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Novartis Research and Development

Clinical Trial Protocol Title:

(PLATINUM): A multi-part, multi-center PLATform study to assess the efficacy, safety, tolerability and pharmacokinetics of anti-malarial agents administered as monotherapy and/or combination therapy IN patients with Uncomplicated *Plasmodium falciparum* Malaria

Clinical Trial Protocol Number: CADPT13A12201 / NCT05750628

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Brief Title: Platform study to evaluate the efficacy and safety of anti-malarial agents **in** patients with **u**ncomplicated *Plasmodium falciparum* **m**alaria (PLATINUM)

Study Phase: Phase 2

Sponsor Name: Novartis

Regulatory Agency Identifier Number(s): Not applicable

Approval Date: 21-Jun-2023

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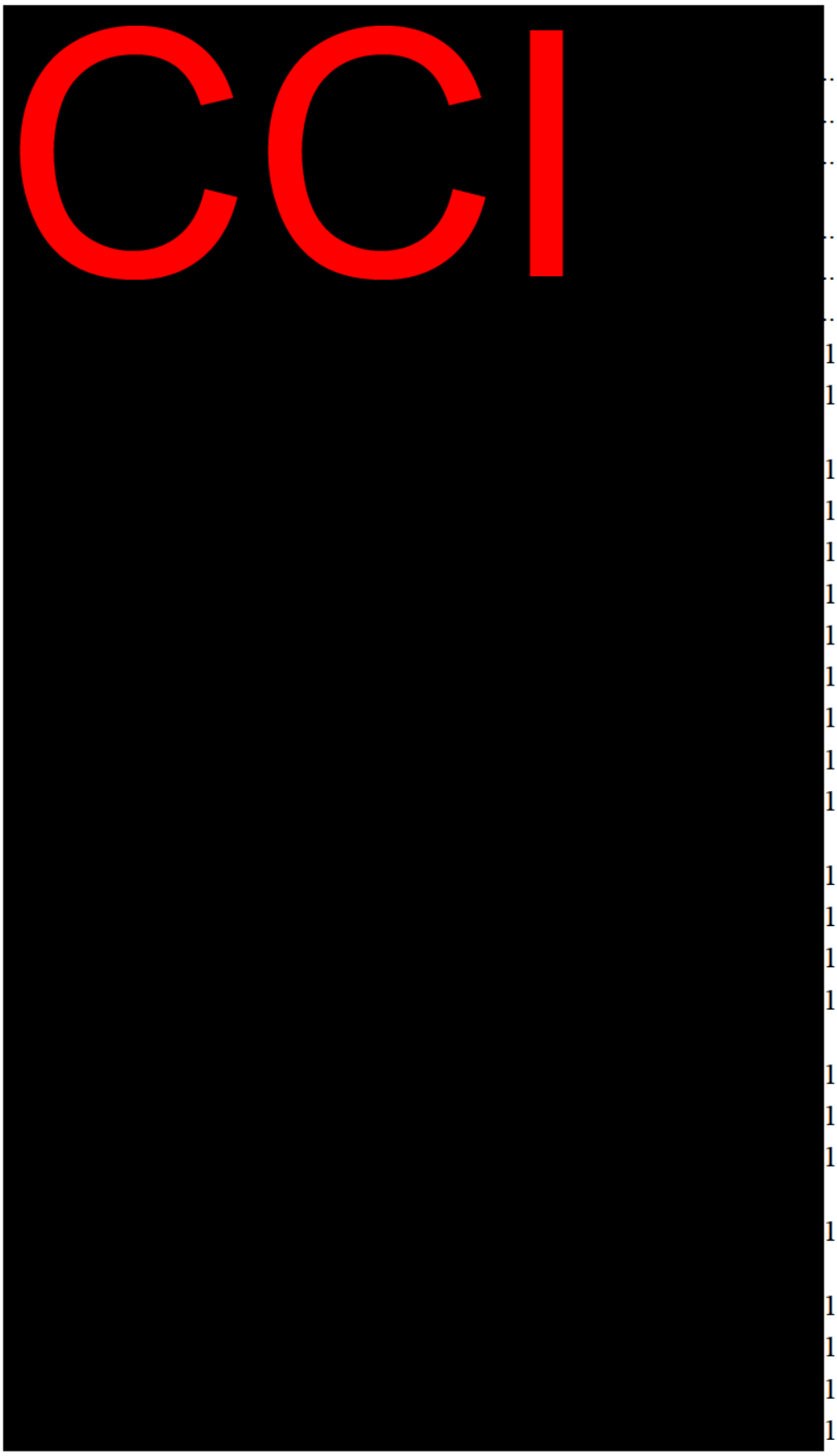

