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Novartis Research and Development

KAE609/cipargamin

Clinical Trial Protocol CKAE609B12201 / NCT04675931

An adaptive, randomized, active-controlled, open-label, sequential cohort, multicenter study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of intravenous cipargamin (KAE609) in adult and pediatric participants with severe Plasmodium falciparum malaria (KARISMA – KAE609's Role in Severe Malaria)

Document type:	Clinical Trial Protocol
EUDRACT number:	Not applicable
Version number:	00 (Original Protocol)
Clinical Trial Phase:	II
Release date:	14-Oct-2020 (content final)

Clinical Trial Protocol Template Version 3.0 dated 31-Jan-2020

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List of abbreviations

AAG	Alpha-1-acid glycoprotein
ACT	Artemisinin-based Combination Therapy
ADME	Absorption, Distribution, Metabolism, Excretion
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ASAQ	Artesunate-Amodiaquine
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATP	Adenosine Triphosphate
AUC	Area under curve
AV Block	Atrioventricular block
b.i.d. or bd	twice a day
BCS	Blantyre Coma Score
BMI	Body Mass Index
BUN	blood urea nitrogen
CFR	Code of Federal Regulation
CI	Confidence Interval
CL/F	The total body clearance of drug from the plasma (volume x time-1)
Cmax	It is the highest concentration of a drug in the blood after a dose is given
CMH	Cochran-Mantel-Haenszel
CMO&PS	Chief Medical Office and Patient Safety
COVID-19	Corona virus disease 2019
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTT	Clinical Trial Team (Novartis)
CV	coefficient of variation
CYP	Cytochrome
DBIL	Direct Billirubin
DHA	Dihydroartemisinin
DMC	Data Monitoring Committee
DNA	Desoxyribonucleic acid
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency

EOS	End of Study
EU	Eurpean Union
FAS	Full Analysis Set
FCT	Fever clearance time
FIH	First in human
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
h or hr	hour
Hb	Hemoglobin
HIV	human immunodeficiency virus
HMG CoA	3-Hydroxy-3-Methylglutaryl-Coenzym-A
CCI	[redacted]
i.e.	That is (id est)
i.v. or IV	intravenous
IA	Interim Assessment
IC50	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IM	Intramuscular
IN	Investigator Notification
INR	International Normalized Ratio (blood clotting test)
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD/IUS	Intrauterine Device/Intrauterine System
CCI	[redacted]
KDIGO	Kidney Disease Improving Global Outcomes
KM	Kaplan-Meir
LC-MS	Liquid Chromatography - Mass-Spectrometry
LDH	lactate dehydrogenase
LFT	Liver function test
LLOQ	lower limit of quantification
LOQ	limit of quantification
m or min	Minutes
MDMA	3,4-Methylendioxy-N-methylamphetamine
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mg/dL	Milligrams per deciliter
CCI	[redacted]
ml	milliliter(s)
mmHg	millimeters of mercury

mmol/L	Millimoles per Liter(s)
MRI	Magnetic Resonance Imaging
MUAC	Mid-upper arm circumference
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
P.	Plasmodium
PBPK	Physiology-Based Pharmacokinetic modeling
PCE	Parasite Clearance Estimator
PCR	Polymerized chain reaction
PCT	Parasite clearance time
PD	pharmacodynamic(s)
PfATP4	Plasmodium falciparum ATP4
PI	Prescribing Information
PK	pharmacokinetic(s)
PoC device	Point of Care device
PPS	Per-protocol set
PRR	Parasite reduction ratio
PSW	Premature Study Withdrawal
Q24h	Every 24 hour
QMS	Quality Management System
QRS	The QRS Complex is a group of usually three spikes seen in an ECG (electrocardiogram), where each spike represents a depolarization of both heart chambers
QT	QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	Heart rate-corrected QT
QTcB	QTc corrected by Fridericia
QTcF	QT interval corrected by Fridericia’s formula
R Value	ALT/ALP x ULN
RBC	red blood cell(s)
REB	Research Ethics Board
RRT	Renal Replacement Therapy
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SC	subcutaneous
SCr	Serum creatinine
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SMQ	Standardized MedDRA Query
SNPs	Single-Nucleotide Polymorphism
SS	Safety Set

SUSAR	Suspected Unexpected Serious Adverse Reactions
T1/2	The elimination half-life associated with the terminal slope (lz) of a semi logarithmic concentration-time curve (time)
TB	Tuberculosis
TBIL/TBL	Total Bilirubin
ULN	upper limit of normal
US	United States
Vz/F	The apparent volume of distribution during terminal phase (associated with λz) (volume)
WBC	white blood cell(s)
WHO	World Health Organization
WWARN	World Wide Antimalarial Resistance Network
µl	Microliter(s)

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Biomarker	A naturally occurring molecule, gene, or characteristic by which a particular pathological or physiological process, disease, etc. can be identified.
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
Enrollment	Point/time of subject entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Estimand	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 each of the treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest. It also specifies of how the intercurrent events are addressed and provides a population-level summary for the variable.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
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
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.

Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Non-investigational medicinal Product (NIMP)	Products which are not the object of investigation (e.g. any background therapy administered to each of the clinical trial subjects, regardless of randomization group, rescue medication, active drug run-ins etc.)
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient	An individual with the condition of interest
PBPK model	Physiologically based pharmacokinetic (PBPK) modeling is a mathematical modeling technique for predicting the absorption, distribution, metabolism and excretion (ADME) of synthetic or natural chemical substances in humans and other animal species.
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
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Premature subject withdrawal	Point/time when the subject 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 number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	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
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.

Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

Protocol summary

Protocol number	CKAE609B12201
Full Title	An adaptive, randomized, active-controlled, open-label, sequential cohort, multicenter study to evaluate the efficacy, safety, tolerability and pharmacokinetics of intravenous cipargamin (KAE609) in adult and pediatric participants with severe *Plasmodium falciparum* malaria (KARISMA – KAE609's Role In Severe Malaria)
Brief title	To evaluate efficacy, safety, tolerability and PK of intravenous cipargamin in participants with severe *Plasmodium falciparum*
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to identify the safe and effective dose of intravenous cipargamin in participants with moderately severe and severe malaria. The study also intends to evaluate clinical treatment success using a novel clinical endpoint for drug development in severe malaria. Severe malaria is a medical emergency and is affecting primarily young children in Africa. Injectable artesunate is the standard of care for the treatment of severe malaria and is highly efficacious. However, the spread of artemisinin-resistance in *Plasmodium falciparum* in Asian countries poses a threat for future treatment of patients with this life-threatening disease. To mitigate this risk, there is a need of another drug in malaria endemic countries. Cipargamin treatment results in rapid clearance of parasites including artemisinin resistant parasites.
Primary Objective(s)	The primary objective is to assess the efficacy of different doses of intravenous cipargamin vs artesunate by evaluating the proportion of participants with ≥ 90% reduction of parasitemia at 12 hours post administration of the first dose.
Secondary Objective(s)	The key secondary objective is to assess the clinical outcome as measured by the proportion of participants with clinical success at 48 hours. The other secondary objectives are: 1. To assess the presence/absence of severe malaria related individual signs over time 2. To evaluate parasite clearance dynamics and proportion of participants with recrudescence and reinfection 3. To assess recovery of participants as measured by time (days and hours) to discharge from hospital or recovery from prostration 4. To evaluate the safety and tolerability of IV cipargamin 5. To assess the risk of long term neurological sequelae for participants at Day 29 6. The assess the risk of hemolysis (early and delayed) during the study duration 7. To characterize the plasma pharmacokinetics of IV cipargamin

Study design	This will be an adaptive, multicenter, randomized, open label, sequential cohort study in participants aged ≥ 12 years (Cohorts 1-2) and ≥ 6 months to < 12 years (Cohorts 3-5) with a diagnosis of moderately severe and severe *P. falciparum* malaria. This study is investigating the efficacy (parasite reduction and clinical outcome), safety, tolerability and pharmacokinetics of different injectable dose regimens of cipargamin in comparison to injectable artesunate. The first cohort (Cohort 1) will be small, and will include participants aged 12 years or over, diagnosed with moderately severe malaria and high parasitemia. This cohort will be used for initial evaluation of safety and parasite clearance rates before continuing into Cohorts 2-5, which will include only severe malaria patients according to WHO criteria. Progressively younger participants will be included with each new cohort from Cohort 2 onwards. This design aims at minimizing risks for pediatric participants < 12 years.
Study population	The study population will consist of male and female participants, including pediatric participants aged ≥ 6 months or older. Approximately 252 participants (60 participants of ≥ 12 years and 192 participants < 12 years) will be randomized.
Key Inclusion criteria	• Cohort 1: Participants aged ≥ 12 years with moderately severe malaria as defined in Barnes et al (2004) (prostration and/or repeated vomiting) without presence of other signs of severe malaria as per Section 16.4 (and with high *P. falciparum* parasitemia (60,000-250,000 parasites per µl) • Subsequent Cohorts 2 to 5: Participants diagnosed with severe malaria as defined in modified version of WHO criteria (Section 16.4) and *P. falciparum* parasite count of ≥ 5000 per µl • Cohort 2: Participants aged ≥ 12 years • Cohort 3: Participants aged 6 - < 12 years • Cohort 4: Participants aged 2 - < 6 years • Cohort 5: Participants aged ≥ 6 months - < 2 years
Key Exclusion criteria	**Exclusion criteria applying to all Cohorts 1 to 5:** -Mixed Plasmodium infections -Treatment with quinine or artemisinin derivative or any other antimalarial drug or any antibiotic with known antimalarial activity within 12 hours of screening. -Signs/symptoms of severe malnutrition in general accordance with WHO guidelines: 1. Under 18 years: <-3 Z-scores of WHO growth standard for weight-for-height/length (in children < 5 years) or BMI for age (5-18 years), or very low mid-upper arm circumference (MUAC < 115 mm in children < 12 years, < 160mm 12-18 years), or bilateral pitting edema 2. Over 18 years: BMI < 16 kg/m^2 or MUAC < 160mm or bilateral pitting edema -Known underlying illness, surgical or medical condition, which is not related to ongoing event of severe malaria and which might jeopardize the participant's health in case of participation in the study or which might alter the distribution, metabolism or excretion of study treatment. For example: 1. neurological or neurodegenerative disorders, 2. cardiac, renal, or hepatic disease, diabetes, 3. epilepsy, cerebral palsy,

	4. known or suspected to be HIV-1 positive and/or receiving antiretroviral treatment 5. malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases 6. known or suspected cases of active infections or concurrent febrile illness such as TB, Typhoid, COVID-19 etc. **Additional exclusion criteria are as follows:** **Exclusion criteria for Cohort 1:** -ALT > 5 x the upper limit of normal range (ULN), regardless the level of total bilirubin -Total bilirubin is > 3 mg/dL -Body weight of < 35 kg or >75 kg **Exclusion criteria for Cohort 2:** -Body weight of < 35 kg or >75 kg -Participants diagnosed as moderately severe malaria due to repeated vomiting without presence of any of the symptoms of severe malaria **Exclusion criteria for Cohorts 3 to 5:** -Body weight of < 5 kg -Participants diagnosed as moderately severe malaria due to repeated vomiting without presence of any of the symptoms of severe malaria
Study treatment	Study treatments: • Cipargamin 10 mg/ml and/or 15mg/ml vial (investigational drug) for intravenous administration • Artesunate 60 mg vials (control drug) for intravenous administration Study treatment will be followed by a full course of oral standard of care antimalarial. Additional treatments: • Oral standard of care: artemether/lumefantrine • Rescue medication: IV artesunate
Treatment of interest	IV cipargamin versus IV artesunate
Efficacy assessments	• Parasitemia • Clinical outcome as measured as normalization of signs of severe malaria
Pharmacokinetic assessments	Standard PK parameters of cipargamin and alpha-1-acid glycoprotein level over time
Key safety assessments	• Adverse event monitoring • Physical examination • Vital signs • Laboratory assessments of blood and urine • ECG assessment

Other assessments	CCI
Data analysis	For the proportion of participants with ≥ 90% reduction at 12 hours, two-sided 90% confidence intervals (CI) for the difference between each cipargamin dose regimen vs artesunate will be provided using the Wilson uncorrected method based on FAS; these will be evaluated within each cohort separately except Cohort 1, which will be combined with Cohort 2. The lower limit of CI will be used to determine if a cipargamin dose regimen is non-inferior to artesunate based on non-inferiority margin of -10%. For the clinical success at 48 hours, 2-sided 90% CIs for the difference between a cipargamin dose regimen and artesunate will be provided on pooled data from all cohorts using a Mantel-Haenszel estimate of the common risk difference stratified by cohort where Cohorts 1 and 2 will be combined. Incidence rates of recrudescence and reinfection at Study Day 29 will be estimated by Kaplan-Meier method based on the subset of FAS participants who have clearance of initial infection by Study Day 7. An exposure-response relationship using the PK exposure with parasite reduction and other efficacy and safety parameters may be explored.
Key words	Severe malaria, cipargamin, artesunate, intravenous, pediatric, dose-finding

1 Introduction

1.1 Background

Severe malaria is a medical emergency and affects primarily young children in Africa. Severe malaria is defined by presence of one or more of the systemic signs such as impaired consciousness, respiratory distress in relation to metabolic acidosis, convulsions, prostration, severe anemia, hypoglycemia, acidosis, liver and renal impairment, significant bleeding, shock, pulmonary edema and hyperparasitemia (WHO 2014). Injectable artesunate is the standard of care for the treatment of severe malaria and is highly efficacious. However, the spread of artemisinin-resistance *Plasmodium falciparum* in Asian countries poses a risk for future treatment of patients with this life-threatening disease. Treatment of severe malaria with IV artesunate should always be followed by a complete treatment course of an appropriate oral antimalarial regimen.

Cipargamin is a novel spiroindolone class drug with potent and fast-acting schizonticidal activity, which acts by disrupting the malaria parasite Na^+ homeostasis by inhibition of the ATPase PfATP4. Cipargamin is being currently evaluated as an oral treatment for uncomplicated malaria and has demonstrated good efficacy in several clinical studies. Most recently, a phase IIa safety study with approximately 190 participants was completed in 2020 (Investigator`s Brochure). Because of its rapid clearance of parasites (median parasite clearance time <12 hours) and because of its activity against artemisinin resistant parasites (Naß and Efferth 2019), cipargamin will be evaluated in the treatment of adults and children with severe malaria as an injectable treatment followed by a full course of standard oral artemisinin-based therapy Coartem®.

In this study, different doses of IV cipargamin will be compared to the standard of care, IV artesunate, with the goal of identifying efficacious and safe dose of injectable cipargamin to be administered in a subsequent phase III study. Both IV drugs will be followed by a full course of Coartem in accordance to WHO treatment guidelines.

1.2 Purpose

The purpose of this study is to identify safe and effective dose of intravenous cipargamin in moderately severe (Cohort 1) and severe malaria participants (Cohorts 2-5) in an age-descending manner (refer Barnes et al 2004 for definition of moderately severe malaria and Section 16.4 for the definition of severe malaria). The study also aims to evaluate clinical success as a novel clinical outcome endpoint, which will be implemented in the confirmatory Phase III study.

The purpose of Cohorts 1 and 2 will be to establish efficacy, PK and safety of IV cipargamin in participants aged ≥ 12 years. Two cipargamin dose regimens will be evaluated in each of Cohorts 1 and 2. Based on the data obtained, one IV cipargamin dose will be selected for pediatric participants in Cohorts 3-5. Participants aged from 6 months to <12 years will be dosed using weight bands and age-specific considerations.

2 Objectives and endpoints

All objectives and endpoints are in comparison of IV cipargamin to IV artesunate in participants with moderately severe or severe *P. falciparum* malaria.

Table 2-1 Objectives and related endpoints

Objective(s)	**Endpoint(s)**
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the efficacy of IV cipargamin	• Proportion of participants with ≥ 90% *P. falciparum* parasite reduction at 12 hours, see Section 2.1 for the primary estimand
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess clinical outcome	• Proportion of participants with clinical success (see Section 8.3.1.1.) over time. Clinical success at 48 hours is considered as the key secondary endpoint, see Section 2.2 for the secondary estimand.
• To assess the presence/absence of individual signs of severe malaria	• Proportion of participants with individual signs of severe malaria over time (see Section 8.3.1.2).
• To assess the risk of hemolysis	• Proportion of participants developing hemolysis (early and delayed) after treatment (see Section 10.2.3)
• To assess the risk of long term neurological sequelae	• Proportion of participants with neurological sequelae at Day 29
• To evaluate parasite clearance dynamics	• Proportions of participants with ≥ 90% parasite reduction at 24 and 48 hours PCE slope half-life Time to *P. falciparum* parasite clearance (PCT) *P. falciparum* parasite reduction ratios (PRR) at 12, 24 and 48 hours Proportion of participants with recrudescence and reinfection by Day 29
• To assess other efficacy endpoints	• Time (days and hours) to switch to oral therapy Day of discharge from hospital Time (hours) to recover from prostration
• To evaluate the safety and tolerability of IV cipargamin	• Standard safety/tolerability assessments (incidence of serious adverse events (SAEs), mortality, in-hospital mortality, adverse events (AEs), and routine safety and laboratory assessments)
• To assess the plasma pharmacokinetics of IV cipargamin	• PK parameters of cipargamin: Cmax, $T_{1/2}$, AUC, CL and Vz Alpha-1-acid glycoprotein level over time and correlation of AAG concentration with cipargamin PK parameters

Objective(s)	Endpoint(s)
Exploratory objective(s)	Endpoint(s) for exploratory objective(s)

2.1 Primary estimands

An 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 each of the treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest. It also specifies how intercurrent events are addressed and provides a population-level summary for the variable. The structured framework of estimand detailed in ICH E9 (R1) was newly adopted by the Regulatory Members of the ICH Assembly under Step 4 in Nov-2019.

The clinical question of interest is: What is the difference between IV cipargamin and IV artesunate in early reduction of asexual parasite load in participants with severe *P. falciparum* malaria who are treated with at least one dose of IV treatment?

The justification for targeting this treatment effect is that severe *P. falciparum* malaria is caused by asexual parasite burden, leading to sequestration and microvascular obstruction. Rapid reduction of *P. falciparum* asexual parasites by 12 hours should prevent participants from further deterioration, and so allow eventual recovery from the disease.

The primary estimand is described by the following attributes:

1. Population: Participants with severe *P. falciparum* malaria and who have been treated with at least one dose of IV study medication (either cipargamin or artesunate). Further details about the population are provided in Section 5.
2. Variable: A binary outcome indicating ≥ 90% reduction in *P. falciparum* parasite at 12 hours (H12) after first IV dose as compared to baseline.
3. Treatment of interest: IV cipargamin vs IV artesunate. Further details about cipargamin and artesunate are provided in Section 6.
4. Intercurrent events: (1) taking IV rescue antimalarial medication prior to H12 parasite assessment, or (2) mortality prior to H12 parasite assessment. Details on how to handle the intercurrent event are provided in Section 12.4.3.
5. Summary measure: Difference in proportion of participants with ≥ 90% reduction in baseline parasite count between IV cipargamin dose regimen and IV artesunate will be

evaluated within each cohort separately except Cohort 1, which will be combined with Cohort 2.

2.2 Secondary estimands

The secondary clinical question of interest is: What is the difference between IV cipargamin and IV artesunate in clinical success at 48 hours without the need of IV rescue antimalarial medication?

