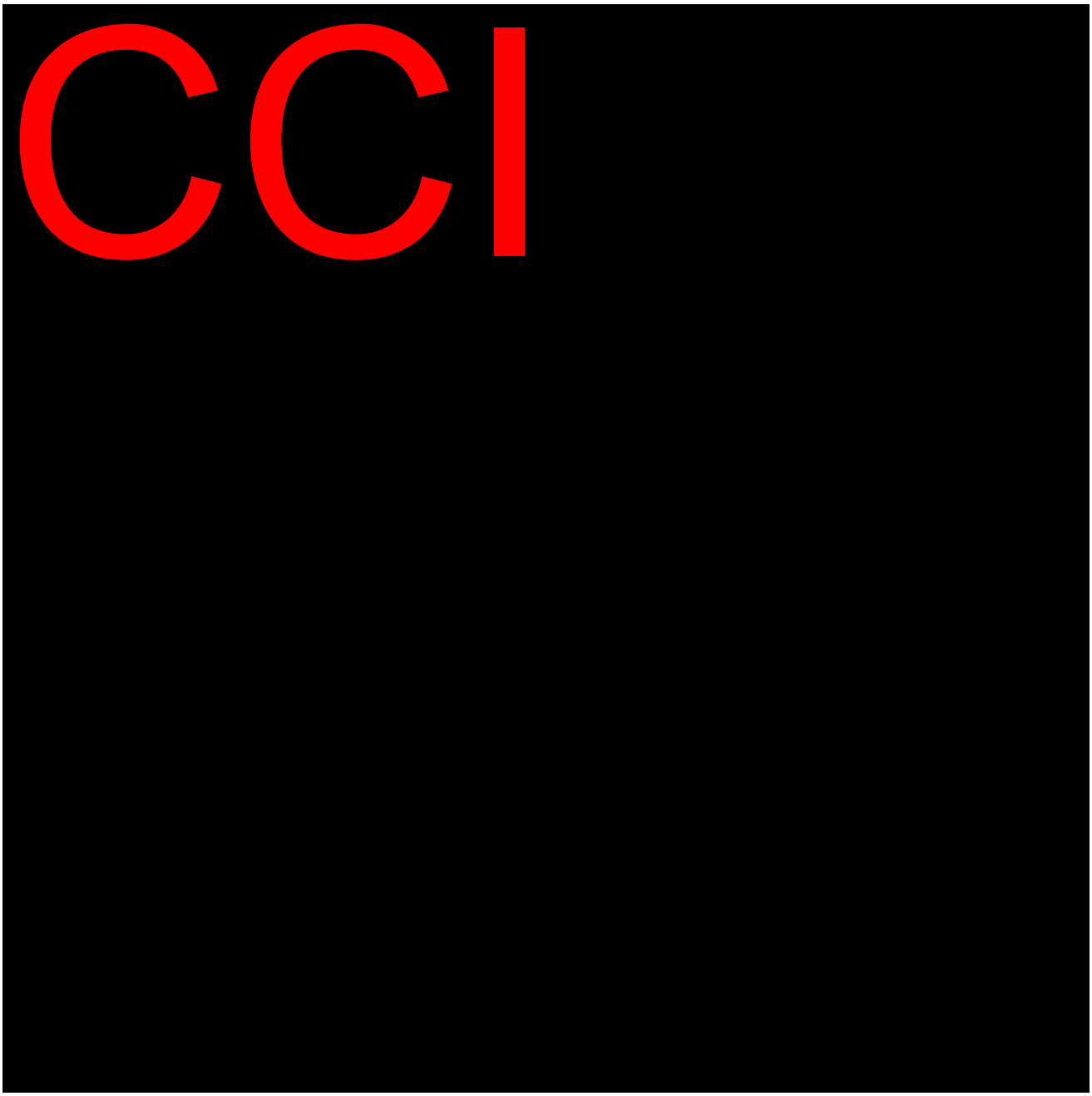
9.3.5 CCI





9.3.6 CCI

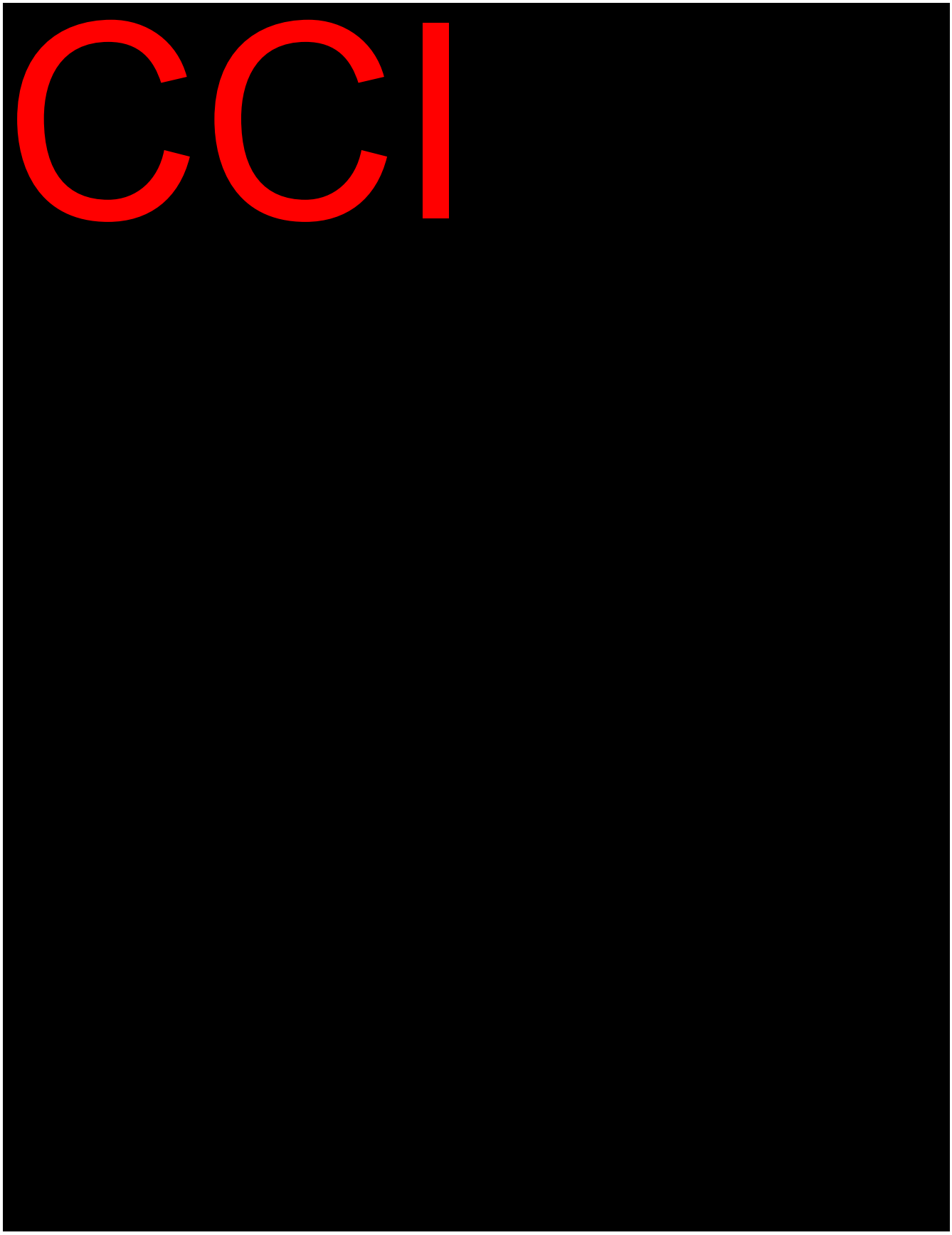




9.4 CCI

9.4.1 CCI




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9.4.2 CCI

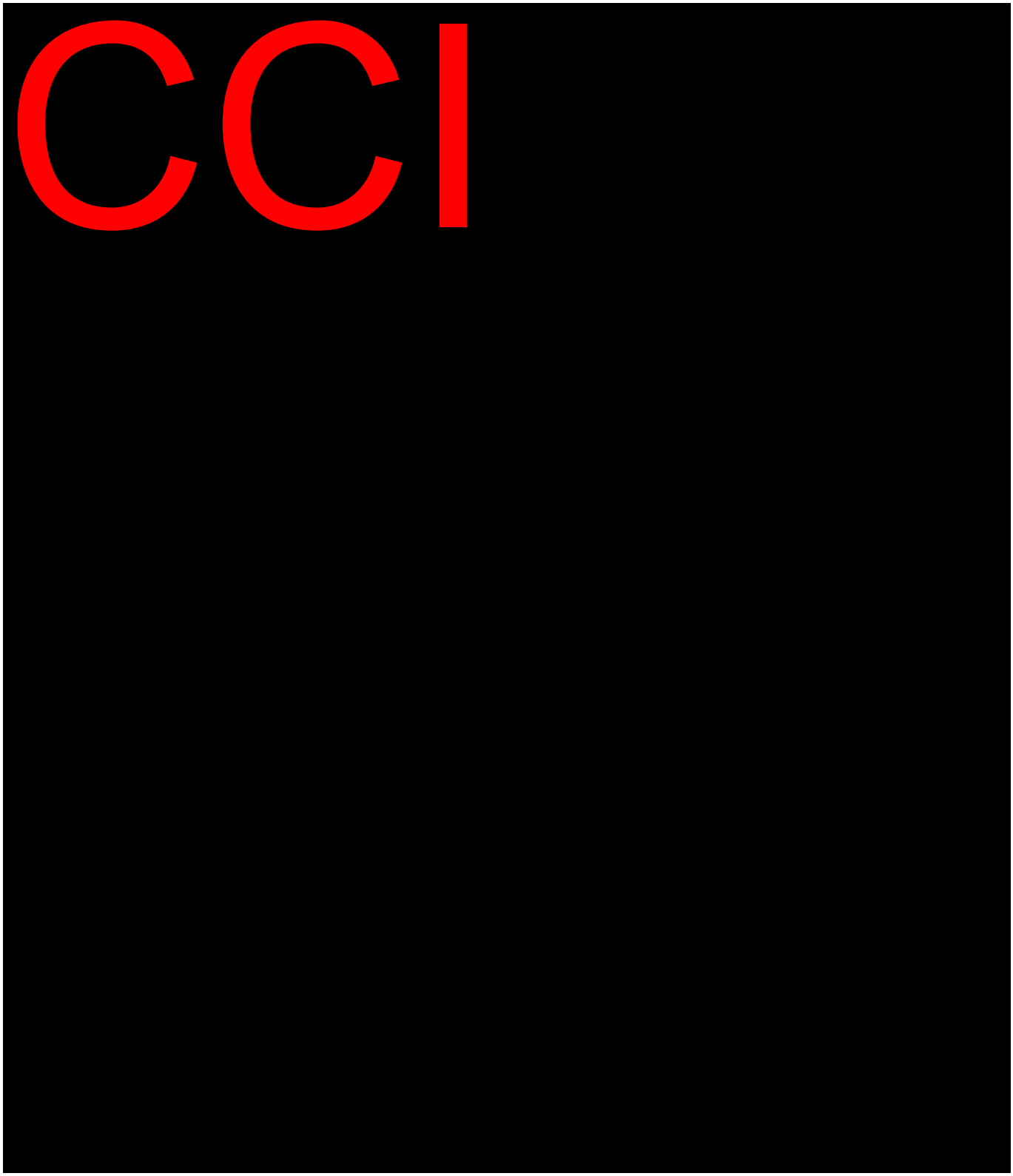



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9.5 Exploratory endpoint(s)/estimand(s) analysis





9.6 (Other) Safety analyses

Not applicable

9.7 Other analyses

9.7.1 Analysis for US NDA submission

For the US New Drug Application (NDA) submission, the uncorrected ACPR at Day 29 will be the primary endpoint and PCR-corrected ACPR at Day 29 will be the key secondary endpoint for the Core phase of the study, in accordance with FDA requirements for demonstrating antimalarial drug efficacy. The details of the US FDA specific endpoints and analyses will be provided in the Statistical Analysis Plan (SAP).

9.7.2 CCI

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9.8 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 patients have been dosed and followed up to at least Day 22 and the second DMC analysis will be performed after 750 patients have been dosed and followed up to at least Day 22. The DMC analyses will be performed by a separate independent Biostatistics Team who will share the reports with the DMC committee directly.

At each scheduled DMC analysis for the Core phase, any available data from the Extension phase will also be analyzed.

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

9.9 Sample size determination

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9.9.1 Primary endpoint(s)

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Table 9-1 CCI

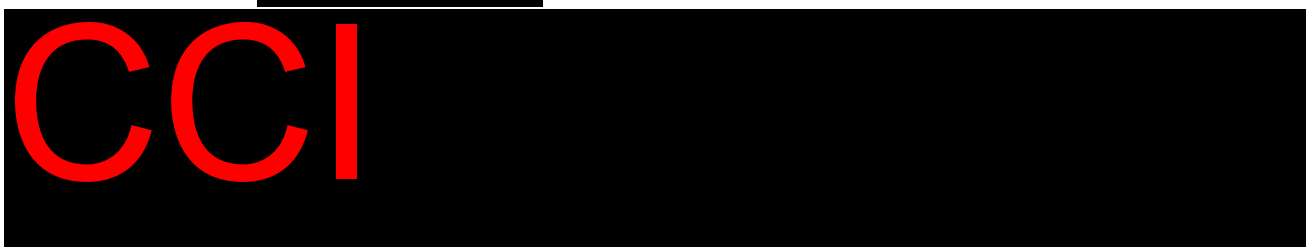
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9.9.2 CCI

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Table 9-2 CCI