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List of abbreviations

CCI	
ACPR	Adequate Clinical and Parasitological Response
ACT	Artemisinin combination therapies
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ASAQ	artesunate-amodiaquine
AST	Aspartate Aminotransferase
AUC	Area under the curve
BID	Twice a day
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CMO&PS	Chief Medical Office and Patient Safety
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CTA	Clinical Trial Application
CTC	Common Terminology Criteria
CTT	Clinical Trial Team
CV	coefficient of variation
DBP	Diastolic Blood Pressure
DDI	Drug-drug interaction
DHA	Dihydroartemisinin
DIN	Drug Inducted Nephrotoxicity
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
CCI	[redacted]
EC50	Half maximal effective concentration
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	estimated glomerular filtration rate
EOS	End of Study
ETF	Early Treatment Failure
FAS	Full Analysis Set
FDA	Food and Drug Administration
CCI	[redacted]
FIH	First in Human

GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GI	gastrointestinal
GLDH	Glutamate Dehydrogenase
GLP	Good Laboratory Practices
h	Hour
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
hERG	human Ether-à-go-go-Related Gene
HIV	Human immunodeficiency virus
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intra-Uterine Device
IUS	Intra-Uterine System
LC-MS	Liquid chromatography–mass spectrometry
LCF	Late Clinical Failure
LDH	lactate dehydrogenase
LFT	Liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantification
LPF	Late Parasitological Failure
CCI	[redacted]
MDMA	3,4-Methylendioxy-N-methylamphetamin
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MoA	Mechanism of action
MPC	minimum parasiticidal concentration
MRI	Magnetic resonance imaging
MS	mass spectrometry
NOAEL	No Observed Adverse Effect Level
NSAIDs	Non-steroidal anti-inflammatory drugs

p.o.	Oral(ly)
PC	Parasite Clearance
CCI	[redacted]
PCP	Phenyl-cyclohexyl-piperidin
PCR	Polymerase Chain Reaction
PCT	Parasite Clearance Time
PCV	Packed cell volume (hematocrit)
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PPS	Per-protocol Set
CCI	[redacted]
PT	prothrombin time
CCI	[redacted]
qRT-PCR	quantitative reverse-transcription polymerase chain reaction
QTcF	QT interval corrected by Fridericia's formula
RAS	Randomized Analysis Set
RBC	Red Blood Cell
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SCID	severe combined immunodeficiency
sCr	Serum creatinine
SD	standard deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SoC	Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	upper limit of normal
WBC	White Blood Cells
WHO	World Health Organization
WWARN	World Wide Antimalarial Resistance Network

Definitions

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
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Control drug	A study intervention (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study intervention administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g., 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
Estimand	As defined in the ICH E9 (R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.

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
Medication number	A unique identifier on the label of medication kits
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e., concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
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.
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.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant
Remote	Describes any trial activities performed at a location that is not the investigative site.
Rescreening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Run-in Failure	A participant who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to participant's intervention or other treatment)
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource

Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the investigator will conduct the trial.
Treatment group	A treatment group defines the dose and regimen or the combination,and may consist of 1 or more cohorts.
Treatment arm	A treatment arm defines the dose and regimen or the combination within a cohort
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 (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	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/or biological samples AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding informed consent form.

Amendment 2 (June 2023)

Amendment rationale

The purpose of this amendment is to add blinding of the microscopists based on feedback from Health Authorities and Ethics Committees.

Minor typographical and administrative errors have been corrected throughout the protocol to increase quality.