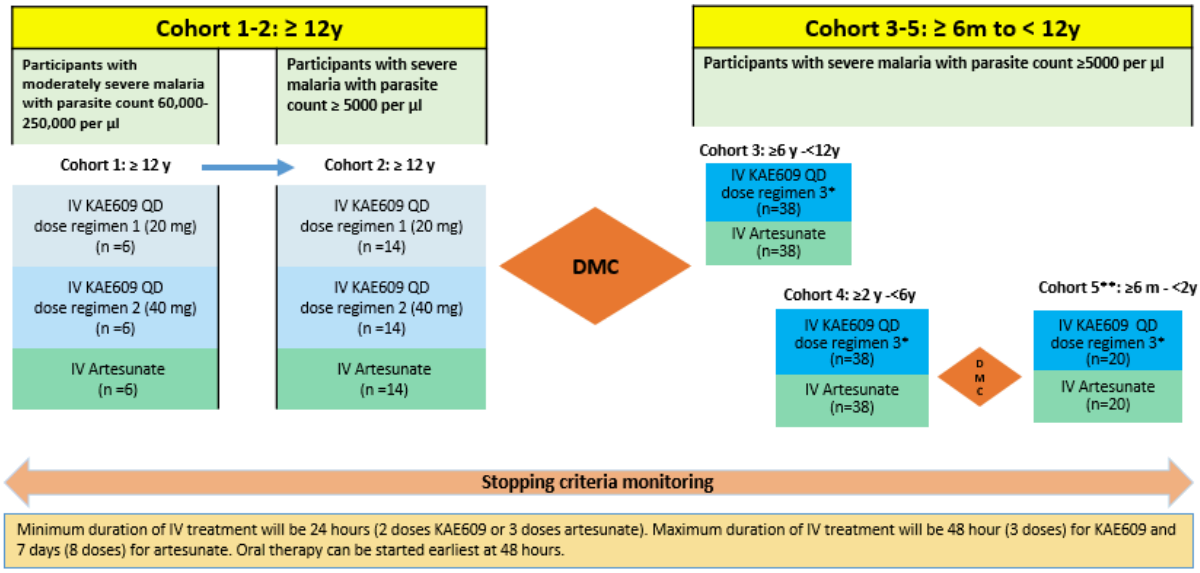
The justification for the secondary estimand is that it will reflect the clinical outcome including recovery from the most severe symptoms of the disease with IV treatment before earliest possible administration of oral antimalarial medication at 48 hours. This objective is being evaluated for possible use in Phase III study. Further details can be found in Section 12.

The secondary estimand is described by the following attributes:

1. Population: participants with severe *P. falciparum* malaria and treated with at least one dose of IV study medication. Further details about the population are provided in Section 5.
2. Variable**:** A binary outcome indicating clinical success- participant is alive and has absence of asexual parasites and no critical signs of severe malaria (See Section 8.3.1.2 for further details) at 48 hours.
3. Treatment of interest: IV cipargamin vs IV artesunate. Further details about cipargamin and artesunate are provided in Section 6.
4. Intercurrent event**:** receive IV rescue antimalarial medication before assessing the clinical success prior to H48.
5. Summary measure: Proportion of participants with clinical success with 90% CI within a treatment group as well as the difference between the cipargamin and artesunate treatment group.

3 Study design

Figure 3-1 Study design



Notes:
KAE609 (Cipargamin)
Moderately severe malaria – Prostration and/or repeated vomiting (Barnes et al 2004)
Study to progress from Cohort 1 to Cohort 2 without interruption if none of the KAE609 arms in Cohort 1 meets the stopping criteria.
*Results from Cohort 1 and Cohort 2 will be analyzed to determine the safe and efficacious exposure range and the corresponding doses (KAE dose regimen 3) for participants in Cohorts 3 to 5.
Doses for Cohort 4 will be confirmed after PK analysis from upto 6 KAE609 participants from Cohort 3 and for Cohort 5, it would be post completion of Cohort 4 .
** Cohort 5 recruitment is dependent on availability of adequate toxicology package to dose down to ≥ 6 m
KAE609 doses across the study will be adaptive depending on the safe and efficacious exposure range identified before the study (for Cohorts 1-2) and after interim assessment of Cohort 1 & 2 (for Cohorts 3-5)

This will be an adaptive, multicenter, randomized, open label, sequential cohort study in participants aged ≥ 12 years old in Cohorts 1-2 and < 12 years old to ≥ 6 months in Cohorts 3-5 with a diagnosis of moderately severe and severe *P. falciparum* malaria (Section 16.4). This study is investigating the efficacy (parasite reduction and clinical outcome), safety, tolerability and pharmacokinetics of different injectable dose regimens of cipargamin in comparison to injectable artesunate. Cohort 1 includes only 18 participants aged ≥ 12 years old. As IV cipargamin has not yet been evaluated in patients with severe malaria, this first Cohort includes participants that are diagnosed with moderately severe malaria. Cohort 1 participants will have a minimum parasite count of 60,000 per µl and these high parasitemia levels will help to determine parasite clearance rates for the two dose regimen. In Cohorts 2-5 participants with severe malaria and a minimum parasite count of 5,000 per µl will be enrolled in an age-decreasing manner. This design aims at minimizing risks for pediatric participants < 12 years and at ensuring sufficient number of participants with severe malaria signs to evaluate their clinical improvement in the secondary endpoint. In all cohorts, participants on IV cipargamin arms will receive one daily injection of IV cipargamin over a minimum of 2 days and a maximum of 3 days; with IV artesunate as rescue medication. Participants in the IV artesunate arm will be administered a minimum of 3 doses during the first 2 days of treatment. Participants in all arms will receive Coartem bid for 3 days following IV therapy.

See sections Section 6.1.1, Section 6.1.2.1 and Section 6.2.1 for details of each treatment arm.

Cohorts 1-2:

In Cohorts 1 and 2, 18 and 42 participants ≥ 12 years, who satisfy the inclusion/exclusion criteria will be randomized in the ratio 1:1:1 to one of three treatment arms. :

- IV cipargamin (KAE609) dose regimen 1
- IV cipargamin (KAE609) dose regimen 2
- IV artesunate

The two doses of IV cipargamin for Cohorts 1 and 2 have been selected based on the rationale described in Section 4.2. The doses might be adjusted before the study start based on results obtained from the first in human (FIH) study in healthy volunteers to ensure exposure is maintained within the predicted safe and efficacious range (AUC $_{0\text{-}24h}$ of 5-42 µg*hr/ml) in the study participants.

Cohorts 3-5:

The results from Cohorts 1 and 2 will be analyzed to determine the safe and efficacious exposure range and the corresponding doses (cipargamin (KAE609) dose regimen 3) for the participants in Cohorts 3 to 5. In these Cohorts all participants will be pediatric and below 12 years of age. Only one dose of IV cipargamin will be selected for use in Cohorts 3-5 (see Section 4.2). For the pediatric participants in Cohorts 3 to 5, a convenient dosing regimen based on weight bands will be defined (Section 4.2). The results from Cohort 1 and Cohort 2 will be summarized for interim assessment (IA), and the data will be reviewed by an Independent DMC before continuing to dose pediatric participants < 12 years in Cohorts 3-5. The IA will be performed on key efficacy, safety and PK data up to Day 29.

In the age descending Cohorts 3 to 5 the PK exposure will be confirmed in up to 6 participants per cohort treated with IV cipargamin before recruiting remaining participants. PK data obtained from these initial participants from every cohort may lead to modification of the selected dose in order to maintain IV cipargamin exposure within the determined safe and efficacious range. At the same time, recruitment in the subsequent younger age Cohort will be started for the first 6 participants. In case of a need for dose modification in a particular Cohort, additional participants maybe recruited into that cohort to ensure data are available for approximately 38 participants at the selected dose level.

- Cohort 3: Pediatric participants ≥ 6 y - < 12 y
- Cohort 4: Pediatric participants ≥ 2 y - < 6 y
- Cohort 5: Pediatric participants ≥ 6 m - <2 y

In Cohorts 3 to 5 approximately 192 participants (aged ≥ 6 months to < 12 years) who satisfy the inclusion/exclusion criteria will be randomized in a 1:1 ratio to one of two treatment arms:

- IV cipargamin (KAE609) dose regimen 3
- IV artesunate

Study conduct

Participants will be admitted to the hospital on Day 1 and screened for inclusion in the study. If they meet the eligibility criteria they will be randomized to treatment within 3 hours of

admission. Participants will be hospitalized under close supervision for at least 72 hours after start of IV treatment and until oral treatment with Coartem has been initiated. Hospitalization can be extended, if needed, for participants based on disease signs, until IV treatment has been completed and oral treatment with Coartem has been initiated. All participants should be followed up until Day 29. Visits to assess safety and efficacy will be scheduled during the follow-up period as described in the assessments schedule (Table 8-1, Table 8-2). If malaria symptoms re-emerge outside the scheduled study visits or any other adverse events occur, participants will be instructed to contact the investigator. Study design and assessments will slightly vary between cohorts, details are captured in Section 5 and Table 8-1, Table 8-2. The safety of the entire study will be monitored by a Data Monitoring Committee (DMC) and stopping criteria (based on safety and lack of efficacy criteria) are in place throughout the study (Table 3-1). Recruitment in any treatment arms with cipargamin (KAE609) will be paused if stopping criteria are met. In event of recruitment pause, all relevant data will be reviewed in an ad-hoc DMC meeting and the next steps to be taken with the relevant IV cipargamin dose will be decided by Novartis based on the DMC's recommendation. Planned DMCs will occur at the end of Cohort 2 and at the end of Cohort 4. Additional DMC meetings may be conducted depending on the need.

Participants in all cohorts will be closely monitored through parasitological, biochemical, hematology, physical and neurological examinations (Table 8-1, Table 8-2 and Section 8.3.1). Rich PK sampling will be done in Cohorts 1 - 3 and sparse PK sampling will be done in Cohorts 4-5 for IV cipargamin participants.

Stopping criteria for the study

Data related to participant's efficacy and safety will be continuously monitored by the sponsor. If participants randomized to any IV cipargamin arms meet either the safety criteria or lack of efficacy criteria as listed in Table 3-1 below, the study may be paused and a DMC review conducted.

Table 3-1 Criteria to temporarily pause the recruitment and initiate DMC review

Cohorts with planned recruitment	Number of participants meeting the safety criteria*	Number of participants meeting the lack of efficacy criteria**
Cohort with 6 participants	2	2
Cohort with 14 participants	2	2
Cohort with 20 participants	3	3
Cohort with 38 participants	6	6
Throughout the study (116 participants within a single IV cipargamin treatment arm)	14	14
*Safety criteria - All cause death or SAE possibly related to cipargamin **Lack of efficacy criteria – Use of IV artesunate as rescue medication (as per protocol defined criteria) in participants randomized to IV cipargamin		

4 Rationale

4.1 Rationale for study design

As severe malaria is primarily a disease of young children, children down to 6 months have been included in this clinical study to obtain data in the relevant patient population. In order to ensure adequate efficacy and safety, pediatric participants will be included in an age descending manner with the youngest participant between 6 months and 2 years of age enrolled in the final cohort after IA and DMC.

As IV cipargamin has not yet been evaluated in patients with severe malaria, Cohort 1 will start with a study population, which is less severely ill and ≥ 12 years old. Participants diagnosed with moderately severe malaria and high parasitemia (60,000-250,000 parasites per µl) at baseline and without significant elevations in liver function tests (ALT and total bilirubin, see Section 5.2) will be randomized to Cohort 1. The selected inclusion criteria should limit the variability of the disease signs of participants included in Cohort 1, while allowing for efficacy assessment based upon parasite clearance and initial safety monitoring. If stopping criteria (Table 3-1 in Section 3) are not met in any of the IV cipargamin arms in Cohort 1, recruitment of Cohort 2 will be initiated after LPLV (last patient last visit) of Cohort 1. In case of any efficacy/safety concerns identified in Cohort 1, PK data will be analyzed and the following actions could be taken in consultation with the data monitoring committee (DMC):

- Up to six additional participants per treatment arm may be recruited in Cohort 1 before proceeding to Cohort 2
- Dose for Cohort 2 may be modified (increased or decreased) to ensure exposure within the safe and efficacious range

In Cohort 2, participants in the same age population of ≥ 12 years diagnosed with severe malaria (Section 16.4) will be enrolled. Participants in Cohorts 2 to 5 will be enrolled with parasitemia levels of at least 5,000 parasites per µl. An interim assessment after Cohort 2 will evaluate efficacy, safety and PK results of the two IV cipargamin doses compared to IV artesunate. Based on these results, a safe and efficacious exposure range will be defined for the use in Cohorts 3-5. The dose for Cohorts 3-5 will be selected to ensure that exposure in children < 12 years of age remains within the determined safe and efficacious range.

Parenteral artesunate is the first line treatment for severe malaria as recommended by WHO 2015. All participants will be treated with IV cipargamin or IV artesunate for at least 24 h (minimum of 2 doses of IV cipargamin and 3 doses of IV artesunate) and until oral therapy can be tolerated. IV therapy will be followed by oral antimalarial therapy as per standard treatment practice. The oral treatment is a 3-day course of Coartem to ensure complete elimination of parasites in participants.

The open label design is chosen since the dosing frequency and method of administration of test drug and comparator is not similar. Hence, blinding the treatment would require multiple placebo injections in a double dummy design which is ethically not acceptable considering the severity of the disease and need for inclusion of pediatric participants. Furthermore, the risk of bias arising out of the open-label design is minimized due to the objectivity of the primary endpoint, which is based on reduction of parasitemia.

4.1.1 Rationale for choice of background therapy

Parenteral antimalarial treatment followed by a full course of oral antimalarial therapy is the standard of care for management of parasitemia and achieving cure in severe malaria patients (WHO 2015). In addition, supportive treatment is required to manage severe malaria. Such treatments include but are not limited to blood transfusions, fluid replacement therapy, anticonvulsants and glucose transfusions. Supportive treatment for management of severe malaria will be administered as per local treatment guidelines and will be documented as concomitant medication in the study database. A minimum basic standard of supportive treatment will be maintained across all the sites participating in the study. Participants should not receive any additional antimalarial drug unless used as rescue medication as per protocol.

4.2 Rationale for dose/regimen and duration of treatment

The primary aim of the intravenous antimalarial treatment in severe malaria is a rapid reduction of the initial parasite load. The efficacy of oral cipargamin in terms of parasite clearance has been demonstrated in previous studies using single doses between 10 mg and 150 mg. In study CKAE609A2202, aparasitemia was achieved by as early as 12 hours post-dose in the majority of the subjects treated with a single dose of oral cipargamin of ≥ 25 mg and by 24 hours post-dose in the majority of the subjects treated with oral cipargamin irrespective of dose. CCI

IV artesunate, the standard of care for severe malaria, has reported mean PRR_{24} values between 7 and 43 across studies (Newton et al 2001, Nealon et al 2002, Newton et al 2003, Maude et al 2014). The CCI from four oral cipargamin studies including more than 150 participants with uncomplicated malaria (CKAE609X2201, CKAE609X2202, CKAE609A2201 and CKAE609A2202) is shown in Figure 4-1. In these studies, participants with baseline parasitemia of up to 60,000 parasites per µl were included CCI oral cipargamin treatment. The full exposure-response relationship in participants with hyperparasitemia, as expected in severe malaria, remains to be elucidated.

In the same study CKAE609A2202, no safety concerns in patients with uncomplicated malaria were associated with CCI The doses of IV cipargamin in this study have been selected in order not to exceed these mean exposures from the previous study.

The PK exposures of cipargamin following IV administration were predicted using a population PK model based on preliminary data from the first two cohorts of the ongoing phase 1 study CKAE609X2111. An adjustment in predicted exposures was made CCI (Silamut et al 1991) and the impact of CCI observed in studies in uncomplicated malaria and in healthy volunteers study, CCI CKAE609X2111.

Based on the above criteria, selected doses for Cohorts 1-2, i.e. 20 and 40 mg once every 24 hours, are expected to provide exposures within the safe and efficacious range. Due to the half-life of cipargamin of approximately 24 hours, cipargamin is expected to accumulate with daily

dosing. To limit the total exposure of IV cipargamin in this first study of IV cipargamin in malaria patients, participants will receive a maximum of 3 daily doses. For severe cases, the total duration of IV therapy (either IV cipargamin followed by IV artesunate or IV artesunate alone) will be defined by the medical condition of the participants and the prescribing information of IV artesunate.

Cohorts 1-2

The lowest dose selected for Cohorts 1-2 i.e. 20 mg is expected to CCI [redacted] As such, this dose is expected to provide equivalent or faster initial parasite clearance than the standard of care i.e. artesunate and thereby minimize the risk for severely ill participants due to slow parasite clearance.

A dose of 40 mg is expected to provide CCI [redacted] observed with oral cipargamin in participants with uncomplicated malaria (refer Figure 4-1 below). Hence, a fast parasite clearance rate is expected to be achieved in all the participants and a full dose response curve can be obtained to ensure that the appropriate benefit risk relationship is established in adolescent and adult participants before dosing children below 12 years in Cohorts 3-5. The anticipated exposure with 40 mg dose is comparable to the highest exposure, which was achieved in oral cipargamin in study CKAE609A2202 without any safety issues.

In conclusion, the inclusion of 20 and 40 mg doses in Cohorts 1-2 will cover a wider exposure range and facilitate the selection of an appropriate dose for later Cohorts 3-5.

Cohorts 3-5

A single dose level with the best benefit risk potential will be evaluated in participants < 12 years old based on interim assessment of data from Cohorts 1 and 2. The population PK and / or PBPK model will be developed / up-dated with this data to predict exposures in participants from Cohort 3-5. If required, the speed of IV bolus administration may be adjusted to keep the Cmax within the safe range as determined in Cohorts 1-2. CCI [redacted]

Figure 4-1 CCI

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

Parenteral artesunate is the WHO recommended first line treatment for severe malaria (WHO 2015). Three IV doses are given over the first 24 h (0, 12 and 24 h) and then q24h until oral therapy can be tolerated. A full course of oral treatment (artemisinin based combination therapy, Coartem in this study) is given afterwards to ensure elimination of the malaria parasite. Other treatments available for severe malaria are such as IM artesunate, IV quinine and intramuscular artemether. However, these treatments are only recommended when IV artesunate is not available.

4.4 Purpose and timing of interim analyses/design adaptations

An interim assessment (IA) will be performed after completion of Cohort 2. The study team and an independent DMC will review key PK/efficacy/safety data including the proportion of participants with ≥ 90% parasite reduction at 12 hours as well as at 24 and 48 hours and parasite reduction ratios, relevant safety data and PK data from all participants of Cohorts 1 and 2. Based on data from Cohorts 1 and 2, the highest safe and effective exposure will be determined and used to select doses for Cohorts 3-5.

For subsequent Cohorts 3-5, randomization will start with the next descending age group. Novartis pharmacokineticist will review the PK exposure and AAG (if required) in up to 6 participants treated with IV cipargamin. After confirming that the exposures are adequate,

enrollment of participants will continue in the initial cohort (applicable for Cohorts 3-5) and the next lower age cohort will be opened for enrollment. However, enrollment for Cohort 5 will only be initiated post completion of Cohort 4 and a DMC meeting. In case, the dose for a specific age group has to be adjusted, additional participants with the modified dose may be recruited.

Additional IAs may be conducted (for e.g. after Cohort 4) to support decision making concerning the current clinical study, the sponsor's clinical development projects in general, or in case of any safety concerns.

Following dose and design adaptations are permitted in the study as per below Table 4-1:

Table 4-1 Dose and design adaptations permitted in the study

For Cohorts 1-2, CCI [redacted]	-	**Cohort 1**	**Cohort 2**	**Interim assessment to identify safe and efficacious exposure range (**CCI [redacted]**) for Cohorts 3-5**	**Cohort 3-5**
	Doses	20 mg and 40 mg May be modified before start of study based on IV cipargamin PK data from FIH study	20 mg and 40 mg May be modified based on emerging PK data from Cohort 1 or if one of the IV cipargamin treatment arms meets the stopping criteria		Age and weight band based dose may be modified based on PK data from up to first 6 participants in each of the cohort to achieve adequate exposure identified for Cohorts 3-5
	Sample size	Up to six additional participants per treatment arm may be recruited before proceeding to Cohort 2 if doses selected at start of the study for Cohort 2 are modified	Up to 14 additional participants per treatment arm may be recruited before proceeding to Cohorts 3-5 if IA suggest benefit of using higher exposures in Cohorts 3-5		Additional participants may be recruited in each cohort after dose modification to ensure 38 evaluable participants on the same dose level

4.5 Risks and benefits

Severe malaria is a medical emergency and is affecting primarily young children in Africa. With currently only one WHO recommended IV treatment, there is considerable medical need for an additional treatment option as injectable antimalarial. Based on the preclinical and clinical evaluation to date, as presented in the Investigator`s Brochure, oral cipargamin has been

generally safe and well tolerated. Healthy subjects have been dosed up to single oral doses of 300 mg, and repeated oral doses up to 150 mg q24h for 3 days, and patients up to single oral doses of 150 mg, and repeated oral doses of 50 mg. The participants in this study will be receiving IV cipargamin for the treatment of severe malaria and based on the positive efficacy results with the oral formulation in the treatment of uncomplicated malaria, they are expected to receive benefit from it. The risk to participants (as per Investigator`s Brochure) will be minimized by adherence to the inclusion/exclusion criteria, stopping rules, close clinical monitoring (including multiple laboratory evaluations as per the Assessment Schedule), the staggered design of the study with PK and safety reviews between cohorts. The exposure CCI with selected doses of IV cipargamin is not expected to exceed exposures already observed with oral cipargamin.