9.9.3 CCI



10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, Investigational directions for use [IDFU], and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by this/these board(s) before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

Protocols and any substantial amendments/modifications to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study patients.

The Investigator will be responsible for the following:

- Signing a protocol signature page confirming their agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required.
- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulation (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.
- Informing Novartis immediately if an inspection of the clinical site is requested by a regulatory authority.

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable

local regulations (including European Directive 2001/20/EC or European Clinical Trial Regulation 536/2014, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

10.1.2 Informed consent process

Novartis will provide to Investigators in separate documents the proposed informed consent forms that comply with the International Conference on Harmonization (ICH) GCP guidelines and regulatory requirements and are considered appropriate for this study. Any changes to the proposed consent forms suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

The Investigator or their representative will explain the nature of the study, including the risks and benefits, to the patient or their legally authorized representative (LAR) and answer all their questions regarding the study.

Patients or their LAR must be informed that their participation is voluntary. Patients or their LAR will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

Informed consent must be obtained before conducting any study-specific procedures (e.g., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

A copy of the ICF(s) must be provided to the patient or their LAR.

The main ICF (Core phase screening ICF) will contain a separate section that addresses the use of remaining mandatory samples for optional additional research. The Investigator or authorized designee will explain to each patient the objectives of the additional research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a patient’s agreement to allow any remaining specimens to be used for additional research. Patients who decline to participate in this optional additional research will document this.

Eligible patients may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

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

Information about common side effects already known about the investigational treatment can be found in the IB and Prescribing Information for marketed drugs like Coartem. This information will be included in the patient informed consent and should be discussed with the

patient or their LAR upon obtaining consent and also during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an IN or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the patient or their LAR.

The informed consent forms included in this study are:

- A pre-screening informed consent form to be signed prior to performing any pre-screening assessments at the pre-screening visit
- A Core phase screening informed consent form to be signed prior to performing any screening assessments at the screening visit
- An Extension phase informed consent form to be signed prior to performing any eligibility assessment for KLU156 treatment in the Extension phase of the study.