Changes to the protocol

IRBs/IECs

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

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

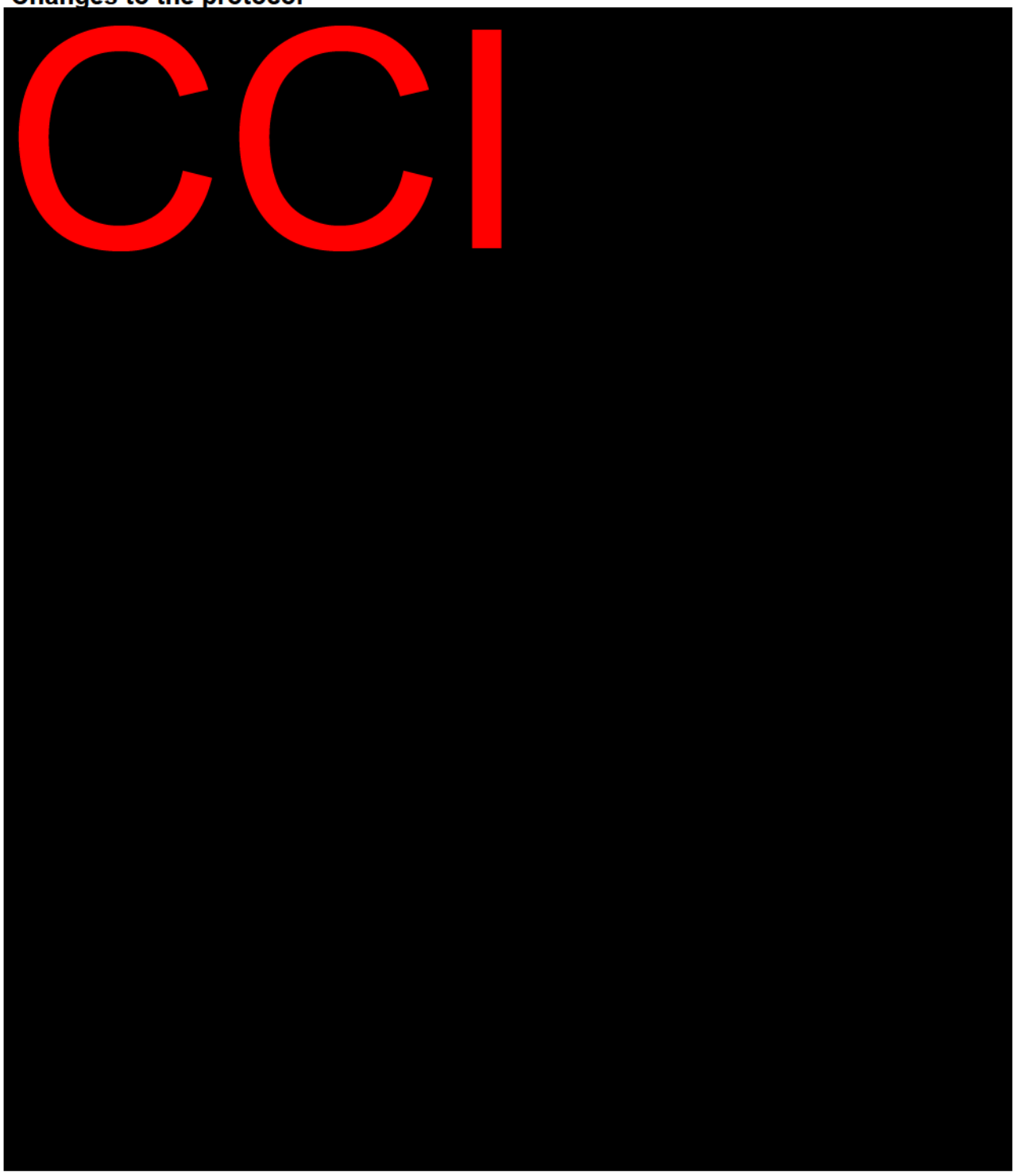
Amendment 1 (May 2023)

Amendment rationale

The purpose of this amendment is to add a Data Monitoring Committee (DMC) and other requests based on feedback from Health Authorities.

Minor typographical and administrative errors have been corrected throughout the protocol to increase quality.

Changes to the protocol



IRBs/IECs

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

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

Protocol summary

Protocol number	CADPT13A12201
Full Title	PLATINUM: A multi-part, multi-center PLATform study to assess the efficacy, safety, tolerability and pharmacokinetics of anti-malarial agents administered as monotherapy at multiple dose levels and/or combination therapy IN patients with Uncomplicated *Plasmodium falciparum* Malaria
Brief title	**Plat**form study to evaluate the efficacy and safety of anti-malarial agents **in** patients with **u**ncomplicated *Plasmodium falciparum* **m**alaria (PLATINUM)
Sponsor and Clinical Phase	Novartis, Phase 2
Investigation type	Drug(s)
Study type	Interventional
Purpose and rationale	The purpose of this platform study is to evaluate the parasiticidal effect and potential for cure with different anti-malarial agents administered as monotherapy and/or in combination therapy with other anti-malarial agents in adult and adolescent patients with uncomplicated *Plasmodium falciparum* malaria. Additionally, the safety, tolerability, and pharmacokinetics of these anti-malarial agents will be evaluated for dose selection for future studies.
Primary Objective(s)	Part A: To assess the parasite clearance time (PCT) of oral doses of an anti-malarial agent administered as monotherapy in patients with uncomplicated P. falciparum malaria Part B: To assess the effect on adjusted 28-day cure rate of an anti-malarial agent administered orally as combination therapy versus the standard of care (SoC) in patients with uncomplicated *P. falciparum* malaria
Secondary Objectives	Part A: To assess the effect on adjusted 28-day cure rate of an anti-malarial agent administered orally as monotherapy in patients with uncomplicated *P. falciparum* malaria Part B: To assess the parasite clearance time (PCT) of oral combinations of anti-malarial agents versus SoC in patients with uncomplicated *P. falciparum* malaria All parts: To characterize PK of each anti-malarial agent administered orally as monotherapy [Part A] and/or as combination therapy [Part B] in patients with uncomplicated *P. falciparum* malaria To assess the safety and tolerability of each anti-malarial agent administered orally as monotherapy [Part A] and/or as combination therapy versus SoC [Part B] in patients with uncomplicated *P. falciparum* malaria
Study design	This is a multi-part, multi-center, open-label platform study, including a parallel and adaptive sequential dose level design in Part A followed by an open-label, randomized, controlled design in Part B in patients with uncomplicated *P. falciparum* malaria. Part A will evaluate anti-malarial agents as monotherapy. Part B will evaluate anti-malarial agents as combination therapy.
Study population	The study population will consist of male and female patients aged ≥18 years for Part A and aged ≥12 years for Part B.