Cohort 1 of the current study will include participants aged ≥ 12 years suffering from moderately severe malaria accompanied by a high parasite count. Younger participants will only be enrolled in Cohorts 3-5 of the study in descending age order. There will be safety, efficacy and PK assessments after Cohort 2 to confirm the dose for Cohorts 3-5, which will be administered to children aged ≥ 6 months to 12 years. Participants will be hospitalized under close supervision until they are considered fit to be discharged by the investigator. Stopping criteria will be applied as mentioned in Section 3 and all participants will be closely monitored on an ongoing basis. Recruitment in a specific treatment arm can be put on hold, as necessary.

Expected benefits of IV cipargamin

Based on available evidence about rapid parasite reduction with oral cipargamin in uncomplicated malaria, IV cipargamin is also expected to provide rapid parasite reduction in severe malaria patients. Rapid parasite reduction should lead to an improvement in clinical symptoms and overall clinical benefit for the patient.

However, overall clinical outcome in severe malaria patients is dependent on the comprehensive case management including supportive treatment. Hence, at least a basic minimum standard of supportive therapy will be maintained across all the sites in this study.

Potential risks with the use of IV cipargamin

Resistance

The risk of developing resistant strains of parasite is low since IV monotherapy will be followed by oral standard of care in all the patients. Any recrudescence or new infection will be managed with standard of care pharmacotherapy that should effectively eliminate any parasites.

Delayed hemolysis

Based on prospective studies delayed hemolysis has been detected in 7-27% of the severe malaria participants treated with IV artesunate (Rolling et al 2014, Kurth et al 2017). Hyperparasitemia in non-immune travelers and young age in the endemic regions are the confirmed risk factors. The hemolytic event typically peaks 2-3 weeks after the acute phase of malaria. Removal of dead parasites from the erythrocytes in the spleen and leaving behind the "once-infected" erythrocytes, which are characterized by a shorter life span, is one of the assumed mechanism. Based on the mechanism of action of cipargamin, delayed hemolysis might occur also in connection with IV cipargamin therapy. All participants will be followed up closely for at least 4 weeks and given supportive treatment as needed.

Liver safety

Reversible and asymptomatic LFT elevations were observed with 75 mg single dose in a patient study in uncomplicated malaria and with 10 mg single dose in a human challenge study (Investigator`s Brochure). Increase in LFT levels in these studies could have been influenced by the disease condition itself and/or the specific human challenge model (Chughlay et al 2020). Changes in LFTs are often associated with malaria but liver function generally improves as the patient recovers (Reuling et al 2018, Woodford et al 2018). In Cohort 1 of the study, participants with ALT > 5 x ULN (regardless the level of total bilirubin) and total bilirubin is > 3 mg/dL will be excluded. In this study, all participants will be closely monitored, including regular liver function tests, and in addition, it will be ensured that all participants would have access to standardized supportive treatment like IV fluid replacement and transfusion.

Semen discoloration

In the Phase I first-in-human study with oral cipargamin (CKAE609X2101), 29 participants at high doses of oral cipargamin reported transient yellow discoloration of their ejaculate but no other genitourinary symptoms. The symptoms were self-limiting and did not require intervention. Screening semen analysis studies did not reveal significant abnormalities in those taking cipargamin. As a precautionary measure, participants in this study should wear a condom during intercourse for one week following the last dose.

IV preclinical safety risks

To support dosing IV cipargamin to humans, IV toxicology studies with the clinical formulation 1 have been completed in rat and dog (Investigator`s Brochure). The target organ of toxicities identified were mostly comparable to the ones identified in oral toxicity studies performed previously and included liver, adrenal glands and bone marrow. The main target organ of concern was the adrenal gland (Investigator`s Brochure). Lesions were seen in oral and IV toxicology studies in dogs, but so far no clinical correlates have been seen in animals or humans. Adrenal function will continue to be monitored in clinical studies.

In addition, signs of inflammation (neutrophil increase) were observed in blood and a few tissues in both species and a mild decrease in reticulocytes in dogs. The mechanism is unknown and these observations were reversible. Participants in this study will be monitored for any signs of increased inflammation.

The clinical formulation 1 (intravenous cipargamin injection) lead to local reaction (thrombus) in rat but not in dog. The human relevance is unknown and potential local reaction at injection site will be monitored in patients. In this clinical study, clinical formulation 2 (10mg/ml) might be used, which is identical to clinical formulation 1 (15mg/ml) with the exception of one excipient, which is replaced by structurally similar excipient.

During second week of dosing in the dog IV study, cipargamin-related increase in QTc interval was noted. These changes are of unknown relevance, as no changes were observed after single IV dose, or in the oral toxicology studies. In patients, QT changes are not expected; nevertheless, ECG will be monitored for QTcF and cardiac abnormalities.

Cipargamin is non genotoxic and based on animal reproductive and developmental studies, no teratogenicity was noted. However, effects on female fertility and fetotoxicity was seen in rats at doses that were associated with maternal toxicity. The effects of cipargamin on the human

fetus are not known. Therefore, women of childbearing potential may be enrolled only if they have a negative pregnancy test prior to receiving cipargamin. Male and female patients have to agree to adhere to contraceptive requirements outlined in the exclusion criteria (Section 5.2).

Weak phototoxicity seen in an *in vitro* test system did not translate to an *in vivo* mouse model. Nevertheless, participants taking cipargamin are advised to use commonly recommended precautions when in the sun (e.g. sunscreen, hat, protective clothing).

Comparator IV artesunate

The most important reported side effect of parenteral artesunate is a rare severe allergic reaction, which has involved urticarial rash as well as other symptoms, including hypotension, pruritus, edema, and/or dyspnea. More common minor side effects associated with IV administration have included dizziness, light-headedness, rash, and taste alteration (metallic/bitter taste). Nausea, vomiting, anorexia and diarrhea have also been reported, however it is uncertain whether such events have been symptoms of severe malaria (Artesunate PI). Participants will be closely monitored, including for the signs and symptoms for delayed hemolytic anemia.

Additional considerations

As is the case with any new compound in clinical development, there are unknown risks to cipargamin that may be serious and unforeseen.

The current IV cipargamin formulation should not be administered IM or SC (Investigator`s Brochure). For IV administration, monitoring of injection sites is required. If extravasation occurs, the IV administration must be stopped. Observe and manage conservatively.

In summary, the demonstrated efficacy in uncomplicated malaria with the acceptable safety profile in participants from both Phase I and Phase II studies demonstrates an acceptable risk-benefit to investigate the utility of IV cipargamin in the treatment of severe malaria.

5 Study Population

The study population will consist of male and female participants, including pediatric participants ≥ 6 months or older.

The plan is to randomize approximately 252 participants (60 participants of ≥ 12 years or older and 192 participants < 12 years) in approximately 20 sites from Africa and Asia. Enrollment may be increased due to higher drop out or repeat of cohorts as applicable.

5.1 Inclusion criteria

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

1. Cohort 1: Participants aged ≥ 12 years with moderately severe malaria as defined in Barnes et al (2004) (prostration and/or repeated vomiting) without presence of other signs of severe malaria (Section 16.4) and with high *P. falciparum* parasitemia (60,000-250,000 parasites per µl).

   Subsequent Cohorts 2 to 5: Participants diagnosed with severe malaria as defined in Section 16.4 (modified version of severe malaria criteria in WHO 2014) and *P. falciparum* parasite count of ≥ 5000 per µl

   Cohort 2: Participants aged ≥ 12 years

   Cohort 3: Participants aged 6 - <12 years

   Cohort 4: Participants aged 2 - < 6 years

   Cohort 5: Participants aged ≥6 months - <2 years
2. Written informed consent form must be obtained prior to any study related procedure. If the participant is unable to read and write or otherwise incapable of signing an informed consent, then a witnessed consent according to local ethical standards is permitted (formally documented and witnessed, ideally via an independent trusted witness). Participants aged < 18 years, who are capable of providing assent, must provide assent with parental/legal guardian consent or as per local ethical guidelines. The participant or parent/legal guardian (in case of pediatric participants) is able to understand and comply with protocol requirements, instructions and protocol-stated restrictions for their child and is likely to complete the study as planned.

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. **Exclusion criteria applying to all Cohorts 1 to 5:**
   1. Mixed Plasmodium infections
   2. Treatment with quinine or artemisinin derivative or any other antimalarial drug or any antibiotic with known antimalarial activity within 12 hours of screening
   3. Known underlying illness, surgical or medical condition, which is not related to ongoing event of severe malaria and which might jeopardize the participant's health in case of participation in the study or which might alter the distribution, metabolism or excretion of study treatment, e.g. :
      - neurological or neurodegenerative disorders,
      - cardiac, renal, or hepatic disease, diabetes,
      - epilepsy, cerebral palsy,
      - known or suspected to be HIV-1 positive and/or receiving antiretroviral treatment
      - malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
      - known or suspected cases of active infections or concurrent febrile illness such as TB, Typhoid, COVID-19 etc.

4. Known history of ECG abnormalities indicating significant risk of safety for participants such as:
   a. Concomitant clinically significant cardiac arrhythmias, e.g. sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
   b. History of familial long QT syndrome or known family history of Torsades de Pointes
   c. QTcF > 450 ms in males and QTcF > 460 ms in females aged ≥ 12 years old and QTcF > 450 ms in females aged < 12 years.
5. Signs/symptoms of severe malnutrition in general accordance with WHO guidelines:
   - Under 18 years: <-3 Z-scores of WHO growth standard for weight-for-height/length (in children < 5 years) or BMI for age (5-18 years), or very low mid-upper arm circumference (MUAC <115 mm in children < 12 years, <160mm 12-18 years), or bilateral pitting edema
   - Over 18 years: BMI < 16 kg/m2 or MUAC < 160mm or bilateral pitting edema
6. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days, whichever is longer; or longer if required by local regulations
7. Participants taking prohibited medication defined as per Section 6.2.3
8. Pregnant or nursing (lactating) women
9. Female of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective contraception methods (listed below) during dosing and until one week after last IV dose or until start of next menstruation after last dose of oral standard of care (Coartem), whichever is later. Required highly effective contraception methods include:
   a. Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (i.e., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception
   b. Male partner sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that participant
   c. Female sterilization (have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment
   d. Use of oral (e.g. estrogen, synthetic progestins), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormonal vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment. Coartem can reduce the effectiveness of hormonal

contraceptives, female participants using oral, transdermal patch, or other systemic hormonal contraceptives are required to use an additional non-hormonal method of birth control, e.g., barrier contraceptives during dosing of oral Coartem and until the start of next menstruation after completion of oral treatment.

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

f. If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

10. Sexually active males unless they are using highly effective contraception method as listed below:
    a. Use of condom during intercourse while taking drug and until one week after last IV dose and should not father a child in this period.
    b. Use of condom by vasectomized participant in order to prevent delivery of the drug via body fluids.

Additional specific exclusion criteria for Cohorts 1-5 are as follows:

2. **Exclusion criteria for Cohort 1:**
    1. ALT > 5 x the upper limit of normal range (ULN), regardless the level of total bilirubin
    2. Total bilirubin is > 3 mg/dL
    3. Body weight of < 35 kg or > 75 kg
3. **Exclusion criteria for Cohort 2:**
    1. Body weight of < 35 kg or >75 kg
    2. Participants diagnosed as moderately severe malaria due to repeated vomiting without presence of any of the symptoms of severe malaria.
4. **Exclusion criteria for Cohorts 3 to 5:**
    1. Body weight of < 5 kg
    2. Participants diagnosed as moderately severe malaria due to repeated vomiting without presence of any of the symptoms of severe malaria.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Novartis will supply following study drugs (Investigational and control drug) as open label participant specific supplies as per Table 6-1.

- Cipargamin (KAE609) 10 mg/ml and / or 15 mg/ml vial (investigational drug) for intravenous administration
- Artesunate 60 mg vials (control drug) for intravenous administration

Apart from Investigational and control drugs, Novartis will also supply additional treatments as rescue medication (Artesunate 60 mg vials) and oral medication as standard of care (Coartem 20/120 and 80/480 mg tablets).

Table 6-1 Investigational drugs, control drug and oral standard of care

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form and Packaging	Route of Administration	Supply Type	Sponsor (global or local)
KAE609 15 mg/ml	Solution for injection; 1 vial per box	Intravenous use	Open label	Novartis global
KAE609 10 mg/ml	Solution for injection; 1 vial per box	Intravenous use	Open label	Novartis global
Artesunate 60 mg/vial*	Powder for reconstitution; 1 vial per box	Intravenous use	Open label	Novartis global
Coartem® 20/120 mg**	Dispersible tablet; 6 tablets in a blister	Oral	Open label	Novartis global
Coartem® 80/480 mg**	Tablets; 6 tablets in a blister	Oral	Open label	Novartis global
*Control drug and rescue medication ** Oral medication as standard of care				

Dosing of study drugs for Cohorts 1-5 are described in below **Table 6-2:**

Table 6-2 Dosing Regimen for IV cipargamin (KAE609) and IV artesunate

Cohort	Treatment arms	Dosing Regimen
1-2	IV KAE609 20 mg - dose regimen 1	Minimum of two doses; q24h (to be administered at 0 hour and 24 hours) and not exceeding three doses (Dose 3 at 48 hours) followed by oral medication (Coartem® bid for 3 days)

Cohort	Treatment arms	Dosing Regimen
1-2	IV KAE609 40 mg - dose regimen 2	Minimum of two doses; q24h (to be administered at 0 hour and 24 hours) and not exceeding three doses (Dose 3 at 48 hours) followed by oral medication (Coartem® bid for 3 days)
3-5	IV KAE609 - dose regimen 3	Minimum of two doses; q24h (to be administered at 0 hour and 24 hours) and not exceeding three doses (Dose 3 at 48 hours) followed by oral medication (Coartem® bid for 3 days).See Section 4.2 for process of dose selection for Cohorts 3-5
1-5	IV Artesunate 2.4 mg/kg (for participants weighing at least 20 kg) IV Artesunate 3 mg/kg (for participants weighing less than 20 kg)	0, 12, and 24 h and q24h for maximum 8 doses (7 days) according to label and until oral medication (Coartem® bid for 3 days) can be given according to label

Coartem is used according to the supplied labels in the study.

The proposed Coartem doses for Cohorts 1-5 are as mentioned in below Table 6-3:

Table 6-3 Cohort 1-5: Coartem® (standard of care) dosing per weight (dosing as per label)

Weight	Coartem® dosage
≥ 35.0 kg (and ≥ 12 years)	80/480 mg BID for 3 days
25 to < 35 kg	60/360 mg BID for 3 days
15 to < 25 kg	40/240 mg BID for 3 days
5 to < 15 kg	20/120 mg BID for 3 days

6.1.2 Additional study treatments

6.1.2.1 Oral medication (standard of care)

All sites will receive Coartem as standard of care for oral treatment as per local practice. Following criteria are recommended for specified timepoints when switching participant from IV therapy to oral therapy as mentioned in below Table 6-4:

First timepoint to switch participant from IV therapy to oral is at 48 hour. However, if a participant is not able to tolerate oral therapy then continue with IV treatments and evaluate again at 72 hour timepoint.

Table 6-4 Criteria for switch to oral medication (standard of care)

Time	Decision criteria	Decision
0 hours	Review screening results	Start dosing with IV therapy
24 hours	Assess rescue medication criteria	Continue IV therapy (and assess rescue medication criteria for participants on IV cipargamin) (see Section 6.2.1)
48 hours (Day 3) (1st timepoint for a switch to oral therapy)	Assess the feasibility of administering oral medication	Start Coartem, if switch criteria are met as per label. Otherwise continue IV therapy (and assess rescue medication criteria per Section 6.2.1)
72 hours (Day 4) onwards	Assess the feasibility of administering oral medication at every 24 hours	Start Coartem, if switch criteria are met as per label. Otherwise continue IV artesunate or switch to IV artesunate therapy (for participants on IV cipargamin as per Section 6.2.1). Hospitalization should be extended till the time participant has not switched to oral therapy and assessments to be repeated as Day 4 if hospitalization is required beyond Day 4 (see Table 8-1, Table 8-2)

Intravenous artesunate can be administered to a maximum of 7 days based as per supplied labels. Most participants after switching to oral therapy will be discharged from hospital with full oral course of Coartem for 3 days. Site to instruct participant (or participant's representative) on intake of oral therapy per label.

After switching to oral therapy (Coartem), if there are efficacy or safety concerns, the participant will be administered another ACT (Section 6.2.1) as per local treatment guidance.

6.1.2.2 Supportive therapies

Supportive treatment is required to manage severe malaria. Such treatments include but are not limited to blood transfusions, fluid replacement therapy, anticonvulsants (refer to Section 6.2.2) and glucose transfusions. Supportive treatment for management of severe malaria will be administered as per local treatment guidelines and will be documented as concomitant medication in the study database. A minimum basic standard of supportive treatment will be maintained across all the sites participating in the study.

6.1.3 Treatment arms/group

Cohorts 1-2

Participants in each Cohorts (1 to 2) will be randomized into three treatment arms in 1:1:1 ratios to each IV cipargamin (KAE609) arms and IV artesunate:

- IV cipargamin 20 mg - dose regimen 1
- IV cipargamin 40 mg - dose regimen 2
- IV artesunate

Cohorts 3-5

Participants in each Cohorts (3 to 5) will be randomized into two treatment arms in 1:1 ratios to IV cipargamin (KAE609) arm and IV artesunate:

- IV cipargamin - dose regimen 3 (See Section 4.2 for process of dose selection for Cohorts 3-5)
- IV artesunate

Dosing regimen as explained in Section 6.1.1

6.1.4 Treatment duration

Participants will be treated with IV cipargamin (KAE609) once daily for at least 24 hours (2 doses) and a maximum of 48 hours (3 doses). Participants requiring prolonged IV treatment will be switched to IV artesunate and treated according to local practice. Participants in control arms will receive IV artesunate for at least 24 hours (3 doses) and for a maximum of 7 days if necessary as per label or until oral Coartem (standard of care) can be tolerated, whichever is earlier (see criteria for switch to oral therapy in Section 6.1.2.1).

6.2 Other treatment(s)

6.2.1 Rescue medication

Management of severe malaria consists of an IV antimalarial (cipargamin or artesunate in the study) followed by a full course of oral standard of care (Coartem in this study). Hence, rescue medication use will also be either IV medication or oral medication as applicable.

Participants randomized to IV artesunate will not be administered any other IV antimalarial as rescue medication since IV artesunate is the only standard of care. Participants randomized to IV cipargamin may be rescued with IV artesunate, if they meet the following pre-defined criteria:

- Parasite clearance < 90% at 24 hours post treatment initiation
- Clinical decline of severe malaria symptoms (per Investigator) at any time
- Participants not able to take oral antimalarial along with presence of parasites at 72 hour post treatment initiation
- Participants developing signs or symptoms of severe malaria after shift to oral standard of care (Coartem) until end of the study (Day 29).

In addition, participants developing safety concerns due to cipargamin (Refer also Section 16.1, Section 16.2) can be rescued with IV artesunate.

After completion of full course of Coartem, participants meeting the following criteria will be administered another ACT (as per local guidance) as an oral rescue medication:

- Parasitemia at any time with or without temperature > 37.5ºC

6.2.2 Concomitant therapy

Prior medications are defined as drugs taken and stopped prior to the first dose of study medication. In this study, all medication administered or taken by the participants up to 72 hours prior first dose has to be reported as prior medication in the appropriate Case Report Forms.

Severe malaria is a multisystem disease and requires treatment for the various signs and symptoms that occur. These will be treated according to the local clinical practice but should not include the administration of additional antimalarials unless the participant meets the criteria for rescue medication. The following medications are recommended for commonly observed symptoms:

- Paracetamol < 3g/day (or equivalent pediatric dosage; 10 to 15 mg/kg orally every 4 to 6 hours) may be used however, exact doses and time should be recorded appropriately.
- Metopimazine for repeated vomiting (or if not available, any other antiemetic which is not known to prolong QT and/or cause torsade de pointes)
- Beta-lactam antibiotics would be preferred in case of a bacterial infection (with the exception of amoxicillin-clavulanic acid because of its potential hepatotoxicity). If needed clindamycin can be given. All other antibiotics, new-quinolones included, should be avoided where possible.
- Lorazepam and furosemide. Diazepam should be allowed only when the suggested alternative lorazepam would not be available.
- Supportive therapy (e.g. blood or glucose transfusion, refer Study Manual)

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 participant or allowing a new medication to be started. If the participant is already enrolled, Novartis should be contacted to determine if the participant should continue participation in the study, if the time permits based on participant condition.