The Core and Extension informed consent forms, also both include:

- A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
- Optional consent for research that may be done outside of the study site.

In addition:

- A Pregnancy Outcomes Reporting Consent form for female patients
- Corresponding assent forms for children/adolescents

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

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g., telephone, videoconference) if allowable by a local health authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g., the presence of an impartial witness, sign/dating separate ICFs by trial patient and person obtaining informed consent, etc.).

10.1.3 Data protection

Patients will be assigned a unique identifier by Novartis. Any patient record or dataset that are transferred to Novartis will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient (or their LAR) must be informed that their personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the patient (or their LAR) who will be required to give consent for their data to be used as described in the informed consent.

The patient (or their LAR) must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

Any data security breach that may impact the confidentiality and protection of study patients' data is recorded and investigated by Novartis as required by applicable laws or regulations and as adequate to the nature of the breach.

Upon identification of any potential data security breach, a Novartis team will perform an initial assessment. Depending on the nature and type of breach, including the categories of data impacted, the data security breach management process may include investigation of the root cause of the incident, and, on a basis of its outcome, determination of the adequate mitigation actions to address any immediate impact, and corrective and preventive measures to prevent recurrence and mitigate any adverse effects, as applicable. The data security breach will be reported to the regulatory authorities and Ethic Committees or IRBs as required by the applicable laws or regulations.

10.1.4 Committees structure

10.1.4.1 Data Monitoring Committee

This study will include a data monitoring committee (DMC) who will function independently of all other individuals associated with the conduct of this clinical trial, including the site Investigators participating in the study. The DMC will assess at defined intervals, the progress of the clinical trial, the safety data and recommend to Novartis whether to continue, modify, or terminate the trial (Section 4.1.1).

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

10.1.5 Data quality assurance

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novartis. No records may be transferred to another location or party without written notification to Novartis.

Efforts should be made to collect all data that are relevant to support a statistical analysis aligned with the estimands of interest.

10.1.5.1 Data collection

Data not requiring a separate written record will be defined in the protocol and Section 1.3 Schedule of Activities and can be recorded directly in the CRF. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

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

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

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

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

10.1.5.2 Database management and quality control

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

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

Dates of pre-screening, screening, randomization, or screen failure and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the patient and all dose changes will be tracked using an IRT. The system will be supplied by a vendor, who will also manage its database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

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

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** (for the Core phase) and made available for data analysis by a programmer and a statistician. Any

changes to the database after that time can only be made after written agreement by Novartis development management.

10.1.6 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. The Investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient). Definition of what constitutes source data and its origin can be found in monitoring guidelines.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization or delegated CRO. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters and provide reports to Novartis clinical teams to assist with trial oversight.

10.1.7 Publication policy

The protocol will be registered in a publicly accessible database such as Clinicaltrials.gov and as required in another public website (e.g., PACTR). In addition, after Core phase completion (defined as last patient last visit in the Core phase) and finalization of the Core study report, the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required health authority websites (e.g., Clinicaltrials.gov, or another public website etc.).

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

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

Summary results of primary and secondary endpoints will be disclosed based upon the global Last Patient Last Visit (LPLV) date in the Core phase, since multinational studies are locked and reported based upon the global LPLV.

10.1.8 Protocol adherence and protocol amendments

This protocol defines the study objectives, the study procedures and the data to be collected on study patients. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an Investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the Investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study patients.

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

10.1.8.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for patient safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

10.2 Appendix 2: Abbreviations and definitions

10.2.1 List of abbreviations

(e)CRF	Case Report/Record Form (paper or electronic)
ACPR	Adequate clinical and parasitological response
ACT	Artemisinin-based Combination Therapy
ADME	Adsorption, Distribution, Metabolism, Excretion
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ART	antiretroviral therapy
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutical Chemical
AUC	Area under the curve
BID	twice a day
BMI	Body Mass Index
CFR	Code of Federal Regulation
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine Kinase
ClinRO	Clinician Reported Outcomes
CMO&PS	Chief Medical Office and Patient Safety
COA	Clinical Outcome Assessment
COVID 19	Coronavirus disease 2019
CRA	Clinical Research Associate
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTT	Clinical Trial Team
CV	coefficient of variation
CYP	Cytochrome P450
DBP	Diastolic Blood Pressure
DHP	Data handling plan
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
CCI	[redacted]
DMP	Data management plan
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End of study
ETF	Early treatment failure
FAS	Full Analysis Set
FBC	Full blood count
FCT	Fever clearance time
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCT	Gametocyte Clearance Time

GGT	Gamma-glutamyl transferase
GLDH	Glutamate Dehydrogenase
GMS	Greater Mekong Subregion
GTD	Global Trial Director
GTM	Global Trial Manager
h	Hour
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IDFU	Investigational directions for use
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine system
LAAM	levomethadyl
LAR	legally authorized representative (legal guardian)
LC-MS/MS	Liquid Chromatography - Tandem Mass Spectrometry
LCF	Late clinical failure
LFT	Liver function test
LLOQ	lower limit of quantification
LPF	Late parasitological failure
LPLV	Last Patient Last Visit
LTF	Late treatment failure
MedDRA	Medical dictionary for regulatory activities
mFAS	Modified Full analysis set
mg	milligram(s)
mL	milliliter(s)
mPAS	Modified Pharmacokinetic analysis set
mRAS	Modified Randomized analysis set
mSAF	Modified Safety analysis set
MUAC	mid-upper arm circumference
NDA	New Drug Application
NI	Non-inferiority
OP	Analysis Set
CCI	[redacted]
PAS	Pharmacokinetic Analysis Set
PCR	Polymerase chain reaction
PCT	Parasite clearance time
CCI	[redacted]

PI	Principal Investigator
CCI	[redacted]
PT	prothrombin time
QD	Once daily
CCI	[redacted]
QTcF	QT interval corrected by Fridericia's formula
RAS	Randomized Analysis Set
CCI	CCI
SAE	Serious Adverse Event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SDF	Solid Dispersion Formulation
SNPs	Single nucleotide polymorphisms
SoA	Schedule of Activities
SoC	Standard of care
spp.	species pluralis
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	tuberculosis
TBL	Total bilirubin
CCI	CCI
UG	Unblinded at the group level
UI	Unblinded to individual patient treatment codes
ULN	upper limit of normal
UNS	unscheduled
URTI	upper respiratory tract infection
WBC	White blood cell(s)
WCBP	Women of Childbearing Potential
WHO	World Health Organization
β-hCG	beta-human chorionic gonadotropin

10.2.2 Definitions

Assessment	A procedure used to generate data required by the study
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Control drug	A study intervention (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Discontinuation from study	Point/time when the patient permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the patient permanently stops receiving the study treatment for any reason (prior to the planned completion of study intervention administration, if any). Patient agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the patient in a time unit (e.g., 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last patient.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained. The action of enrolling one or more patients
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication kit number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system.
Medication number	A unique identifier on the label of medication kits
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the patient's home.
Off-site healthcare Professional (OHP)	A qualified healthcare professional, who performs certain protocol procedures for the patient in an off-site location such as a patient's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Patient	An individual with the condition of interest.
Patient number	A unique number assigned to each patient upon signing the informed consent. This number is the definitive, unique identifier for the patient and should be used

Assessment	A procedure used to generate data required by the study
	to identify the patient throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization	The process of assigning trial patients to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized patient
Remote	Describes any trial activities performed at a location that is not the investigative site.
Screen Failure	A patient who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first patient
Study completion	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug/treatment	Any drug or combination of drugs or intervention administered to the study patients as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the patient permanently stops taking study treatment prior to the defined study treatment completion date.
Tele-visit (tele-consultation)	Procedures or communications conducted using technology such as telephone or video-conference, whereby the patient is not at the investigative site where the Investigator will conduct the trial.
Variable	The variable to be obtained for each patient that is required to address the clinical question. The specification of the variable might include whether the patient experiences an intercurrent event.
Withdrawal of consent (WoC) / Opposition to use of data / biological samples	Withdrawal of consent from the study occurs when the patient explicitly requests to stop use of their data and/or biological samples AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study patient's privacy rights are described in the corresponding informed consent form.

10.3 Appendix 3: Clinical laboratory tests

10.3.1 Clinically notable laboratory values and vital signs

Table 10-1 Criteria for notably abnormal vital signs

		Patient age at visit	
Vital sign		**< 18 years**	**≥ 18 years**
Systolic blood pressure [mmHg]	High	≥ 95th percentile of the age and h eight group[1]	≥ 180 with increase from updatedbaseline5 of ≥20 mmHg
	Low	≤ 5th percentile of the age and hei ghtgroup[1]	≤ 90 with decrease from update d baseline5 of ≥20 mmHg
Diastolic blood pressure [mmHg]	High	≥ 95th percentile of the age and h eight group[1]	≥ 105 with increase from updatedbaseline5 of ≥15 mmHg
	Low	≤ 5th percentile of the age and hei ghtgroup[1]	≤ 50 with decrease from update d baseline5 of ≥15 mmHg
Oral body temperature [°C]	High	≥ 38.4°C	≥ 39.1°C
	Low	≤ 35.0°C	≤ 35.0°C
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	≥120 with increase from update d baseline[5] of ≥15 bpm
	Low	1-6 months <120 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	≤50 with decrease from update d baseline[5] of ≥15 bpm
Weight	High	increase from baseline[3] of ≥ 2 Body Mass Index(BMI)-for-age percentile categories[4]	Weight increase from updated b aseline[5] of ≥ 10%
	Low	decrease from baseline[3] of ≥ 2 B MI-for-age percentile categories[4]	Weight decrease from updated baseline[5] of ≥ 10 %
Respiratory rate [breath per minute][2,6,7]	High	1-6 months >55 6-12 months >50	≥30bpm

Vital sign		Patient age at visit	
		< 18 years	**≥ 18 years**
		12-18 months > 46	
		18-24 months > 40	
		2-3 years > 34	
		3-4 years > 29	
		4-6 years > 27	
		6-8 years > 24	
		8-12 years > 22	
		12-15 years > 21	
		≥ 15 years > 20	
	Low	1-6 months <33	≤ 10bpm
		6-12 months < 30	
		12-18 months <28	
		18-24 months < 25	
		2-3 years < 22	
		3-4 years < 21	
		4-6 years < 20	
		6-8 years < 18	
		8-12 years < 16	
		12-15 years < 15	
		15-18 years < 13	

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

[1] Blood pressure percentiles are calculated for each blood BP record using the method described inAppendix 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.