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

6.2.2.1 Permitted concomitant therapy requiring caution and/or action

CCI [redacted] Examples of drugs metabolized by these enzymes are provided under Section 16.3 in Table 16-5. However, assessments including SimCYP simulation suggests that the potential change in the exposure of these drugs would be less than two fold and unlikely to be of clinical significance.

Nonetheless, caution should be exercised with drugs as outlined in Table 16-5 following ~12 hours from the last dose of cipargamin.

Administration of paracetamol/acetaminophen is acceptable, but daily total dose should not exceed 3g. As for all concomitant medications dose and time of administration must be documented in the Concomitant medications section of the eCRF.

6.2.3 Prohibited medication

Following considerations on prohibited list of medications are required for participants on cipargamin arms (refer below Table 6-5).

For participants on IV artesunate arms, the applicable current prescribing information should be followed, including prohibited medications related to potential adverse events or impact on efficacy. For study specific reasons, the following considerations for specific medications must be taken into account for participants on IV artesunate (refer below Table 6-6).

Regarding prohibited medications for Coartem refer to the current prescribing information.

Table 6-5 Prohibited medications for participants on cipargamin arms

Prohibited Medication	Prohibited period
CCI	
Drug known to cause QTc prolongation Antiarrhythmics of classes IA and III Certain antibiotics including some agents of the following classes: macrolides (including azithromycin), fluoroquinolones, imidazole and triazole antifungal agents Certain non-sedating antihistaminics (terfenadine, astemizole), cisapride	For treatment duration and 7 days after last dose
Drugs used as **antimalarials** other than the study drug, rescue medication and oral standard	12 hours before study entry and during entire study period except as rescue medication

Prohibited Medication	**Prohibited period**
treatment e.g., artesunate-amodiaquine (ASAQ), artesunate-pyronaridine, DHA-piperaquine, chloroquine, amodiaquine, quinine, quinidine, mefloquine, halofantrine, lumefantrine as monotherapy, artemisinin and its derivatives used as monotherapy: artemether, arteether, artesunate, dihydroartemisinin, proguanil, chlorproguanil, pyrimethamine, sulfadoxine, sulfalene, sulfamethoxazole, dapsone, primaquine, atovaquone.	
Herbal medication with antimalarial activity	12 hours before study entry and for entire study period
Other antimicrobials with antimalarial activity azithromycin, tigecycline, tetracycline, erythromycin, rifampicin, doxycycline, trimethoprim	12 hours before study entry and during entire study period
Any other **investigational treatment**	For entire study period
Aspirin and corticosteroids (might increase the risk for gastrointestinal bleeding)	For treatment duration and 7 days after last dose
Potential hepatotoxic drugs Alpha-methyldopa, Amoxicillin-clavulanic acid, Amiodarone, Bosentan, Carbamazepine, Dantrolene, Disulfiram, Etretinate, Fluconazole Glyburide, Halothane, Heparin, HMG-Co A reductase inhibitors, Isoniazid, Ketoconazole, Labetalol, Nicotinic Acid, Nitrofurantoin, NSAIDs (except paracetamol), Phenylbutazone, Phenytoin, Propylthiouracil, Protease inhibitors, Sulfonamides, Terbinafine, Trazadone, Troglitazone (withdrawn), Valproic Acid	For treatment duration and 7 days after last dose
Potential hepatotoxic herbs and alternative medications:Chaparral leaf, Ephedra, Gentian, Germander, Ji Bu Huan, Senna, Kava kava, Scutellaria (skullcap), Shark cartilage	For treatment duration and 7 days after last dose
Illicit drugs: Anabolic steroids, Cocaine, Ecstasy (MDMA), Phencyclidine (PCP)	For treatment duration and 7 days after last dose
Toxins: Carbon tetrachloride, Chloroform, Dimethylformamide, Hydrazine, Hydrochlorofluorocarbons, 2-Nitropropane, Trichloroethylene, Toluene	For treatment duration and 7 days after last dose
For drugs falling in above multiple categories, consider whichever is the longer duration as prohibited period.	

Table 6-6 Prohibited medications for participants on IV artesunate arms

Prohibited medication	Prohibited period
Drugs used as antimalarials other than the study drug, rescue medication and oral standard treatment e.g., artesunate-amodiaquine (ASAQ), artesunate-pyronaridine, DHA-piperaquine, chloroquine, amodiaquine, quinine, quinidine, mefloquine, halofantrine, lumefantrine as monotherapy, artemisinin and its derivatives used as monotherapy: artemether, arteether, artesunate, dihydroartemisinin, proguanil, chlorproguanil, pyrimethamine, sulfadoxine, sulfalene, sulfamethoxazole, dapsone, primaquine, atovaquone.	12 hours before study entry and during entire study period except as rescue medication
Other **antimicrobials with antimalarial activity** Azithromycin, tigecycline, tetracycline, erythromycin, rifampicin, doxycycline and trimethoprim	12 hours before study entry and during entire study period
Herbal medication with antimalarial activity	12 hours before study entry and during entire study period
Any other **investigational treatment**	For entire study period
Illicit drugs: Anabolic steroids, Cocaine, Ecstasy (MDMA), Phencyclidine (PCP)	For treatment duration and 7 days after last dose

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the participant throughout his/her entire participation in the trial. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

6.3.2 Treatment assignment, randomization

At Day 1, all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These

randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

Randomization will be stratified by country and if any pretreatment of antimalarial drugs before screening period for each cohort.

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

6.4 Treatment blinding

This is an open label study so that treatments will not be blinded for participants and investigator staff.

In order to minimize the potential impact of treatment knowledge, treatment allocation, dose information, PK/AAG assessment schedule and concentration data, as well as other data that may result in systematic unblinding will not be available to the Clinical Trial Team (CTT) (particularly clinicians, trial statisticians, trial programmers) until the database is locked after IA of Cohorts 1-2. After interim database lock, the CTT would be unblinded with the results, however, the blinding will then be continued for Cohorts 3-5 until the final database is locked. Further details on data handling are documented in the appropriate data handling plan (DHP)/data management plan (DMP). The pharmacokineticist will be unblinded for PK and AAG data for the entire duration of the study (i.e. Cohorts 1-5). In order to develop suitable exposure-response models, pharmacometrician could have early access of PK and selected efficacy/safety data prior to interim database lock and database lock. Clinical/medical reviewers independent of CTT will have access to unblinded data to review the safety data for decisions relating to the stopping criteria of the cipargamin treatment arms.

If required, summaries of results by treatment arm will be prepared for Data Monitoring Committee (DMC) assessments. The DMC reports will be prepared by an independent team (refer Section 10.2.4).

The bioanalyst will request a copy of the randomization list to facilitate analysis of the samples. The bioanalyst will provide the sample data to the team under blinded conditions. The bioanalyst will keep this information confidential and will share it only post database locks.

6.5 Dose escalation and dose modification

6.5.1 Dose modifications

Investigational or other study treatment dose adjustments and/or interruptions are not permitted at individual participant level. For possible dose adjustments at study level, refer to Table 4-1.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Qualified site personnel will be designated, as appropriate, by the investigator for both preparation and administration of all doses of study medication for each participant. The exact dosages administered (based on the weight bands) will be recorded on the Dosage Administration Record CRF, along with any additional comments.

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all participants, as detailed in Section 12.5.3.

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

6.6.2 Recommended treatment of adverse events

Medication used to treat adverse events (AEs) must be recorded on the appropriate page of the CRF. There is no specific recommendations and AEs should be treated as per local guidance.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs (See Section 6.1.1).

For details on drug management including preparation and handling, please refer to the Pharmacy Manual prior to administration.

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

Investigator staff will identify the study medication kits to dispense to the participant 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 participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatments along with Coartem (standard of care) and IV artesunate (rescue) 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 treatments must be stored according to the instructions specified on the labels and in the Investigator`s Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis designee.

For the specific detailed dosage preparation of IV cipargamin or IV artesunate, refer to Pharmacy Manual. The current IV cipargamin formulation should not be administered IM or SC in humans.

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 participant except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of these treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Participants will be requested to return all dispensed used (or unused) Coartem during their follow-up visits or before the end of the study.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the monitor (Novartis or designated CRO) or to the Novartis address provided in the investigator folder at each site. If the site has a drug destruction policy, they might also be instructed to destroy drugs locally as per their process.

6.7.1.2 Handling of additional treatment

The following additional treatments are to be monitored:

- Coartem as standard of care for oral therapy (dispensed via IRT)
- IV artesunate as rescue medication (dispensed via IRT)
- Other medications including supportive therapies as concomitant medication

Details are described in the CRF completion guidelines.

6.7.2 Instruction for prescribing and taking study treatment

Cipargamin (KAE609)

IV cipargamin should be administered for a minimum of 24 hours (2 doses), regardless of the participant's ability to tolerate oral medication earlier. After at least 2 doses or a maximum of 3 daily doses of IV cipargamin, the participant should be switched to a complete treatment course of oral Coartem or rescue medication (see sections Section 6.1.2.1, Section 6.2.1).

Preparation:

The specified dose of cipargamin should be prepared by withdrawing the calculated volume from the 2ml vial containing either 10mg/ml or 15mg/ml KAE609. For dose preparation refer to the Pharmacy Manual.

As described in Section 4.2 doses in Cohorts 3-5 might be adjusted during the trial to reach optimal exposure in the different age groups.

Administration

Cipargamin should be administered as a slow bolus injection over two minutes by the intravenous route. It should not be administered intramuscularly or subcutaneously.

Artesunate

IV artesunate should be administered for a minimum of 24 hours (3 doses), regardless of the participant's ability to tolerate oral medication earlier. After at least 24 hours of IV artesunate, the participant should be switched to a complete treatment course of oral Coartem (see Section 6.1.2.1).

Artesunate should be prepared according to the supplied instructions in label for IV administration and injected by the IV route as a bolus over 1-2 minutes.

Coartem

Coartem® should be administered according to the supplied label and with food/drink (broth, sweetened condensed milk, etc.) as appropriate.

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

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

7 Informed consent procedures

Eligible participants may only be included in the study after parents, legal guardians or caregivers provide written (witnessed, where required by law or regulation), Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB)-approved informed consent.

In cases where the participant's representative gives consent, the participant should be informed about the study to the extent possible given his/her understanding. If the participant is capable of doing so, he/she should indicate agreement by personally signing and dating the written informed consent document or a separate assent form.

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

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) and assent form that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF or the assent form as suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Information about common side effects already known about the investigational drug can be found in the Investigator`s Brochure and in the Prescribing Information for marketed drugs. This information will be included in the participant informed consent and should be discussed with the participant during the study. Any new information regarding the safety profile of the investigational drug that is identified between Investigator`s Brochure updates will be communicated as appropriate, for example, via an investigator notification or an aggregate

safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Main Study Consent for parents / legal guardians to give consent for their child
- Main Study Consent for participants entering adulthood
  Both Main Study Consents 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
- Model Participant Information and Adolescent Assent 12-17 years old (≥ 12 years to < 18 years).
- Model Participant Information and Adolescent Assent 7-11 years old (7 years to < 12 years).
  for adolescents to express their understanding of the purpose of this study and what will happen to them if their parent(s)/legal guardian(s) give their consent for their participation in this study
- As applicable, Pregnancy Outcomes Reporting Consent for female pregnant participants and pregnant partner of male participants
- There may be a short initial Consent followed by the Main Study Consent, as this disease is to be handled like emergency situations.

Female participants of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male participants must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

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

8 Visit schedule and assessments

Assessment schedules lists all of the assessments when they are performed for participants of Cohorts 1-3 and Cohorts 4-5 separately in Table 8-1 and Table 8-2 respectively. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule Table 8-1 and Table 8-2. Assessments should be performed as per the assessment schedules or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final follow-up visit (first IV treatment +28 days) will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

Table 8-1 Assessment Schedule, Cohorts 1-3

Period	Screening	Hospitalization																				Discharge day[1]
Visit Name	Screening[2]	D1[2]									D2						D3[3]				D4
Days	(-3 to 0 h)	1									2						3				4
Time (post-dose)	-	0h[4]	2m	10m	30m	1h	2h	4h	6h	12h	18h	24hm	24.02hm	25h	30h	36h	42h	48hm	48.02hm	49h	60h	72h
Informed consent[5]	X																					
Inclusion / Exclusion criteria	X																					
Demography	X																					
Medical history/current medical conditions	X																					
Malaria Blood Film for parasite count and gametocyte count	X	X[6]				X	X	X	X	X	X	X			X	X	X	X				X
Physical Examination	S								S	S	S	S				S		S				S
Neurological Examination	X								X	X	X	X				X		X				X
Other severe malaria examinations[8]	X								X	X	X	X				X		X				X
Body Temperature	X	X			X				X	X	X	X				X		X				X
Vital Signs (blood pressure, pulse)	X	X			X				X	X	X	X				X		X				X
Blood chemistry - Point of Care device Hepatic Panel	X									X		X				X		X				X
Blood chemistry - Point of Caredevice, Met Lac Panel	X								X	X		X				X		X				X
Hematological assessment - Point of Care device	X									X		X				X		X				X
Blood chemistry (INR and LDH) at local lab[9]		X[6]																				
Electrocardiogram (ECG)[10]		X[6]										X[11]						X[11]				X[11]
PK Collection[12]		X[6]	X	X		X		X		X		X	X	X		X		X	X	X	X	X
Alpha 1-Acid glycoprotein (AAG) blood collection[13]		X[6]										X						X				
Urine analysis - local lab	X											X				X		X				X
CCI																						
CCI																						
CCI																						
CCI																						
CCI																						
Pregnancy Test (serum)[7]	S																					
Body Height	X																					
Body Weight	X													X								
Administration of IV therapy - Cipargamin (KAE609) Or Artesunate[18]		X								X[19]		X						X				
Administration of Oral Therapy (standard of care)[20]																		X[20]				X[20]
Contact IRT	X	X										X						X				X
Adverse Events	Ongoing check																					
Prior and concomitant medications[21]	As required																					

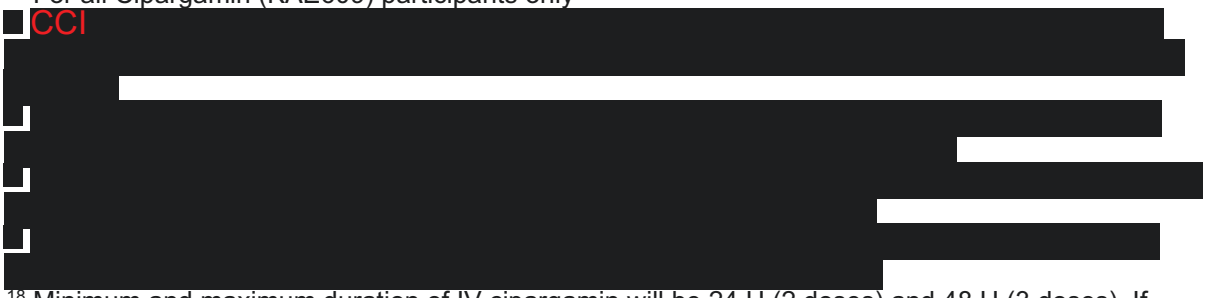
Period	Follow-up					Unscheduled visit
Visit Name	**D6**	**D8**	**D15**	**D22**	**D29 (EOS/PSW)[22]**	**Unscheduled visit**
Days	**6**	**8**	**15±1**	**22±2**	**29±2**	**-**
Time (post-dose)	**120h**	**168h**	**336h**	**504h**	**672h**	**-**
Informed consent[5]						
Inclusion / Exclusion criteria						
Demography						
Medical history/current medical conditions						
Malaria Blood Film for parasite count and gametocyte count	X	X	X	X	X	X
Physical Examination[7]	S	S	S	S	S	S
Neurological Examination	X	X	X	X	X	X
Other severe malaria examinations[8]	X	X	X	X	X	X
Body Temperature	X	X	X	X	X	X
Vital Signs (blood pressure, pulse)	X	X	X	X	X	X
Blood chemistry - Point of Care device Hepatic Panel	X	X	X	X	X	X
Blood chemistry - Point of Care device, Met Lac Panel	X	X	X	X	X	X
Hematological assessment - Point of Care device	X	X	X	X	X	X
Blood chemistry (INR and/or LDH) at local lab[9]		X[9]				
Electrocardiogram (ECG)[10]					X	X
PK Collection [12]	X	X				
Alpha 1-Acid glycoprotein (AAG) blood collection [13]						
Urine analysis - local lab	X	X	X	X	X	X
CCI						
CCI						
CCI						
CCI						
CCI						
Pregnancy Test (serum)[7]					S	
Body Height						
Body Weight					X	
Administration of IV therapy - Cipargamin (KAE609) Or Artesunate[18]						
Administration of Oral Therapy (standard of care)[20]	X[20]	X[20]				
Contact IRT	X	X	X	X	X	As required
Adverse Events	Ongoing check					
Prior and concomitant medications [21]	As required					

X Assessment to be recorded in the clinical database or received electronically from a vendor

S Assessment to be recorded only in source notes

[1] If participant is eligible for oral therapy and can be discharged per investigator opinion, discharge date will be noted. Earliest timepoint for discharge is 72 H (D4). However if a participant is not eligible to switch to oral therapy and needs to be on IV treatment then extend hospitalization and repeat all D4 assessments every 24 H till the participant is ready to take oral therapy.

[2] Screening and Randomization visit (D1, 0H) will occur on the same day within 3 hours of screening due to the acute need to treat severe malaria.
[3] If participant is eligible for oral therapy then first dose of oral treatment (Coartem) should be given at 48 H (D3), else continue IV therapy.
[4] D1 - 0 H is randomization visit.
[5] Prior to start of any study procedure
[6] Sample to be collected pre-dose
[7] Pregnancy results must be confirmed negative before dosing. Refer Section 8.4.6.
[8] Refer modified WHO Table 16-6 in Section 16.4 for detailed assessments.
[9] INR sample to be collected at pre-dose but only to be analyzed when participant is randomized. Follow-up post baseline samples should only be collected when required as per protocol during elevated lab parameters (refer Section 16.1) LDH to be collected at pre-dose and D8, and only to be analyzed when hemoglobin is decreased by ≥10 %
[10] ECG's should be taken in triplicate within 5 min after resting for at least 10 min in the supine position. Last ECG should be taken 24 hours after final IV drug dose. Pre-dose ECG can be taken in less than 30 mins before first dosing and all post baseline ECG assessments (from D2 and D2 onwards) should be taken in less than 15 min post-dose.
[11] ECG assessment after drug administration.
[12] For all Cipargamin (KAE609) participants only. Rich PK collection with 1 ml blood. For scheduled time: Pre-dose samples (0, 24h, 48h, 72h) should be taken in less than 15 min before the dosing; Post-dose samples as following (Day 1: 2 min: + 1 min; 10 min: ± 2 min; >10 min - 3 h: ± 10 min; >3 - <24 h: ± 30 min; Day 2: 24h02m: + 1 min; >24h10 min - 27 h: ± 10 min; >27 - <48 h: ± 30 min; Day 3: 48h02m: + 1 min; >44h10 min - 52 h: ± 10 min; >52 - <72 h: ± 30 min) Exact time to be recorded for samples taken in follow-up period (Day 6 and Day 8).
[13] For all Cipargamin (KAE609) participants only



[18] Minimum and maximum duration of IV cipargamin will be 24 H (2 doses) and 48 H (3 doses). If cipargamin participants require IV therapy beyond 3 doses, refer rescue medication criteria (Section 6.2.1). Minimum and maximum duration of IV artesunate will be 24 H (3 doses) and 7 D (8 doses).
[19] Day 1, 12 h dosing only for participants receiving IV artesunate
[20] First timepoint to switch from IV therapy to oral therapy is at 48 H. If participant is eligible, administer Coartem as per label. However, if participant is not able to tolerate oral therapy then continue with IV treatments and evaluate again at D4 and every 24h until participant receives oral therapy.
[21] All medication administered or taken by the participants up to 72 hours prior first dose has to be reported as prior medication in the appropriate Case Report Forms.
[22] EOS = End Of Study (D29) OR PSW = Premature Study Withdrawal (to be performed at last visit of the participant getting discontinued from the study)

Table 8-2 Assessment Schedule, Cohorts 4-5

Period	Screening	Hospitalization													Discharge day[1]	Follow-up					Unscheduled visit
Visit Name	Screening[2]	D1[2]								D2				D3[3]	D4	D6	D8	D15	D22	D29 (EOS/PSW)[4]	Unscheduled visit
Days	(-3 to 0 h)	1								2				3	4	6	8	15 ±1	22 ±2	29 ±2	-
Time (post-dose)	-	0h[5]	2m	30m	1h	2h	4h	6h	12h	18h	24h	30h	36h	42h	48h	72h	120h	168h	336h	504h	672h	-
Inclusion / Exclusion criteria	X																					
Informed consent[6]	X																					
Demography	X																					
Medical history/current medical conditions	X																					
Malaria Blood Film for parasite count and gametocyte count	X	X[7]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	S							S	S	S	S		S		S	S	S	S	S	S	S	S
Neurological Examination	X							X	X	X	X		X		X	X	X	X	X	X	X	X
Other severe malaria examinations[8]	X							X	X	X	X		X		X	X	X	X	X	X	X	X
Body Temperature	X	X		X				X	X	X	X		X		X	X	X	X	X	X	X	X
Vital Signs (blood pressure, pulse)	X	X		X				X	X	X	X		X		X	X	X	X	X	X	X	X
Blood chemistry - Point of Care device Hepatic Panel	X								X		X		X		X	X	X	X	X	X	X	X
Blood chemistry - Point of Care device, Met Lac Panel	X							X	X		X		X		X	X	X	X	X	X	X	X
Hematological assessment - Point of Care device	X								X		X		X		X	X	X	X	X	X	X	X
Blood chemistry (INR and/or LDH) at local lab[9]		X[7]																X[9]				
Electrocardiogram (ECG)[10]		X[7]									X[11]				X[11]	X[11]					X	X
Alpha 1-Acid glycoprotein (AAG) [12]		X[7]																				
PK Collection [13]			X		X						X				X							
Urine analysis - local lab	X										X		X		X	X	X	X	X	X	X	X
[redacted]																						
Body Height[16]	X																			X[16]		
Head Circumference[17]	X																			X		
Body Weight	X																			X		
Administration of IV therapy - Cipargamin (KAE609) Or Artesunate[18]		X							X[19]		X				X							
Administration of Oral Therapy (standard of care)[20]															X[20]	X[20]	X[20]	X[20]				
Contact IRT	X	X									X				X	X	X	X	X	X	X	As required
Adverse Events	Ongoing check																					
Prior and concomitant medications[21]	As required																					

[X] Assessment to be recorded in the clinical database or received electronically from a vendor.

[S] Assessment to be recorded only in source notes

[1] If participant is eligible for oral therapy and can be discharged per investigator opinion, discharge date will be noted. Earliest timepoint for discharge is 72 H (D4). However if a participant is not eligible to switch to oral therapy and needs to be on IV treatment then extend hospitalization and repeat all D4 assessments every 24 H till the participant is ready to take oral therapy.

[2] Screening and Randomization visit (D1, 0H) will occur on the same day within 3 hours of screening due to the acute need to treat severe malaria.

[3] If participant is eligible for oral therapy then first dose of oral treatment (Coartem) should be given at 48 H (D3), else continue IV therapy.

[4] EOS = End Of Study (D29) OR PSW = Premature Study Withdrawal (to be performed at last visit of the participant getting discontinued from the study)

[5] D1 - 0 H is randomization visit.

[6] Prior to start of any study procedure.

[7] Sample to be collected pre-dose.

[8] Refer modified WHO Table 16-6 in Section 16.4 for detailed assessments.

[9] INR sample to be collected at pre-dose but only to be analyzed when participant is randomized. Follow-up post baseline samples should only be collected when required as per protocol during elevated lab parameters (refer Section 16.1) LDH to be collected at pre-dose and D8, and only to be analyzed when hemoglobin is decreased by ≥10 %.

[10] ECG's should be taken in triplicate within 5 min after resting for at least 10 min in the supine position however only if supine is feasible and triplicates possible. Last ECG should be taken 24 hours after final IV drug dose. Pre-dose ECG can be taken in less than 30 mins before first dosing and all post baseline ECG assessments (D2 and D2 onwards) should be taken in less than 15 min post-dose.

[11] ECG assessment after drug administration.

[12] For all Cipargamin (KAE609) participants only.

[13] For all Cipargamin (KAE609) participants only. Sparse PK collection with 0.5 ml blood. Missed PK sampling time should be taken as soon as possible and actual time should be recorded. For scheduled time: Pre-dose samples (24h and 48h) should be taken in less than 15 min before the dosing; Day 1: 2 min: + 1 min; 60 min: ± 10 min

[CCI] [redacted]

[CCI] [redacted]

[16] Body height at the end of the study to be measured only for children participants < 2 years of age.

[17] Head circumference should be measured only for children participants < 2 years of age.

[18] Minimum and maximum duration of IV cipargamin will be 24 H (2 doses) and 48 H (3 doses). If cipargamin participants requires IV therapy beyond 3 doses, refer rescue medication criteria (Section 6.2.1). Minimum and maximum duration of IV artesunate will be 24 H (3 doses) and 7 D (8 doses).

[19] Day 1, 12 h dosing only for participants receiving IV artesunate.

[20] First timepoint to switch from IV therapy to oral therapy is at 48 H. If participant is eligible, administer Coartem as per label. However, if participant is not able to tolerate oral therapy then continue with IV treatments and evaluate again at D4 and every 24 H until participant receives oral therapy.

[21] All medication administered or taken by the participants up to 72 hours prior first dose has to be reported as prior medication in the appropriate Case Report Forms.

8.1 Screening

The investigator or their delegate will contact the IRT when a participant enters screening.

In the case where a safety laboratory assessment at screening/baseline is outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to randomization and must be completed within 3 hours of the screening period. In this case, another consent/assent would not be required and the original participant ID number assigned will be used. However, if the repeat value remains outside of the specified ranges, the participant must be captured as a screen failure.

Rescreening of a participant with a new episode of malaria who had failed screening assessments earlier in the study is allowed per investigator's discretion and/or after consultation with the sponsor. In this case, a new consent/assent would be required and new participant ID number will be used.

IRT will be recontacted after confirming that the participant fulfills all the inclusion/exclusion criteria, to get a unique medication number for the package of study treatment and the dose level to be dispensed to the participant.

8.1.1 Information to be collected on screening failures

Participants who sign an informed consent form and are subsequently found to be ineligible prior to randomization will be considered screen failures. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see Section 10.1.3 for SAE reporting details). If the participant fails to be randomized, the IRT must be notified that the participant was screen failed.

Participants who are randomized and fail to start treatment, e.g. participants randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

8.2 Participant demographics/other baseline characteristics

Participant demographic and baseline characteristic data to be collected on all participants and to be entered in eCRF by site personnel:

- Age
- Gender
- Body weight
- Head circumference (for children < 2 years)
- Body height
- Body temperature
- Vital signs
- Physical examination (data to be entered only in source notes)

- Neurological examination
- Other severe malaria symptoms examination
- Prior and concomitant medications
- Blood chemistry and hematology
- Urinalysis
- Pregnancy test (data to be entered only in source notes)
- Malaria blood film for parasites and gametocytes count and plasmodium species determination
- Medical history
- Triplicate 12-lead ECG

The following data are not to be assessed or entered by clinical site, these will be generated by third parties:

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

8.3 Efficacy

Efficacy assessments will be based on initial parasite clearance and clinical outcome of severe malaria signs (including neurological sequelae).

8.3.1 Clinical outcome in moderately severe and severe malaria

8.3.1.1 Clinical success

Clinical success in study participants will be evaluated at various time points throughout the study. Clinical success at 48 hours is considered as a key secondary endpoint. Clinical success is a composite endpoint based on the criteria shown below (Table 8-3).

Table 8-3 Definition of clinical success in the study at any time point

Disease criteria	Clinical failure (participant meeting any of the criteria)	Clinical success (participant has to meet all criteria)
Dead or Alive	Dead#	Alive
Presence of asexual parasites	Yes	No
Presence of any of the key signs of severe malaria*	Yes	No
# Death - All in hospital deaths and malaria related deaths (as per adjudication committee) occurring after hospital discharge * Key signs of Severe Malaria defined as 1) Altered consciousness (including prostration) – Prostration (inability to sit or drink or breast feed) or Glasgow Coma Score < 11 (in participants > 5 years of age) or a Blantyre coma score of < 3 in children (≤ 5 years) 2) Renal impairment – SCr ≥ 3x ULN or Absolute SCr >3mg/dL or use of Renal Replacement Therapy (RRT) 3) Acidosis – Plasma lactate > 4 mmol/L or Respiratory distress defined as rapid, deep and labored breathing (costal indrawing, use of accessory muscles and nasal flaring).		

8.3.1.2 Signs of severe malaria

Participants will be monitored for the presence of the following signs of severe malaria during the entire study duration:

- Altered consciousness - Prostration or GCS < 11 for participants > 5 years / BCS < 3 for participants ≤ 5 years of age
- Renal Impairment - Serum creatinine > 3xULN or > 3 mg/dL or need for renal replacement therapy
- Acidosis - Serum lactate > 4 mmol/L
- Respiratory distress - present or absent
- Severe anemia - Hb < 5 g/dl or Hb < 7g/dl in pediatric and adults respectively or need of blood transfusion
- Jaundice - Serum bilirubin > 3 g/dl
- Hypoglycemia- plasma glucose < 40 mg/dL

8.3.1.3 Neurological assessment

Detailed neurological examination will be conducted and relevant medical history collected under the following categories to assess the extent of neurological signs and symptoms at baseline and to monitor the extent of neurological sequelae in follow-up visits:

Table 8-4 Summary of Neurological assessment

Assessment parameter		**Type of information in CRF**
Consciousness	Glasgow Coma Score (GCS*) for participants > 5 years Blantyre Coma Score (BCS*) for participants ≤ 5 years	Score for individual component of GCS and BCS Total GCS or BCS calculated centrally based on individual components
	Prostration	Yes or No
Cranial Nerve Palsy	4th, 6th and 7th Nerve	Palsy – present or absent If present – Right or Left nerve palsy
Motor system	Posturing	Abnormal posture - Yes or No If yes, Type of posture - Decerebrate/Decorticate/Opisthotonus/ Hemiplegic
	Cerebellar Ataxia	Present or Absent
	Strength	Presence or absence of following - Monoplegia or Monoparesis - Hemiplegia or Hemiparesis - Quadriplegia or Quadriparesis
	Deep Tendon reflex (Biceps, Triceps, Knee and Ankle) increased	Yes or No
	Increased Tone (Upper Limb and Lower Limb)	Yes or No
Convulsions	Type of convulsion	Generalised/Focal/Focal with secondary generalisation
	Presence of ≥ 2 episodes of convulsions excluding febrile seizures in the last 24 hours (for baseline visit) or since last visit (for follow-up visits)	Yes or No
	Any episode of convulsion lasting ≥ 15 min	Yes or No
Sense organs (Examination more useful at time of hospital discharge and in follow-up visits)	Vision	Check both eyes individually Graded as: • Child can see • Visual impairment unilateral/bilateral • Total blindness unilateral/bilateral

Assessment parameter		**Type of information in CRF**
	Hearing	Check both ears individually Graded as: • Can hear well • Possible hearing impairment unilateral / bilateral • Total deafness unilateral/bilateral

Assessment parameter		Type of information in CRF
	Speech	To be checked only for kids > 18 months Graded as: • Normal • Speech Impairment • Unable to speak
For details of GCS and BCS refer to Section 16.6		

Detailed methodology for each of the neurological assessments will be provided in a neurological assessment manual and the relevant site staff will be trained prior to the start of the study to maintain uniform standard of neurological examination across the study sites.

Based on the results from the neurological examination of every participant, neurological sequelae will be graded by the neurological sequelae adjudication committee. Further details about grading of neurological sequelae will be mentioned in adjudication committee charter.

8.3.1.4 Other clinical outcome assessments

In addition to the composite endpoint for clinical success as defined in Section 8.3.1.1, individual signs of severe malaria as defined in Section 8.3.1.2 will be closely monitored and assessed throughout the study.

Furthermore, participants will be monitored for time to start oral therapy, time to hospital discharge and time to recover from prostration also to gather holistic information about the clinical outcome of participants across treatment arms.

8.3.2 Parasitemia assessment

Malaria blood films will be prepared to determine parasite counts of asexual and sexual forms of *P. falciparum* at baseline and all visits during the study. This data will be used to assess parasite reduction or reappearance over entire study duration. Primary endpoint of proportion of participants with at least 90% *P. falciparum* parasite reduction at 12 hours is based on this assessment as well as a number of secondary endpoints related to parasitological response and parasite reduction or clearance.

Details of all parasitemia related assessments are outlined in respective manual. Quality checks of parasite readings will be part of the process.

Blood samples for molecular diagnostic purposes

Blood will be sampled for parasite genotyping as indicated in the assessment schedule (Table 8-1 and Table 8-2).

At screening, a blood sample will be collected in all participants fulfilling eligibility criteria for inclusion in the study. A second blood sample will be analyzed only in participants with re-appearance of parasites. This will allow to distinguish between recrudescence and a new infection. Sample analysis will be performed at a pre-selected reference laboratory.

Microscopic identification of *Plasmodium* species might be confirmed with PCR-based methods on blood samples collected at relevant time points.

All parasite samples at baseline and other selected time points including re-appearance of parasites will also be screened for specific genes/single-nucleotide polymorphisms (SNPs) that are known as markers for *P. falciparum* drug resistance.

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

8.3.3 Appropriateness of efficacy assessments

Parasite count is a standard assessment in malaria studies as it allows to quantify the efficacy of the study drug in eliminating the parasites. In this study parasite reduction ≥ 90% at 12h is used as the primary endpoint as it is expected to allow differentiation between IV cipargamin and IV artesunate.

The composite clinical endpoint is used in this study for the first time. It is a secondary endpoint and if it is demonstrated to capture the patient's clinical course appropriately might be used as primary endpoint in phase III studies. Previous studies in severe malaria have used mortality-based endpoints. Through these studies the current standard of care (IV artesunate) has been established and generally demonstrates high efficacy. As such, a very large sample size would be required in today's situation to demonstrate statistical significance and exposing large numbers of patients to an investigational treatment is not considered appropriate. Additionally, mortality as an endpoint does not capture the clinical improvement of the treated patients adequately.

The individual assessment of all symptoms of severe malaria as secondary endpoints, will allow an in-depth analysis of the drug efficacy.

8.4 Safety

Safety assessments to be conducted in the study include:

- Physical examination
- Vital signs
- Height and weight (including Head circumference of children < 2 years)
- Laboratory evaluations
- ECG evaluations
- Pregnancy assessment

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

8.4.1 Physical Examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological assessment.

Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made

after signing informed consent that meet the definition of an Adverse Event must be recorded as an adverse event.

8.4.2 Vital signs

Vital signs will include systolic and diastolic blood pressure, temperature, pulse rate, and respiratory rate as per Table 8-1 and Table 8-2. After the participant has been still for five minutes (as much as possible), systolic and diastolic blood pressure will be measured three times using a standard device, with an appropriately sized cuff. Repeat measurements will be made at 1-2 minute intervals and the mean of the three measurements will be used.

Temperature will be taken using a standard thermometer, for 5 minutes before reading.

8.4.3 Height and Weight

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 Table 8-1 and Table 8-2.

For children < 2 years, head circumference will be measured at baseline and study completion.

8.4.4 Laboratory evaluations

The following laboratory assessments will be performed as per the schedule mentioned in Table 8-1 and Table 8-2. Details of the assessments are mentioned below in Table 8-5.

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate.

Table 8-5 Details of Laboratory Assessments

Test Category	Test Name
Hematology	Hemoglobin, hematocrit, red cell count (RBC and reticulocytes), white blood cell (WBC) count with differential (absolute value preferred, percentages are acceptable) (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other), and platelet count to be assessed from point of care device. In case of non-availability of the point of care device due to any reason, local laboratory evaluation is preferred.
Chemistry	Albumin, Alkaline phosphatase (ALP), ALT (SGPT), AST (SGOT), Bicarbonate, Direct Bilirubin (DBIL), Bilirubin (TBIL), Blood urea nitrogen (BUN), Calcium, Creatinine, eGFR, Potassium, Glucose, Lactate and Sodium from point of care device. LDH, INR at local laboratory. In case of non-availability of the point of care device due to any reason, local laboratory evaluation is preferred.
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) To be assessed at locally
Additional tests	CCI
Pregnancy Test	Serum pregnancy test to be assessed at locally (via serum pregnancy kits, if not available then as local laboratory)

8.4.5 Electrocardiogram (ECG)

ECGs should be taken in triplicate within 5 minutes (after 10 minutes rest in the supine position to ensure a stable heart rate according to the ECG investigator manual) for participants in Cohorts 1-3. For participants in Cohorts 4-5 ECG should be taken in the supine position if feasible and in triplicates if possible. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. For assessments where PK samples are required at 2 mins post drug administration then in those instances after drug administration, first PK sample will be collected followed by ECG, vital signs and then remaining blood sampling.

Heart rate-corrected QT interval (QTc) should be calculated by using both Fridericia's and Bazett's QT correction formula (QTcF and QTcB, respectively). Fridericia formula (QTcF) should be used for making clinical decisions.

Triplicate 12 lead ECGs are to be collected with ECG machines supplied by the central laboratory. Initial manual readout will be done locally in order to detect significant safety findings and allow for immediate response if needed. Local readout will be used for inclusion/exclusion purposes as central readout is not available within 3 hours.

In the event that a clinically significant ECG abnormality is identified at the site (e.g., severe arrhythmia, conduction abnormality of QTcF > 500 ms) the SAE must be reported according to the procedure described in Section 10.1.2. If the participant is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

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

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

Any post-dose average QTcF > 500 ms will result in treatment discontinuation (for details refer to Section 6.2.1 and Section 9.1.1).

Assessments will be done as indicated in the study assessment Table 8-1 and Table 8-2. All ECGs will be assessed centrally by an independent and blinded (with age of participant identified) cardiologist.

8.4.6 Pregnancy

All pre-menopausal female participants who are not surgically sterile will have pregnancy testing as per Section 8.1. Serum pregnancy test will be performed at screening and at the end of the study. If the screening serum pregnancy test is positive, the participant will not be enrolled in the study. Additional pregnancy testing might be performed if required locally. If during the study, the participant is found to be pregnant, the participant must contact the investigator immediately and study treatment will be discontinued (see details in Section 9.1.1).

Pregnancy test and associated results will not be collected on the CRF.

Participants of child-bearing potential are defined as all women physiologically capable of becoming pregnant. This includes female pediatric participants who are menarchal or become menarchal during the study.

The required contraception methods and their duration for women participants are described under exclusion criteria.

For sexually active male participants also follow recommendation as per Section 5.2 under exclusion criteria.

8.4.7 Appropriateness of safety measurements

CCI

8.5 Additional assessments

8.5.1 Pharmacokinetics

PK samples will be collected at the visits defined in the assessment schedule (Table 8-1 and Table 8-2). Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing and shipment. See the potential use of residual samples for more information.

In order to better define the PK profile, the timing of the PK sample collection may be altered based on emerging data.

Pharmacokinetic (PK) samples will be obtained and evaluated in all participants randomized to cipargamin (KAE609).

The parent drug concentration in plasma samples will be determined by a validated LC-MS/MS method; the anticipated Lower Limit of Quantification (LLOQ) is 1 ng/ml or better.

Concentrations will be expressed in mass per volume units and will refer to the free base.

Concentrations below the LLOQ will be reported as “zero” and missing data will be labeled as such in the Bioanalytical Data Report.

For standard pharmacokinetic abbreviations and definitions, see the list provided at the beginning of this protocol.

The following pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher) wherever possible: C_{max}, T_{max}, AUC_{last}, AUC_{inf}, AUC_{0-t}, and $T_{1/2}$ from the plasma concentration-time data. In case of sparse sampling, summary statistics of concentrations-time data will be listed.

The linear trapezoidal rule will be used for AUC calculation. Regression analysis of the terminal plasma elimination phase for the determination of $T_{1/2}$ will include at least 3 data points after

C_{max}. If the adjusted R^2 value of the regression analysis of the terminal phase is less than 0.75, no values will be reported for $T_{1/2}$, AUC_{inf} and CL/F.