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

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

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

[5] Updated baseline is the last value collected before the 18th birthday.

[6] Eldridge L. What is a Normal Respiratory Rate?, Updated May 16, 2014;

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

10.4 Appendix 4: Participant Engagement

The following patient engagement initiatives are included in this study and will be provided, as available, for distribution to study patients or their LAR at the time points indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank You letter

- CCI [redacted].

10.5 Appendix 5: Liver safety monitoring

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

Please refer to Table 10-2 for complete definitions of liver laboratory triggers.

Once a patient is exposed to study treatment, every liver event defined in Table 10-2 should be followed up by the Investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Section 10.5.1.

- Repeat liver chemistry tests (i.e., ALT, AST, TBL, ALP, albumin and GGT) to confirm elevation.
- Add another measure: PT/INR. Prothrombin time/International Normalized Ratio (PT/INR) should not be performed routinely, but only in case of liver event as defined in Table 8-1.
- In case of an elevation of AST or ALT >3 x ULN (see Table 10-2), INR should also be performed to further qualify the event (i.e., if INR > 1.5) as part of liver follow-up testing.
- These liver chemistry repeats should be performed using the local laboratory used by the site (or a nearby laboratory). Repeated laboratory test results must be reported as appropriate.
- If the initial elevation is confirmed, close observation of the patient will be initiated until resolution of the liver event including:
  - consideration of treatment interruption if deemed appropriate.
  - Discontinuation of the investigational drug (Section 7.1), if appropriate
  - Hospitalization of the patient if appropriate
  - Causality assessment of the liver event
  - Thorough follow-up of the liver event can include, based on the Investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

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

NOTE: For specific ALT elevations in absence or presence of bilirubin increase (Table 10-3), additional follow-up requirements are specified in the same table (Table 10-3).

10.5.1 Liver event and laboratory trigger definitions & follow-up requirements

Table 10-2 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	● ALT or AST > 5 × ULN ● ALP > 2 × ULN (in the absence of known bone pathology) ● Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) ● ALT or AST > 3 × ULN and INR > 1.5 ● Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) ● Any clinical event of jaundice (or equivalent term) ● ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia ● Any adverse event potentially indicative of a liver toxicity
If ALT or AST abnormal at baseline:	● ALT or AST > 3 x baseline AND > 5xULN

Table 10-3 Follow up requirements for liver laboratory triggers - ALT, AST, TBL

ALT	**TBL**	**Liver symptoms**	**Action**
ALT increase without bilirubin increase:			
If normal at baseline: ALT > 3 x ULN If elevated at baseline: ALT > 2 x baseline or > 300 U/L (whichever occurs first)	Normal For patients with Gilbert's syndrome: No change in baseline TBL	None	● Measure ALT, AST, ALP, GGT, TBL, INR, albumin, Creatine Kinase (CK) and GLDH in 48-72 h. ● Follow-up for symptoms. ● Report in the Local lab Liver Safety Follow-Up CRF page.
If normal at baseline: ALT > 5 x ULN If elevated at baseline: ALT > 3 x baseline AND > 5 x ULN	Normal For patients with Gilbert's syndrome: No change in baseline TBL	None	● Measure ALT, AST, ALP, GGT, TBL, INR, albumin, CK, and GLDH in 48-72 h. ● Follow-up for symptoms. ● Report in the Local lab Liver Safety Follow-Up CRF page. ● Initiate close monitoring and workup for competing etiologies.
ALT increase with bilirubin increase:			
If normal at baseline: ALT > 3 x ULN If elevated at baseline: ALT > 2 x baseline AND > 3 x ULN	TBL > 2 x ULN (or INR > 1.5) For patients with Gilbert's syndrome: Doubling of direct bilirubin	None	
If normal at baseline: ALT > 3 x ULN If elevated at baseline: ALT > 2 x baseline AND > 3x ULN OR ALT > 300 U/L	Normal or elevated *	Severe fatigue, nausea, vomiting, right upper quadrant pain	

* This situation suggests liver injury based on (i) elevation of ALT, and (ii) the presence of symptoms of liver injury. Even if bilirubin is normal, the presence of liver symptoms indicates potentially severe liver injury.

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's

consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

If any of the criteria specified in Table 10-3 is met, the Investigator or designated personnel at the trial site should follow-up the patient according to the following steps:

- Repeat liver chemistry test to confirm the elevated value (ALT, AST, TBL, ALP, GGT, albumin).
- Add other measures as listed in the action panel of Table 10-3: PT/INR, CK and GLDH.
- Depending on availability of reagents and equipment and measurement capacity, measurement of Creatine Kinase (CK) or Glutamate Dehydrogenase (GLDH) may not be feasible.
    - If measurement of both CK and GLDH is feasible, site should proceed with measurement of these parameters and report the values in the Liver Safety Follow-Up CRF page.
    - If measurement of CK only is feasible, site should proceed with measurement of this parameter and report the values in the Liver Safety Follow-Up CRF page.
    - If neither measurement of CK nor of GLDH is feasible, site should perform physical examination of the subject for the detection of signs of rhabdomyolysis e.g. muscle pain, redness or bruising, limited motion, muscle spasms, swelling, dark urine, fatigue, malaise.
    - If any of the above parameters are found to be abnormal, close monitoring of the patient must be initiated.