8.5.2 CCI

CCI

Table 8-6 CCI

CCI

8.5.3 Other Assessments

8.5.3.1 Exploratory assessments

CCI

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

Discontinuation of study treatment for a participant occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the participant or the investigator.

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

Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment (see Section 6.2.3)
- Use of IV rescue medication (see Section 6.2.1)
- Any situation in which study participation might result in a safety risk to the participant (eg., see Section 16.1, Section 16.2)
- Diagnosed with COVID-19 infection

If discontinuation of study treatment occurs, then investigator should make a reasonable effort to understand the primary reason for the participant’s premature discontinuation of study treatment and record this information.

Participants 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 'Withdrawal of Informed Consent' section). **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, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

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

After study treatment discontinuation, 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 participant’s discontinuation from study treatment.

9.1.1.1 Replacement policy

For any cohort, enrollment of additional participants to the current cohort will be considered if there is less than the required number of evaluable participants. If the dose is considered unsuitable in the first few participants of the current cohort, enrollment of another set of new participants to the cohort to be treated with a different dose will be considered.

9.1.2 Withdrawal of informed consent

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a participant:

- Does not want to participate in the study anymore
- Does not allow further collection of personal data, and
- Does not want any further visits or assessments

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

Where consent to the use of personal and coded data is not required, participant therefore cannot withdraw consent. They still retain the right to object to the further use of personal data.

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 participant are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the participant's study withdrawal should be made as detailed in the assessment table (Table 8-1 and Table 8-2).

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

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

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant and/or care giver (accompanied with participant), e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including

slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as prematurely withdrawn. 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 participant's interests. The investigator or sponsor, depending on the local regulation, will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

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

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

Participants who discontinue study drug and are put on rescue medication will be followed for the entire study duration (i.e., until study Day 29).

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

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

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a participant or clinical investigation participant 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 individual participant and identifying adverse events.

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

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

Adverse events must be recorded 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 10.1.2):

1. The Common Toxicity Criteria (CTC) AE grade version 5

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version.

2. its relationship to the study treatments (ie IV cipargamin or IV artesunate). 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 participant
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment

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

- Dose not changed
- Drug interrupted/withdrawn

6. its outcome (i.e. recovery status or whether it was fatal)

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

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

Adverse event monitoring should be continued until the end of study visit.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (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 can be found in the Investigator`s Brochure. For comparator and oral standard of care treatments, safety-related information is listed in the product information.

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

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

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

10.1.2 Serious adverse events

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

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant 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 was more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition eg hospitalized for follow-up visit without worsening of underlying condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the participant'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 participant 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 participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

- Protocol specific SAEs
    - Hepatic: Refer to Table 16-2, including potential Hy's Law cases as defined in Table 16-1
    - Cardiac: Absolute QTcF > 500 ms (confirmed by repeat ECGs)

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

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

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

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant (or participant's representative) has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

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

If the SAE is not previously documented in the Investigator`s Brochure for IV cipargamin or Package Insert for IV artesunate (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department (Novartis safety department) associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced more than 30 days after the last administration of study treatment should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Following delivery, the newborn should be followed up for up to 12 months for any development abnormality or any

issue not seen at birth as per the standard safety processes concerning follow-up for pregnancy outcome and related data in CT cases.

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 with any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

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

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

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

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

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

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure participant 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 16-1 in Appendix 1 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2. Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

These liver chemistry repeats should be performed using the local laboratory used by the site. Repeated laboratory test results must be reported as appropriate.

- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
- These investigations can include based on 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.

10.2.2 Renal safety monitoring

Once a participant is exposed to study treatment, renal laboratory alerts or renal safety events should be monitored and followed up by the investigator or designated trial staff as summarized in Table 16-3 and Table 16-4.

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

Renal events in the pediatric population should be defined as 25% decrease in eGFR using age-specific normal values for eGFR and serum/urinary normal values. The Schwartz age- specific eGFR formula (Schwartz and Furth 2007) is commonly used to estimate eGFR in the pediatric population. Refer to Section 16.3 for Schwartz formula calculation guidance, and normal age-related pediatric eGFR values. Due to the low values of serum creatinine, small changes can be interpreted as substantial changes in eGFR which can be ignored if eGFR is > 90 ml/min/1.73 m^2.

10.2.3 Special Hematology monitoring

Hematology parameters are closely monitored throughout the study to detect early and delayed hemolytic anemia.

Early Hemolytic anemia is defined as 10% or greater decrease in hemoglobin levels and an increase of LDH levels to >390 U/L, or an increase of ≥10% above baseline occurring up to Day 8 of the study.

Delayed hemolytic anemia might occur > 7 days after initiation of parenteral study drug (IV artesunate or IV cipargamin) during the study period. The event is characterized by a 10% or

greater decrease in hemoglobin levels accompanied by increase of LDH levels to >390 U/L, or an increase of ≥ 10% compared to the values measured at Day 8 of the study.

Decrease in hemoglobin 10% or greater (compared to baseline up to Day 8 and compared to Day 8 values after until the end of study), must be always followed by LDH measurement for confirmation of hemolysis and requires close observation, follow-up monitoring and contributing factors are to be recorded on the appropriate CRFs.

10.2.4 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. Planned DMCs will occur at the end of Cohort 2 and at the end of Cohort 4. Additional DMC meetings may be conducted depending on the need per study data. The DMC will assess at defined intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify, or terminate a trial.

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

10.2.5 Adjudication committee

Two independent adjudication committees will be set up to assess if deaths reported in the study are malaria related and to grade reported neurological sequelae respectively. Further details of the adjudication committee's composition, organization and responsibilities will be described in the adjudication committee charter.

11 Data Collection and Database management

11.1 Data collection

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 EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

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

After final database lock, the investigator can retrieve participant data from a portable document format (PDF) generator or will receive copies of participant data for archiving at the investigational site.

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

11.2 Database management and quality control

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

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

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

Once all the necessary actions have been completed and the database has been declared to be complete and accurate. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis / delegated CRO representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a Novartis/delegated CRO organization.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the

study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

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

12.1 Analysis sets

The analysis includes the following data sets:

- Randomized set: all participants who are randomized.
- Full analysis set (FAS): the FAS will be comprised of all participants from Randomized set that have baseline *P. falciparum* count > 0 and take at least one dose of IV study treatment during the treatment period. Following the intent-to-treat principle, participants will be analyzed according to the treatment group assigned at randomization.
- Per-protocol set (PPS): Participants in the FAS who satisfy the inclusion criterion for severe malaria and do not have protocol deviations that impact on efficacy.
- Safety set (SS): All participants who take at least one dose of study drug during the treatment period. Participants will be analyzed according to treatment received.
- PK analysis set: All participants who have at least one valid (i.e. not flagged for exclusion) PK concentration measurement, receive at least one dose of study drug, and do not have any protocol deviations that impact on PK data.

Full details will be described in the statistical analysis plan (SAP). Important protocol deviations for exclusion from PPS or PK analysis set will be identified by the clinical team before Cohort 1 and 2 database lock and the final database lock.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed by cohort and treatment group and summarized descriptively by treatment group for each cohort, Cohorts 1 and 2 pooled), and all cohorts pooled for the FAS and Safety set if Safety set is different from FAS.

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

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, and treatment group for each cohort, Cohorts 1 and 2 pooled and all cohorts pooled for the FAS period.

12.3 Treatments

The Safety set will be used for the analysis below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum, and maximum will be presented.

The duration of exposure in number of doses and days to IV cipargamin (KAE609), IV artesunate, and Coartem will be summarized by means of descriptive statistics.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by cohort and treatment group and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group for each cohort and all cohorts pooled.

12.4 Analysis of the primary endpoint(s)/estimand(s)

The primary objective is to show that IV cipargamin is non-inferior to IV artesunate in the proportion of participants with ≥ 90% *P. falciparum* parasite reduction at 12 hours. These will be evaluated within each Cohort separately except Cohort 1, which will be combined with Cohort 2. The analysis will be performed on the FAS.

12.4.1 Definition of primary endpoint(s)/estimand(s)

A participant is considered as achieving ≥ 90% reduction in *P. falciparum* parasite from baseline at 12 hours (after the first IV dose) if *P. falciparum* asexual parasite reading at 12 hours is either absent or with a positive value that is ≤ 10% of the baseline value. See Section 2.1 for detailed definition of estimand.

12.4.2 Statistical model, hypothesis, and method of analysis

The statistical null hypothesis is that the difference in proportion of participants with ≥ 90% reduction at 12 hours between a cipargamin dose regimen and artesunate is ≤ -0.1 with the alternative hypothesis that the difference is > -0.1.

The statistical hypothesis will be tested at the 2-sided 10% significance level without multiplicity adjustment for multiple comparison due to multiple cipargamin dose regimen. Two-sided 90% confidence intervals (CI) for the difference between each cipargamin dose regimen vs artesunate will be provided using the Wilson uncorrected method based on FAS; a cipargamin dose regimen is said to be non-inferior to artesunate if the lower limit of CI is > -0.1.

The hypothesis will be tested for each Cohort separately except Cohort 1, which will be combined with Cohort 2.

Data from participants in Cohorts 1 and 2 will be pooled together to allow evaluation of non-inferiority to artesunate since both cohorts include participants aged ≥ 12 years although participants in Cohort 1 are milder in clinical condition compared to participants in Cohort 2. The underlying assumptions are (1) the participants for each treatment group follow a binomial distribution separately in each Cohort separately except Cohort 1, which will be combined with Cohort 2 (2) participants for each treatment group, follow the same binomial distribution in Cohorts 1 and 2.

12.4.3 Handling of intercurrent events of primary estimand

The primary estimand will account for the different intercurrent events as follows:

- If a participant receives any IV rescue antimalarial medication prior to the *P. falciparum* asexual parasite assessment at 12 hours, the participant will be classified as not achieving ≥ 90% reduction,
- If a participant dies prior to the *P. falciparum* asexual parasite assessment at 12 hours, the participant will be classified as not achieving 90% reduction.

Composite strategy is used to handle intercurrent events as the intercurrent events indicate that the study IV treatment is not working quickly enough to prevent clinical deterioration.

12.4.4 Handling of missing values not related to intercurrent event

All participants should be hospitalized at the time of 12 hours post treatment unless death or discontinuation from the study have occurred. Death is considered as an intercurrent events and is handled in Section 12.4.3. Any missing data not related to intercurrent events will be handled according to Table 12-1.

Since participants are hospitalized at 12 hours, these missing data should be rare. After receiving the IV study medication, a participant's parasite load should decrease over time such that the parasite count is lower at 12 hours than at previous visits (6 hours or earlier). That is, the probability that a participant achieves at least 90% parasite reduction is higher at 12 hours than at 6 hours. Therefore, the imputation of using parasite assessment at the latest visit prior to 12 hours is conservative. This imputation may slightly under estimate the proportion of participants with at least 90% parasite reduction at 12 hours.

Table 12-1 Handling of other events that may occur and affect derivation of primary endpoint

Event	Outcome
Discontinuation of study prior to parasite assessment at 12 hours, such as withdrawal of consent, COVID-19, etc.	Impute using the latest assessment prior to 12 hours including baseline. Note: the outcome is 'no' if baseline value is used.
Intermediate parasite count missing at 12 hours due to other reason (such as missing sample, technical reason, etc.)	

12.4.5 Sensitivity analyses for primary endpoint/estimand

After receiving antimalarial medication, a participant's parasite usually decreases log-linearly after a lag stage (White 2011, Flegg et al 2011). For artemisinin derivatives, parasitemia starts to decline in a log-linear manner almost as soon as parasiticidal drug concentrations are reached (White 2011). The Tmax is about 0.5 to 15 minutes for IV artesunate (Artesunate PI). The Tmax is about 4 hours for oral cipargamin and should be much shorter for IV cipargamin. Missing data of parasite counts at 12 hours could be well estimated using a log linear interpolation of the 2 parasite counts immediate before and after 12 hours. Since there are 3 planned parasite assessments on or after 2 hours, missing parasite count at 12 hours due to early discontinuation could be estimated using participant specific log linear regression if there are at least 2 parasite counts prior to the discontinuation. A sensitivity analysis will be performed using interpolation for missing data at intermediate time points and extrapolation using a log linear regression if there are at least 2 parasite counts prior to discontinuation. In the event that a participant does not have at least 2 parasite counts prior to discontinuation, the participant will be imputed as not achieving ≥ 90% reduction at 12 hours. Parasite counts below the limit of detection will be substituted using the half limit of detection.

The severity of disease is different between Cohort 1 and Cohort 2, which might impact the ability to achieve ≥ 90% parasite reduction, ie., resulting in a different binomial distribution between Cohorts 1 and 2. Therefore, two-sided 90% confidence intervals (CI) for the difference between each IV cipargamin dose regimen vs IV artesunate will be provided for Cohort 1 and Cohort 2 separately, using handling of missing values not related to intercurrent events specified in Section 12.4.4 and in this section.

12.4.6 Supplementary analysis

For each Cohort (except Cohort 1, which will be pooled with Cohort 2), the difference between a cipargamin dose regimen and artesunate in the proportion of participants with ≥ 90% reduction in parasite at 12 hours will be performed using the Fisher exact test.

For each cipargamin dose regimen that is selected for Cohorts 3-5, the difference versus artesunate in proportion of participants with ≥ 90% reduction in parasite at 12 hours will be evaluated by pooling data from all cohorts to show if the IV cipargamin dose regimen is superior to IV artesunate. The treatment difference will be evaluated based on 2-sided 95% CIs using a Mantel-Haenszel estimate of the common risk difference stratified by cohort (Cohorts 1 and 2 will be pooled together and used as a single stratum)(SAS manual version 13.2). P-values will be provided using a Cochran-Mantel-Haenszel test (CMH) stratified by cohort.

Similarly, between treatment difference will be evaluated in children by repeating the above supplemental analysis on pooled Cohorts from 3-5 only.

These supplement analyses target a different hypothesis to show superiority of each cipargamin dose regimen over artesunate and will be performed using the FAS and handling of missing values not related to intercurrent events according to Section 12.4.4 and Section 12.4.5.

12.4.7 Supportive analyses

The analyses specified in Section 12.4.2, Section 12.4.5 and Section 12.4.6, will be repeated using the PPS.

12.5 Analysis of secondary endpoints/estimands

Secondary endpoints will be descriptively presented and tabulated (n, mean, standard deviation, median, minimum, and maximum for continuous variables; n and percent for categorical variables) by treatment group for each cohort separately. Cohort 2 will be also evaluated together with Cohort 1. For stratified analysis, Cohort 1 will be combined with Cohort 2. The cipargamin dose regimen that is dropped after reviewing data from Cohorts 1-2 will be included only in the by-cohort analyses. For those treatment groups that are selected for Cohorts 3-5, descriptive statistics will be provided by treatment group using all pooled Cohorts (1-5) as well as separately pooled Cohorts 3-5. When data from different cohorts are pooled, an IV cipargamin regimen in Cohorts 3 to 5 (aged < 12 years) will be analyzed together with the equivalent IV cipargamin regimen as used in Cohorts 1 and 2 (aged ≥ 12 years). Such an IV cipargamin dose regimen will be denoted and labeled using the same cipargamin treatment group.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Secondary efficacy endpoints include:

- Clinical success at 24 hours, 48 hours, 72 hours, 96 hours, hospital discharge, Day 6, Day 8, Day 15, Day 22, and Day 29. See Table 8-3 for detailed information of defining clinical success. Clinical success at H48 is considered as a key secondary endpoint with a secondary estimand.
- Individual signs of severe malaria over time
  - Altered consciousness - Prostration or GCS < 11 for participants > 5 years old or BCS < 3 for participants ≤ 5 years old
  - Renal Impairment- Serum creatinine > 3 x ULN or > 3 mg/dL or need for renal replacement therapy
  - Acidosis- Serum lactate > 4 mmol/L
  - Respiratory distress – present or absent
  - Severe anemia- Hb < 5 g/dl or Hb < 7g/dl in pediatric and adults respectively with parasite count of > 10,000/µl or need of blood transfusion
  - Jaundice- Serum bilirubin > 3 g/dl with parasite count of > 100,000/µl
  - Hypoglycemia- plasma glucose < 40 mg/dL
- Proportion of participants with convulsion developing or persisting > 6 hour after start of IV study treatment
- Proportion of participants developing any new severe malaria signs (as per WHO severe malaria criteria) after treatment
- Proportion of participants with neurological sequelae at Day 2
- Proportions of participants with ≥ 90% *P. falciparum* asexual parasite reduction from baseline at 24 and 48 hours
- *P. falciparum* asexual parasite reduction ratios (PRR) at 12, 24 and 48 hours
- Time to *P. falciparum* asexual parasite clearance (PCT) (in hours), defined as time from the first IV study medication until the first total and continued disappearance of asexual parasite forms which remained at least a further 48 hours,

- Time to fever clearance (FCT) (in hours), defined as time from the first IV study medication until the first time the axillary body temperature decreased below and remained below 37.5°C axillary or 38.0°C oral/tympanic/rectal for at least a further 24 hours,
- Time to recover from prostration (in hours)
- PCE slope half-life
- Proportion of participants with recrudescence and reinfection by Day 29

Analysis of secondary estimand

The clinical success at 48 hours (see Table 8-3) for definition of clinical success and Section 2.2 for definition of estimand) will be evaluated using the FAS with data from all cohorts pooled.

Intercurrent events and other non-intercurrent events including partial missing data that may occur and affect the derivation of secondary estimand will be handled in Section 12.2. Note: partial data missing should be rare since participants are still hospitalized at 48 hours.

Table 12-2 Handling of intercurrent events and other events that may occur and affect the derivation of secondary estimand

Event	Outcome
Receive IV antimalarial rescue medication prior to 48 hours	Not clinical success
Discontinue the study prior to 48 hours, such as withdrawal of consent, COVID-19, etc.	Not clinical success due to early discharge
Missing parasite assessment at 48 hours[$]	• Not clinical success if asexual parasites present in the latest visit prior to 48 hours • Ignored[*] otherwise
Altered consciousness: missing Prostration, missing Glasgow Coma Score or missing Blantyre coma score in relevant age groups[$]	Use the result from the latest visit prior to 48 hours (including baseline) for each missing item
Renal impairment: missing SCr[$]	• Not clinical success if Renal Replacement Therapy is used at 48 hours • Use the latest SCr prior to 48 hours
Acidosis and respiratory distress: missing plasma lactate or missing respiratory distress assessment[$]	Use the result from the latest visit prior to 48 hours (including baseline) for each missing item
[*] determination of clinical success depends on other assessments. [$] Partial data missing, unlikely since participants are in the hospital	

Two-sided 90% confidence intervals (CI) for the proportion of participants with clinical success at 48 hours will be provided based on the exact method (Clopper-Pearson method). In addition, 2-sided 90% CIs for the difference between a cipargamin dose regimen and artesunate will be provided using a Mantel-Haenszel estimate of the common risk difference stratified by cohort where Cohorts 1 and 2 will be combined. Mantel-Haenszel estimate is a weighted risk difference with weight roughly proportional to strata size. It's an unbiased estimation of risk difference in the population under the following assumptions either (1) the risk difference is

same across different strata or (2) the strata sizes in study resemble the strata size in the disease population at large.

For participants who discontinue the study prior to the H48 assessments, such as withdrawal of consent, COVID-19, etc, the worst outcome (not clinical success) is used. This may under estimate the clinical success rate at 48 hours. A sensitivity analysis will be performed by imputing missing outcome using the best outcome as "Clinical success".

Descriptive statistics will be provided by cohort in addition to all cohorts pooled.

Supplementary analysis for secondary estimand

Analysis defined for secondary estimand will be repeated by pooling all participants from Cohorts 3-5.

Analysis of clinical success at timepoints other than 48 hours

The clinical success defined in Table 8-3 at Hours 24, 72, and 96, at hospital discharge, Days 8, 15, 22, and 29 will be evaluated using the FAS and data from all cohorts pooled.

Intercurrent events and non-intercurrent events that may occur and affect the derivation of clinical success are handled in Table 12-3.