These tests should be performed at the local laboratory used by the site or a nearby laboratory. Laboratory test results must be captured within 48-72h in the Liver event CRF in RAVE EDC with the respective assessment date. Also, any finding detected during physical examination should be reported in the adverse events CRF. If extrahepatic cause of liver enzyme elevation is suspected, the patient should be thoroughly monitored, and the sites should reach out to the sponsor contact for further advice.

10.6 Appendix 6: WHO Definitions of treatment failures and Adequate Clinical and Parasitological Response

Early Treatment Failures (ETF)

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

Late Clinical Failure (LCF)

- Development of danger signs or severe malaria in the presence of parasitemia on any day between Day 5 and Day 43 in patients who did not previously meet any of the criteria of early treatment failure;

- presence of parasitemia on any day between Day 5 and Day 43 with axillary temperature ≥ 37.5 °C in patients who did not previously meet any of the criteria of early treatment failure.

Late Parasitological Failure (LPF)

- Presence of parasitemia on any day between Day 8 and Day 43 with axillary temperature < 37.5°C in patients who did not previously meet any of the criteria of early treatment failure or late clinical failure.

Adequate Clinical and Parasitological Response (ACPR):

- Absence of parasitemia on Day 29, irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure or late parasitological failure.

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

Note: The first day of treatment with study medication is defined as Day 1 while the day prior to the first day of treatment is defined as Day -1. Compared to WHO 2015 which defined Day 0 as the first day of treatment with study medication, days after treatment referred to in this protocol are 1 day greater. For example, Day 29 in this protocol corresponds to Day 28 by WHO 2015.

See Section 10.7 for signs/symptoms indicative of severe/complicated malaria

10.7 Appendix 7: Signs/symptoms of severe/complicated malaria

Danger signs:

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

Signs of severe malaria:

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

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

Group 1

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

Group 2

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

Group 3

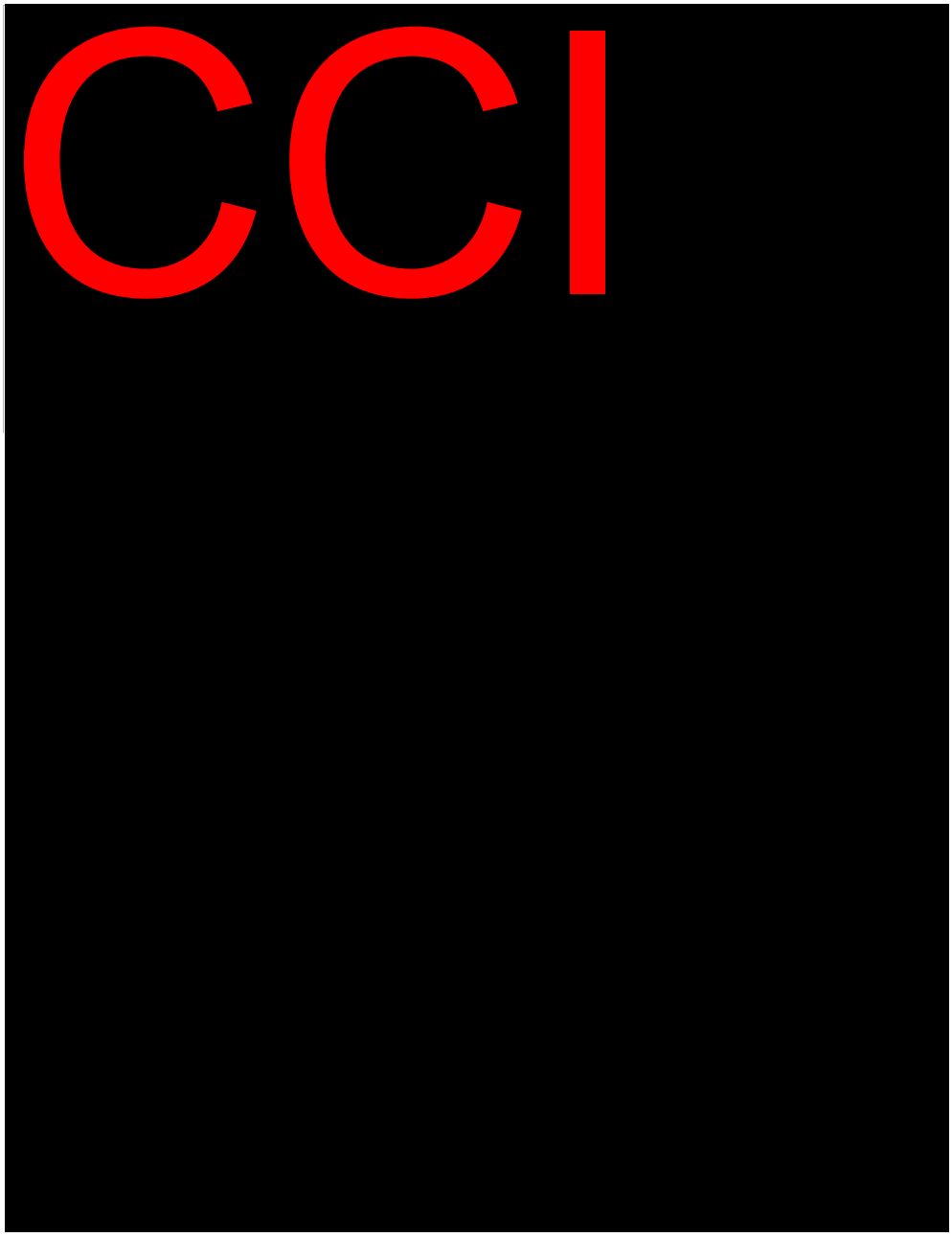
Children who require parenteral treatment because of persistent vomiting but who lack any specific clinical or laboratory features of groups 1 or 2 (above).