Table 12-3 Handling of other events that may occur and affect the derivation of clinical success at a visit other than 48 hours

Event	During hospital period (H24,72, and 96, and hospital discharge)[$]	After discharge from hospital (Days 8, 15, 22, and 29)
Receive IV antimalarial rescue medication prior to the visit	Not clinical success	Not clinical success
Death not related to malaria (as per adjudication committee)	Not applicable	Use the worst clinical success outcome between the hospital discharge visit and the last available visit
Discontinue the study prior to the visit due to other reasons, such as withdrawal of consent, lost to follow-up, COVID-19, etc.	Not clinical success due to early discharge	Use the worst clinical success outcome between the hospital discharge visit and the last available visit
Skipping the visit	Use the worst clinical success outcome from the visit before or visit after	Use the worst clinical success outcome from the visit before or visit after
Missing parasite assessments with visit	• Not clinical success if asexual parasites present in the previous visit • Ignored[*] otherwise	• Not clinical success if asexual parasites not cleared at the hospital discharge or parasites reappearance in a previous visit • Ignored[*] otherwise

Event	**During hospital period (H24,72, and 96, and hospital discharge)[$]**	**After discharge from hospital (Days 8, 15, 22, and 29)**
Altered consciousness: missing Prostration, missing Glasgow Coma Score in adults or missing Blantyre coma score in children	Use the latest visit (including baseline) prior to the visit for each missing item	• Not clinical success if prostration or coma is reported as AEs for the visit • Ignored[*] otherwise
Renal impairment: missing SCr	• Not clinical success if Renal Replacement Therapy is used at the visit • Use the latest SCr prior to the visit	• Not clinical success if Renal Replacement Therapy is used at the visit • Not clinical success if renal failure or renal impairment is reported as AE for the visit • Ignored[*] otherwise
Acidosis and respiratory distress: missing plasma lactate or missing respiratory distress assessment	Use the result from the latest visit prior to the visit for each missing item	• Not clinical success if lactic acidosis or respiratory distress is reported as AE for the visit • Ignored[*] otherwise
[$] Partial data missing is unlikely prior to hospital discharge [*] Participant is considered as clinical success unless the participant does not meet clinical success due to other criterion		

At each visit, 2-sided 90% CIs for the proportion of participants with clinical success for each treatment group will be provided based on the exact method. In addition, 2-sided 90% CIs for the difference between a cipargamin dose regimen and artesunate will be provided using a Mantel-Haenszel estimate of the common risk difference stratified by cohort where Cohorts 1 and 2 will be combined.

At each visit, 2-sided 90% CIs for the proportion of participants with clinical success for each treatment group will be provided based on the exact method and 2-sided 90% CIs for treatment difference vs artesunate will be provided using the Wilson uncorrected method by cohort. For death not related to malaria and discontinuation of study after the hospital discharge, the following 2 sensitivity analyses will be performed:

- Use the last available clinical success outcome prior to death or discontinuation.
- Use multiple imputation methods, which will be specified in the statistical analysis plan.

Analyses of clinical and laboratory assessments and signs related to severe malaria

All analyses described below will be performed using the FAS without imputation for missing assessments, ie., missing assessments will be excluded from analysis.

For the following individual signs of severe malaria, the shift table of post-baseline presence relative to baseline presence or not will be provided by visit (24 hours, 48 hours, 72 hours, 96 hours, at hospital discharge, Day 6, Day 8, Day 15, Day 22, and Day 29), cohort, and treatment group:

- Altered consciousness - Prostration or GCS < 11 for age > 5 yrs / BCS < 3 for age <= 5 years
- Renal Impairment- Serum creatinine > 3 x ULN or > 3 mg/dL or need for renal replacement therapy
- Acidosis- Serum lactate > 4 mmol/L
- Respiratory distress – present or absent
- Severe anemia- Hb < 5 g/dl or Hb < 7g/dl in pediatric and adults respectively with parasite count of > 10,000/µl or need of blood transfusion
- Jaundice- Serum bilirubin > 3 g/dl with parasite count of > 100,000/µl
- Hypoglycemia- plasma glucose < 40 mg/dL

Number and percent of participants will be provided by cohort and treatment group for the following events related to severe malaria:

- Convulsion developing or persisting > 6 hour after the IV study treatment. Note: "persisting > 6 hour" means that convulsion is present at baseline and again at a visit that is > 6 hours after IV study treatment.
- New severe malaria signs (as per WHO severe malaria criteria) after the IV study treatment
- Neurological sequelae (by adjudication) at Day 29

Neurological Examination results will be summarized descriptively by visit, cohort, and treatment group.

For the following time to event variables, the first visit with the event will be used to calculate the time if a participant experiences the event. If a participant does not experience the event, the time will be censored at the last visit assessment for specific type of event (such as last sit assessment, etc.) with the exception of date of discontinuation (or death) for time to oral antimalarial therapy.

- Time to oral antimalarial therapy (in hours),
- Time to recover prostration in participants who are prostrated at baseline

Descriptive statistics will provided using the Kaplan-Meier method and Kaplan-Meier curves will be presented by cohort and treatment.

Day of discharge from hospital will be summarized descriptively by cohort and treatment group. Day of death will be used in case of death during hospitalization.

Analysis of secondary endpoints related to parasite clearance dynamics

All analyses will be performed using the FAS.

Proportions of participants with ≥ 90% *P. falciparum* asexual parasite reduction from baseline at 24 and 48 hours: missing data due to intercurrent and non-intercurrent events will be handled similar to the primary efficacy endpoint (See Section 12.4.3, Section 12.4.4). These 2 variables will be analyzed using the statistical methods specified in Section 12.4.2, Section 12.4.5 and Section 12.4.6.

PRRs at 12, 24 and 48 hours: PRR is defined as the ratio of asexual parasite at baseline divided by asexual parasite at post-baseline. If the asexual parasite count at post-baseline is 0, the half value of detection limit will be used to calculate the ratio. Missing values will not be imputed. For each PRR, 2-sided 90% CIs for each treatment group and for treatment ratio between each IV cipargamin regime vs IV artesunate by cohort will be provided using an analysis of covariance (ANCOVA) model on the log scale with log baseline value as a covariate and treatment group as a factor. For all cohorts pooled, the analysis will be performed with cohort as an additional factor in the ANCOVA model.

PCT and FCT: PCT will be calculated based on uncorrected *P. falciparum* asexual parasite counts. If a participant does not experience an event (such as *P. falciparum* parasite clearance, etc.), the time to the event will be censored at the last relevant assessment (such as last *P. falciparum* parasite assessment, etc.) participants who do not have the health condition at baseline (eg, fever, etc.) will be excluded from the corresponding time to event analysis (eg., FCT, etc.). Descriptive statistics will provided using the Kaplan-Meier method and Kaplan-Meier curves will be presented by treatment and cohort. For all cohorts pooled, difference for the cipargamin regimen vs artesunate will be evaluated using a log-rank test stratified by cohort. Two-sided 90% CIs for the hazard ratio will be provided.

PCE slope half-life: PCE slope half-life will be calculated for each participant using the WWARN (World Wide Antimalarial Resistance Network) Parasite Clearance Estimator as described in Flegg et al 2011. 2-sided 90% CIs for each treatment group and for treatment ratio between each IV cipargamin regime vs IV artesunate by cohort will be provided using an analysis of covariance (ANCOVA) model on the log scale with log baseline value as a covariate and treatment group as a factor. For all cohorts pooled, the analysis will be performed with cohort as an additional factor in the ANCOVA model.

Incidence of recrudescence and reinfection during the study

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

Recrudescence is defined as appearance of asexual parasites after clearance of initial infection with a genotype identical to that of parasites present at baseline. Recrudescence must be confirmed by PCR analysis.

Incidence rates of recrudescence and reinfection at Study Day 29 will be estimated by Kaplan-Meier method based on the subset of FAS participants who have clearance of initial infection by Study Day 7. Time to recrudescence/reinfection will be calculated from the time of first IV study medication to the date of first event if a participant experience the event and be censored at the time of last parasite assessment if a participant does not experience the event.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings will be presented by cohort, treatment group, participant and visit/time if applicable. Summary tables will be presented by cohort (including pooled cohort,) and treatment group.

Secondary safety endpoints include:

- Standard safety/tolerability assessments (incidence of serious adverse events (SAEs), mortality, in-hospital mortality, adverse events (AEs), and routine safety and laboratory assessments)
- Proportion of participants developing early hemolysis after treatment (as defined in Section 10.2.3).
- Proportion of participants developing delayed hemolysis after treatment (as defined in Section 10.2.3).

Adverse events

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

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

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

Separate summaries will be provided for study medication related adverse events, mortality, in hospital mortality, mortality related to malaria by adjudication, serious adverse events, other significant adverse events leading to discontinuation, and adverse events leading to dose adjustment. Summaries will also be provided separately for adverse events occurring during the IV study period (prior to oral standard of care, Coartem) and for adverse events post the IV study period (after taking oral Coartem).

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

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

Vital signs

All vital signs, body height, body weight, and head circumference data will be listed by cohort, treatment group, participant, and visit/time. If ranges are available, abnormalities (and relevant orthostatic changes) in vital signs will be flagged and listed by cohort, treatment group, participant, and visit/time. Summary statistics will be provided by cohort, treatment group, and visit/time.

12-lead ECG

Abnormal ECG data will be flagged and will be listed by cohort, treatment group, participant and visit/time. Summary statistics may be provided by cohort, treatment group and visit/time.

The analysis results for categorical outliers and T-wave morphology will be summarized in frequency tables with counts and percentages for both number of participants and number of

timepoints. For categorical outliers, the number of participants (%) and timepoints will be determined by treatment group for the following:

- increase in QTcF from baseline of ≥ 30 msec and ≥ 60 msec
- increase in QTcB from baseline of ≥30 msec and ≥ 60 msec
- absolute QTcF values > 450 msec, > 480 msec, and > 500 msec
- absolute QTcB values > 450 msec, > 480 msec, and > 500 msec
- PR change from baseline > 25% increase resulting in PR > 200 msec
- QRS change from baseline > 25% increase resulting in QRS > 120 msec
- heart rate change from baseline > 25% decrease resulting in heart rate < 50 beats per minute
- heart rate change from baseline > 25% increase resulting in a heart rate > 100 beats per minute

For T-wave morphology, the analysis will be focused on the treatment emergent changes.

The relationship between change from baseline in QTcF/QTcB and cipargamin plasma concentration will be assessed graphically with change from baseline in QTcF/QTcB plotted against cipargamin plasma concentrations.

This concentration-QT relationship may also be explored using linear mixed effects model (Garnett et al 2018). The change from baseline in QTcF/QTcB will be the dependent variable in the model, baseline QTcF/QTcB, cipargamin treatment flag (yes or no) cipargamin plasma concentrations as a covariate and time as a categorical variable. A random intercept for each participant will be specified. Control (artesunate) participants will be included in the analysis with a plasma concentration of 0. The control-corrected change from baseline in QTcF/QTcB and the two-sided 90% confidence interval will be extracted from the model at the geometric mean maximum plasma concentration for cipargamin.

Clinical laboratory evaluations

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

The number (and proportion) of participants with early hemolysis and number (and proportion) of participants with delayed hemolysis (see Section 10.2.3) will be summarized by visit, cohort, and treatment group.

The number (and proportion) of participants with serum lactate < 2 mmol/l will be summarized by visit (8, 12, 36, 48, and 72 hours), cohort and treatment group in participants with hyperlactemia (serum lactate > 4 mmol/L) at baseline.

The percentage change from baseline in plasma lactate level will be summarized by visit (4, 8, 12, and 24 hours), cohort and treatment group.

The time to normalized blood lactate level (in hours) in participants with baseline blood lactate level above normal will be summarized descriptively using the Kaplan-Meier method by cohort

and treatment group. Kaplan-Meier curve will be also presented. If a participant does not normalize the blood lactate, the time will be censored at the last blood lactate assessment.

12.5.3 Pharmacokinetics

Only cipargamin pharmacokinetics will be determined in this study. For each cohort, cipargamin plasma concentration data will be listed by cohort, treatment, participant, and visit/sampling time point. Descriptive summary statistics will be provided by cohort (including pooled cohort), treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

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

Table 12-4 Non-compartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
AUCinf	The AUC from time zero to infinity (mass x time x volume-1)
AUC0-t	The AUC from time zero to time t (e.g. 24h) (amount x time x volume-1)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1)
Ct	Concentration at time t (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
T1/2	The elimination half-life associated with the terminal slope (lz) of a semi logarithmic concentration-time curve (time).
CL/F	The total body clearance of drug from the plasma (volume x time-1)
Vz/F	The apparent volume of distribution during terminal phase (associated with λz) (volume)

Pharmacokinetic variables:

The following pharmacokinetic parameters will be determined using non-compartmental method(s) for IV cipargamin:

AUC_{inf}, $AUC_{0\text{-}t}$, C_{max}, C_{2min}, T_{max}, $T_{1/2}$, CL, and Vz.

Bio-fluid concentrations will be expressed in mass per volume units. All concentrations below the limit of quantitation or missing data will be reported as such in the concentration data listings. Concentrations below the limit of quantitation will be treated as zero in summary statistics.

The pharmacokinetic parameters will also be listed by cohort, treatment and participant.

12.5.4 CCI

12.5.5 CCI

12.6 Analysis of exploratory endpoints and assessments

CCI

12.7 Interim assessment

An interim assessment (IA) after Cohort 2 will be conducted to decide upon the dosing regimen for Cohorts 3-5. All randomized participants in Cohorts 1-2 with key efficacy, safety and PK data up to Day 29 will be included in this IA.

An independent Data Monitoring Committee (DMC) will review participant safety at several time points during the study. If notable adverse events or safety concerns are found at one of the planned dose levels, the DMC may recommend dose and/or age adjustment, stopping a cohort or the study early for safety reasons.

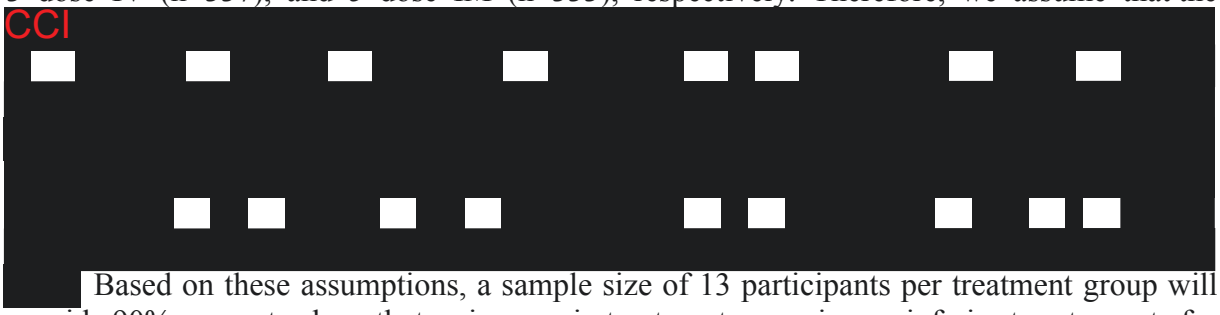
An additional IA may be conducted (for e.g. after Cohort 4) to support decision making concerning the current clinical study, the sponsor's clinical development projects in general or in case of any safety concerns.

The clinical team may be communicated interim results (e.g. information needed for planning/modifying another study) to relevant Novartis teams for information, consulting and/or decision purposes.

12.8 Sample size calculation

12.8.1 Primary estimand

The primary objective is to show that an IV cipargamin dose regimen is non-inferior to the IV artesunate in proportion of participants with ≥ 90% *P. falciparum* parasite reduction at 12 hours for each cohort. In the artesunate Phase III studies SEAQUAMAT (Dondorp et al 2005) and AQUAMAT (Dondorp et al 2010), proportion of participants with ≥ 90% *P. falciparum* parasite reduction was not reported for both artesunate and quinine. Therefore, a non-inferiority margin in proportion of participants with ≥ 90% parasite reduction for IV cipargamin vs IV artesunate cannot be derived statistically based on historical data. A non-inferiority margin of 10% is set based on clinical judgement. The KM plot for time to > 90% parasite clearance by Kremsner et al (2016) indicated that the proportion of participants with 90% parasite reduction at 12 hours was about 50%, 45%, and 40% for artesunate 3 dose IM (n=341), 3 dose IV (n=337), and 5 dose IM (n=333), respectively. Therefore, we assume that the



Based on these assumptions, a sample size of 13 participants per treatment group will provide 90% power to show that a cipargamin treatment group is non-inferior to artesunate for each cohort in the proportion of participants with ≥ 90% *P. falciparum* parasite reduction at 12 hours using a non-inferiority margin of 10% absolute difference at the 1-sided 5% significance level (nQuery 7.0 Table PTE1a). Considering that 5% of participants that may be excluded from the analysis (Kremsner et al (2016)), at least 14 participants will be randomized to each treatment arm in each cohort except Cohort 1 to achieve 13 evaluable participants per arm for the primary analysis. The sample size for Cohort 1 will be 6 participants in each arm, which is not based on the statistical justification (no formal testing will be performed in this Cohort 1) but based on clinical judgment to rule out the risk of any potential untoward safety or lack of efficacy issues in this small group of moderately severe malaria participants before enrolling the severe malaria participants into the study.

12.8.2 Secondary endpoint(s)

Secondary estimand of clinical success at 48 hours:

The key secondary estimand of clinical success at 48 hours may be used as a primary efficacy endpoint for the Ph.3 study. The key secondary objective is to estimate clinical success rates for cipargamin and artesunate individually as well as the difference between two treatment groups at 48 hours with good precision. The cipargamin treatment group for this estimation will

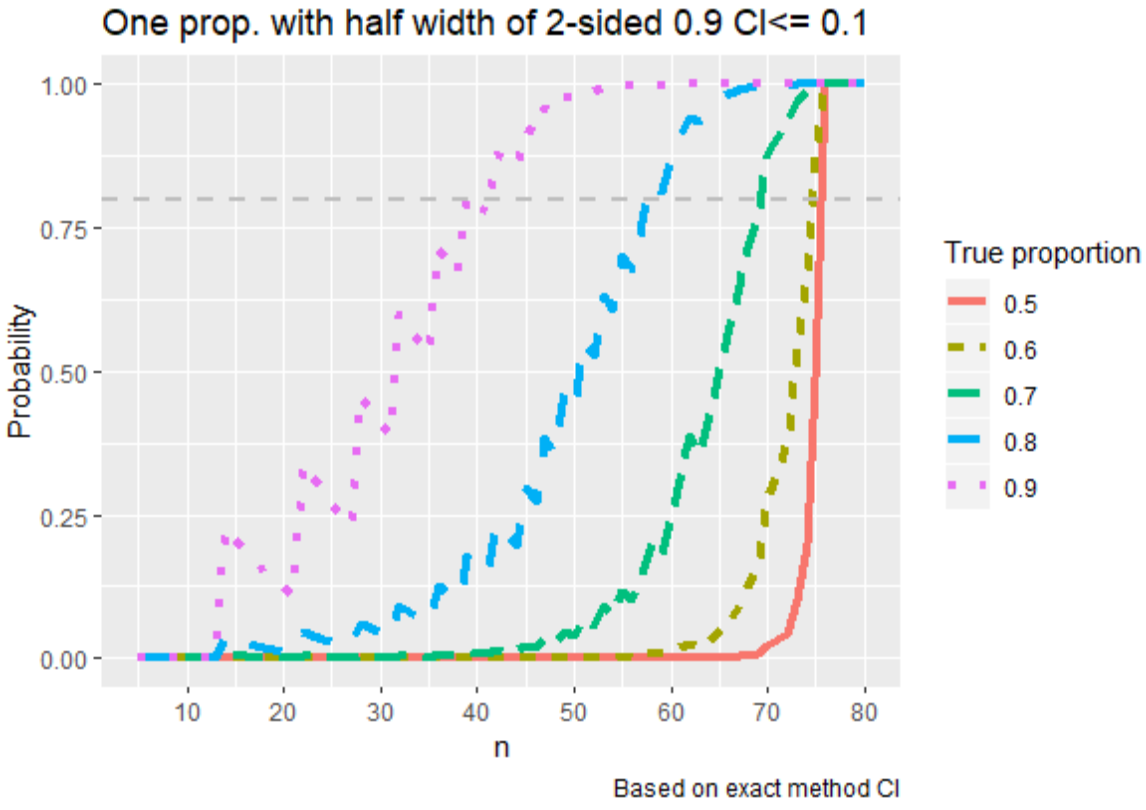
be the one, which is used in all the cohorts across the study; participants from this treatment group will be pooled from all Cohorts. Similarly, for the artesunate group, participants will be pooled from all Cohorts.

The sample size calculation considers the precision of the estimates for the individual treatment groups as well as the difference between the two treatment groups; and the precision is measured in the form of half width of the associated 90% CI as mentioned below.