10.8 Appendix 8: Cardiac Alert Threshold Values and Actions

Table 10-4 Cardiac alert threshold values and actions

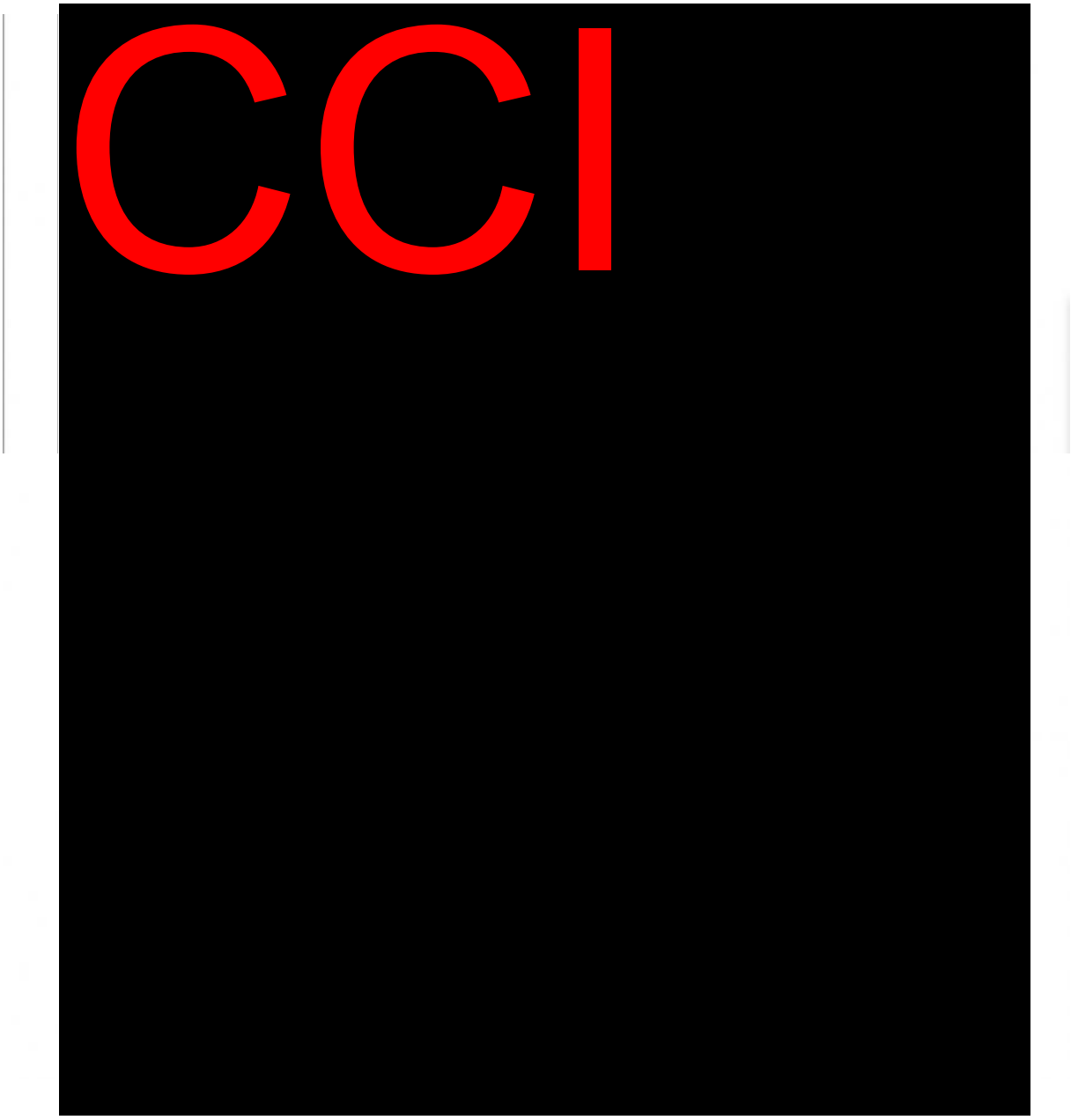
	Values	Actions
QTcF Cardiac rhythm	● QTcF> 500. ● Sustained ventricular tachycardia lasting 30 sec or more, or ventricular fibrillation, or any hemodynamically compromising cardiac arrhythmia	● If confirmed as mean of the triplicate ECG, check and correct the patient's serum potassium and magnesium immediately. ● Transmit to central vendor immediately for prompt review. ● Discontinue patient from study therapy. ● Monitor ECG hourly until at least 2 consecutive hourly ECGs performed are back to baseline
QTcF Resting heart rate	● Increase from baseline ≥ 60 ms ● HR < 50/min with > 25% decrease from pretreatment baseline verified by ECG	● If confirmed as mean if triplicate ECG, check and correct the patient's serum potassium and magnesium immediately. ● Transmit to central vendor immediately for prompt review.

10.9 Appendix 9: CCI [redacted]




CCI


CCI


CCI

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