Precision of the estimates of single proportion

For a binary endpoint, let X be a number of clinical successes with n participants, X follows a binomial distribution $Bin(n, p)$ where p is the true proportion of participants with clinical success for a treatment group at a visit. Proportion (p) is estimated by X/n with a 90% CI based on the exact method; and the half-width of 90% CI is considered as the precision of the estimate. Consider d as the targeted half width of CI and P_l and P_u as lower and upper limits of 90% CI based on X and n (exact method), the probability that the observed half width ($0.5[P_u - P_l]$) is at most the targeted half, ie., $Pr\{0.5(P_u - P_l) \leq d | Bin(n,p))$ will be used to justify the sample size for a single proportion.

Figure 12-1 Plot of probability that half width of 2-sided 90% CIs for a single proportion is at most 0.1 for various true proportions



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For designated half width d, the sample size, n is chosen so that the probability that the half width of 2-sided exact 90% CI for p is at most d is at least 80% at a likely true p.

Figure 12-1 displays the probabilities that the half width of 2-sided exact 90% CIs for a single proportion ≤0.1 for true proportions of 0.5 to 0.9 by 0.1. To maintain the same probability, such as 80% represented in the horizontal dash line, the sample size is higher when the true proportion is closer to 0.5 and is lower when it is away from the 0.5. For instance, when p =0.5, n=76 is required to estimate the true proportion with at least 80% probability that the half width of 2-sided exact 90% CI is ≤10%. Similarly, when p =0.7, n=70 is required to estimate the true proportion with at least 80% probability that the half width of 2-sided exact 90% CI is ≤10%.

Precision of the estimates of difference between two proportions

For estimating the difference between two proportions, the half width of 2-sided 90% CIs calculated using Wilson's uncorrected method is considered as the precision of the estimation. The probability that the half width of 2-sided 90% CI for difference between 2 proportions is at most a targeted width (d) at likely proportions will be considered for the sample size selection.

Figure 12-2 displays the probability that the half width of Wilson's uncorrected 2-sided 90% CIs for the difference between 2 proportions is most 0.1 for true equal proportions of 0.5, 0.6, 0.7, 0.75, 0.8, and 0.9. To maintain the same probability, such as 80% represented in the horizontal dash line, the sample size is higher when the two equal true proportions are closer to 0.5. For instance, when p =0.5 for both treatment groups, n=133 is required in order to have at least 80% probability that the half width of 2-sided 90% CIs for the difference is at most 0.1. Similarly, when p =0.75 for both treatment groups, n=107 is required in order to have at least 80% probability that the half width of 2-sided 90% CI for the difference is at most 0.1.

Compared with Figure 12-1, Figure 12-2 shows that the required sample size for the precision in estimating the difference between 2 proportions is higher than the corresponding sample size required for the precision in estimating a single proportion. Therefore, the sample size for the study will be justified based on the half width of 2-sided 90% CIs for the difference between 2 proportions.

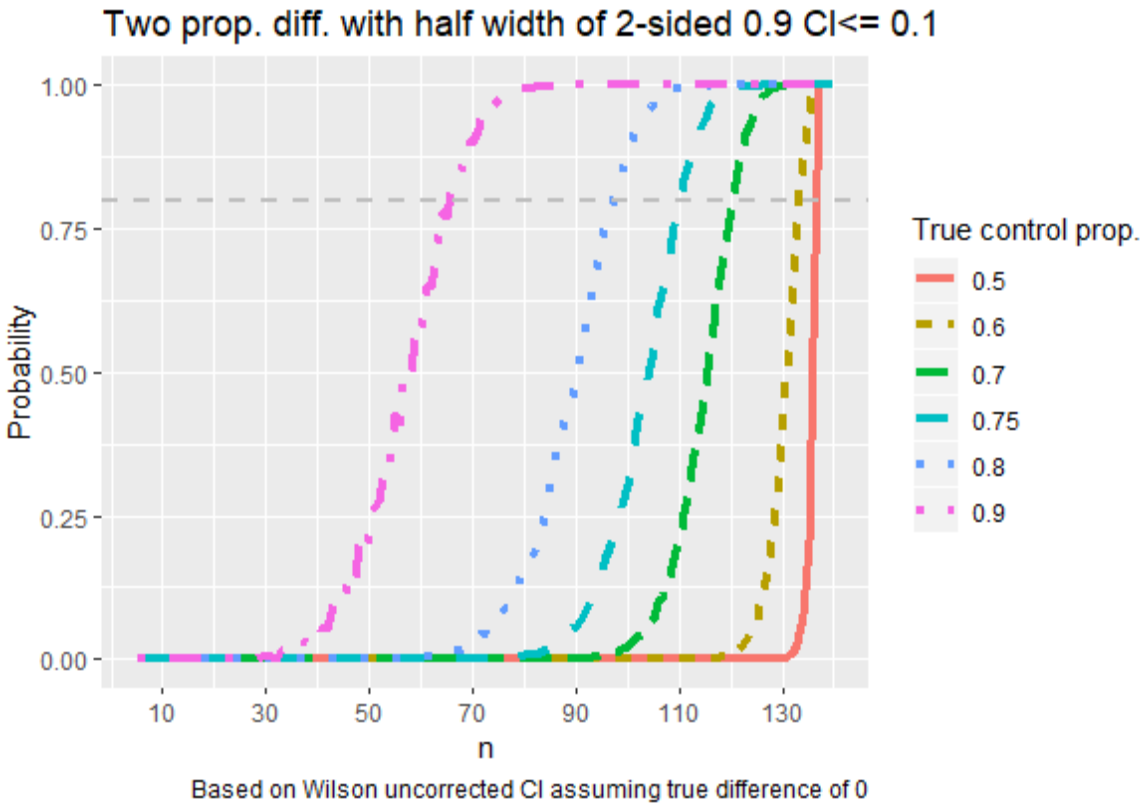
The proportion of participants who were alive without new/worsening complication at the end of study for artesunate was 0.679 in SEQUAMAT and 0.791 in AQUAMAT (private communication). Therefore, it is estimated that the proportion of participants meeting the proposed clinical endpoint is about 0.75 in the artesunate arm. To date, cipargamin has not been tested in patients with severe malaria. It is assumed that the proportion in the cipargamin arm would be same as that of artesunate.

From Figure 12-2, a sample size of n=107 per arm is required in order to have at least 80% probability that the half width of 2-sided 90% CIs for the difference between 2 proportions is at most 0.1 if the true proportion is 0.75 for both treatment groups. As participants treated with the same treatment from all cohorts will be pooled together for the analysis using the FAS, this sample size is considered for the artesunate and the cipargamin dose regimen that is used in all cohorts.

Taking account that about 8% participants may be excluded from the FAS, participants from all cohorts will be randomized to yield about 116 randomized each for the artesunate and the cipargamin dose regimen that is used in all cohorts so that 107 participants per group are evaluable for this analysis. The enrollment may be increased if the number of participants excluded from the FAS is higher. Considering the required sample size for each cohort for the

primary endpoint (see Section 12.8.1) and the potential participant population available for recruitment, the 116 randomized for a treatment group will split into 6 participants for Cohort 1, 14 participants for Cohort 2, 38 participants for Cohorts 3 and 4, and 20 participants for Cohort 5.

Figure 12-2 Plot of probability that half width of 2-sided 90% CIs for 2 proportion difference is at most 0.1 for various true equal proportions



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Safety events

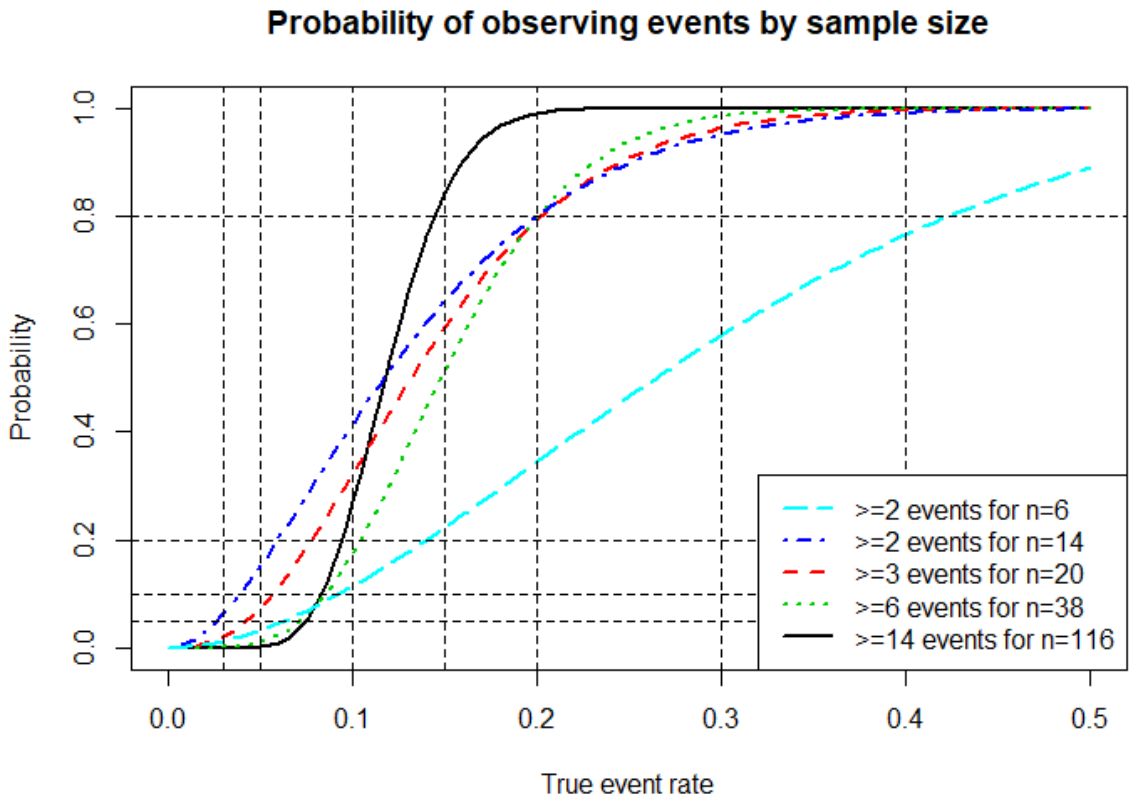
Safety events will be evaluated using the safety set, which is expected to similar to the randomized set. Occurrence of a safety event for a regimen (cipargamin or artesunate) will be evaluated by cohort and overall with all participants pooled from all cohorts. The probability of observing selected minimal number of events is displayed in Figure 12-3 by sample size. From this plot,

- for a treatment group in a cohort with 6 participants, the probability of observing at least 2 events is > 75% if true event rate is ≥ 40% but < 20% if true event rate is ≤ 10%
- for a treatment group in a cohort with 14 participants, the probability of observing at least 2 events is about 80% if the true event rate is ≥ 20% but < 20% if the true event rate is ≤ 5% ;

- for a treatment group in a cohort with 20 participants, the probability of observing at least 3 events is about 80% if the true event rate is ≥ 20% but < 20% if the true event rate is ≤ 7%
- for a treatment group in a cohort with 38 participants, the probability of observing at least 9 events is about 80% if the true event rate is ≥ 20% but < 20% if the true event rate is ≤ 10%
- for a regimen that is selected for Cohorts 3-5 with 116 participants, the probability of observing at least 14 events is > 80% if the true event rate is ≥ 15% but < 20% if the true event rate is ≤ 9%.

The minimal number of events mentioned above may be used a guidance to interpret the occurrence of safety events in a treatment group in a cohort or pooled cohorts.

Figure 12-3 Probability of observing selected minimal number of events by sample size



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13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

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

13.3 Publication of study protocol and results

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

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

13.4 Quality Control and Quality Assurance

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

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

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

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

14.1 Protocol amendments

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

Only amendments that are required for participant 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 participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

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16 Appendices

16.1 Appendix 1: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-1 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 × baseline (in the absence of known bone pathology) • Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) • Potential Hy's Law cases (defined as ALT or AST ≥ 3 × ULN and Total bilirubin ≥ 2 × ULN [> 50% conjugated fraction] with no initial findings of cholestasis (i.e. ALP < 2 × ULN at baseline) and a hepatocellular pattern of injury at the time of liver injury (R ratio ≥ 5)* • 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 > 2x baseline or > 300 U/L (whichever occurs first)
*R ratio: ALT / ALP, using factor of elevation over ULN for both enzymes	

Table 16-2 Follow-up requirements for liver laboratory triggers and liver symptoms

ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase post dose:			
If normal at baseline: ALT > 5 x ULN **If elevated at baseline**: ALT > 3 x baseline	Normal TBL OR If TBL elevated at baseline : no change from baseline TBL	None	• **No change to study treatment** • Measure ALT, AST, ALP, TBIL, DBIL, INR, albumin and LDH within 48 hours and at least 1x per week thereafter until resolved • Follow-up for symptoms • Initiate close monitoring and workup for competing etiologies
ALT > 20x ULN	Normal	None	• **Discontinue IV cipargamin and switch to IV artesunate** • **Continue IV artesunate based on benefit risk assessment of the investigator** • **Report as SAE** • Measure ALT, AST, ALP, TBIL, INR, albumin and LDH in 48 hours and at least 1x per week thereafter until resolved • Follow-up for symptoms • Initiate close monitoring and workup for competing etiologies

ALT	TBL	Liver Symptoms	Action
ALT increase with bilirubin increase post dose:			
If normal at baseline: ALT > 3 x ULN **If elevated at baseline**: ALT > 3 x baseline	TBL ≥ 2 x baseline AND ≥ 2 x ULN AND at least doubling of conjugated (=direct) bilirubin from baseline	None	• **Discontinue IV cipargamin and switch to IV artesunate** • **Continue IV artesunate based on benefit risk assessment of the investigator** • **Report as SAE** • Measure ALT, AST, ALP, TBIL, INR, albumin and LDH in 48 hours and at least 1x per week thereafter until resolved. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies.

Actions related to liver events and laboratory triggers:

- Repeat liver chemistry tests should be performed using the local laboratory used by the site. Test results must be reported as appropriate.
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
  - investigations based on investigator's discretion: serology tests, imaging (abdominal Ultrasound, CT or MRI as appropriate) and pathology assessments,
  - hepatologist's consult,
  - obtaining more detailed history of symptoms and prior or concurrent diseases,
  - obtaining history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
  - exclusion of underlying liver disease

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

16.2 Appendix 2: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-3 Specific Renal Alert Criteria and Actions

Renal event	**Actions**
Confirmed serum creatinine increase 25 – 49%	• Consider causes and possible interventions • Follow-up within 24-48 h
Serum creatinine increase ≥ 50 % **+OR** **if <18 years old, eGFR ≤ 35 ml/min/1.73 m²**	• Consider causes and possible interventions • Repeat assessment within 24-48h • Consider drug discontinuation unless other causes are diagnosed and corrected • Consider patient hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 3+	• Consider causes and possible interventions • Assess serum albumin & serum total protein • Repeat assessment to confirm within 24-48h • Consider drug discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥ 3+ on urine dipstick	• Repeat assessment to confirm within 24-48h • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess sCr • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder
+ Corresponds to KDIGO criteria for Acute Kidney Injury	

Follow-up of renal events:

Assess, document and record in CRF:

• Urine dipstick and sediment microscopy: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells

• Blood pressure and body weight

• Serum creatinine, BUN, electrolytes (sodium, potassium, calcium) and bicarbonate

• Urine output

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

- Blood pressure assessment (after 5-minute rest)
- Signs and symptoms like fever, headache, shortness of breath, back or abdominal pain, dysuria or hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output

- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other diseases or causes, e.g., dehydration due to delirium

Pediatric participants: special considerations

Schwartz formula:

- For **height in cm** and **SCr in mg/dL**: eGFR (ml/min/1.73 m^2) = 0.413 x (height/SCr)
- For **height in cm** and **SCr in µmol/L**: eGFR (ml/min/1.73 m^2) = 36.5 x (height/SCr)

Normal renal GFR values, as measured by inulin clearance (Schwartz and Furth 2007**), are provided in Table 16-4 below:**

Table 16-4 Normal GFR in children and young adults, as assessed by inulin clearance (adapted for pediatric participants included in this study)

Age	**Mean GFR ± SD (ml/min per 1.73 m^2)**
Term babies	
4-6 months	87.4 ± 22.3
7-12 months	96.2 ± 12.2
1-2 years	105.2 ± 17.3
Children	
3-4 years	111.2 ± 18.5
5-6 years	114.1 ± 18.6
7-8 years	111.3 ± 18.3
9-10 years	110.0 ± 21.6
11-12 years	116.4 ± 18.9
13-15 years	117.2 ± 16.1
2.7-11.6 years	127.1 ± 13.5
9-12 years	116.6 ± 18.1
Young adults	
16.2-34 years	112 ± 13

16.3 CCI

Table 16-5 CCI

CCI

16.4 Appendix 4: Modified version of WHO classification of signs of severe P. falciparum malaria

Severe malaria is defined as occurrence of one or more of the following observations, in the absence of an identified alternative cause, and in the presence of *P. falciparum* asexual parasitemia (WHO 2014)

Table 16-6 Definition of severe malaria

Signs	Definition
Impaired consciousness	A Glasgow Coma Score < 11 in adults or a Blantyre coma score < 3 in children
Prostration	Generalized weakness so that the person is unable to sit, stand or walk without assistance
Multiple convulsions	More than two episodes within 24 hours
Acidosis*	venous plasma lactate ≥ 4 mmol. Severe acidosis manifests clinically as respiratory distress – rapid, deep and laboured breathing
Hypoglycaemia	Blood or plasma glucose < 2.2 mmol (< 40 mg/dL)
Severe malarial anaemia	A haemoglobin concentration < 5 g/dl or a haematocrit of < 15% in children < 12 years of age (< 7 g/dl or < 20%, respectively, in adults) together with a parasite count > 10,000/µl
Renal impairment (acute kidney injury)**	Plasma or serum creatinine > 265 µmol/L (3 mg/dL) or ≥ 3x ULN or blood urea > 20 mmol/L
Jaundice	Plasma or serum bilirubin > 50 µmol/L (3 mg/dL) with a parasite count > 100,000/µl
Pulmonary edema	Radiologically confirmed, or oxygen saturation < 92% on room air with a respiratory rate > 30/min, often with chest indrawing and crepitations on auscultation
Significant bleeding	Including recurrent or prolonged bleeding from nose gums or venepuncture sites; haematemesis or melaena
Shock	Compensated shock is defined as capillary refill ≥ 3 s or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure < 70 mm Hg in children or < 80 mm Hg in adults with evidence of impaired perfusion (cool peripheries or prolonged capillary refill)
Hyperparasitemia	*P. falciparum* parasitemia > 10%
* Acidosis definition have been modified to categorize venous plasma lactate ≥ 4 mmol as acidosis . **Renal impairment definition have been modified to include Serum creatinine value of ≥ 3 ULN in the existing WHO definition	

16.5 Appendix 5: Approximate amount of blood withdrawn

Table 16-7 Amount of blood withdrawn per Cohort

Cohort	**Age of Participants**	**Amount of blood withdrawn (ml)* from Participants in total study duration**
1-2	≥ 12 years	~40
3	6 years - < 12 years	~40
4	2 years - < 6 years	~11
5	6 months - < 2 years	~11
*Blood volume indicated are approximate. If for any reason additional blood is withdrawn especially due to safety or repeat assessment please ensure to keep it close to micro sampling especially for children, per local regulations.		

16.6 Appendix 6: Coma Scores used in the study

Table 16-8 Glasgow Coma Scale

Eye Opening (E)	**-**	**Verbal Response (V)**	**-**	**Best Motor Response (M)**	**-**
Spontaneous	4	Oriented	5	Obeying Commands	6
To speech	3	Confused	4	Localizing	5
To pressure	2	Words	3	Normal flexion	4
None	1	Sounds	2	Abnormal flexion	3
-	-	None	1	Extension	2
-	-	-	-	None	1

Table 16-9 Blantyre Coma Score

Eye Opening (E)		**Verbal Response (V)**		**Best Motor Response (M)**	
Able to follow the moving object	1	Normal cry or appropriate speech (for patients who are old enough to talk) in response to painful stimuli	2	Localize pain stimulus	2
Unable to follow the moving object	0	Moan or an abnormal cry in response to painful stimuli	1	Withdraw limb from pain stimulus	1
-	-	No cry with painful stimuli	0	No response or inappropriate response to pain stimulus	0