Key Inclusion criteria	• Male and female patients ≥18 years of age for Part A and ≥12 years of age for Part B at screening. • Patients must have acute uncomplicated *P. falciparum* malaria mono-infection at screening confirmed by a parasite count between CCI [redacted] /µl of blood for *P. falciparum* for Part A and between CCI [redacted] /µl of blood for Part B Patients in Part A must weigh between 40 kg and 90 kg. Patients in Part B must weigh between 35 kg and 90 kg at screening.

Key Exclusion criteria	• Patients with signs and symptoms of severe/complicated malaria at screening or mixed *Plasmodium* infection (i.e., infection with more than one malaria species) at screening
	• Moderate to severe anemia, chronic hemoglobinopathy (Hemoglobin level < 8 g/dL), or known chronic underlying disease such as sickle cell disease at screening
	• Known clinically significant liver disease (e.g., chronic hepatitis, liver cirrhosis (compensated or decompensated), history of hepatitis B or C, hepatitis A or B vaccination in the last 3 months, known gallbladder or bile duct disease, acute or chronic pancreatitis. Clinical or laboratory evidence of any of the following at screening:
	  • AST/ALT > 3 x the upper limit of normal range (ULN), regardless of the level of total bilirubin
	  • AST/ALT > 1.5 and ≤ 2 x ULN and total bilirubin is > ULN
	  • Total bilirubin > 2 x ULN, regardless of the level of AST/ALT
	• Any known/suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection at screening.
	• Pregnant or nursing (lactating) women, women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using methods of contraception as outlined in Section 12, and sexually active patients not willing to practice effective contraception.
	• History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study such as:
	  • Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
	  • History of familial long QT syndrome or known family history of Torsades de Pointe.
	  • Resting heart rate (physical exam or 12 lead ECG) < 60 bpm

Study treatment and Treatment of interest	This study uses a platform type design with the potential to investigate multiple therapies in the context of a single disease. Each new investigational agent to be evaluated will be added to the protocol via a substantial protocol amendment. Refer to Section 12 for cohort-specific information. The standard of care that will be utilized in Part B of the study is Coartem.
Efficacy assessments	Parasitemia and parasite clearance time, ACPR, clinical signs and symptoms of malaria, CCI [redacted]
Pharmacokinetic assessments	PK parameters of study drugs (AUC0-t, AUClast, AUCinf, Cmax, Tmax, T1/2, Cl/F, V/F)

Key safety assessments	Physical examinations, vital signs, ECGs, monitoring of laboratory parameters in blood and urine
Data analysis	
Key words	Malaria, uncomplicated malaria, *P. falciparum*, *P. falciparum* malaria, adults, adolescents, PLATINUM

1 Introduction

1.1 Study rationale

The purpose of this platform study is to evaluate the parasiticidal effect and potential for cure with different anti-malarial agents administered as monotherapy and/or in combination therapy in adult and adolescent patients with uncomplicated *Plasmodium falciparum* malaria. Additionally, the safety, tolerability, and pharmacokinetics of these anti-malarial agents will be evaluated for dose selection for future studies.

A platform study assessing many treatments in one population is considered an efficient way to screen for the pharmacological properties of treatments, either of single compounds or combinations that suggest high efficacy (Woodcock, LaVange 2017). Addition of new anti-malarial agents to the study will be included in protocol amendment(s).

There is an unmet medical need for anti-malarial combination therapies comprising at least one partner drug with a new mechanism of action to reduce the probability of developing resistance as well as to offer an alternate treatment option for patients infected with resistant parasites.

The core part of this PLATINUM platform protocol (Section 1–Section 11) is not expected to change over time significantly. New anti-malarial agents will be added to Section 12 using self-contained, cohort-specific modules in form of amendments. This modular approach is expected to provide a consistent, reliable approach to adding new cohorts with new anti-malarial agents.

CCI [redacted]

1.2 Background

Despite malaria being a preventable and curable disease, there were an estimated 241 million cases worldwide in 2020. There were an estimated 13 million more malaria cases and 47,000 more deaths in 2020 compared to 2019 due to the disruptions to services during the pandemic (WHO 2021). Of the five protozoan parasites causing malaria, *Plasmodium falciparum* and *Plasmodium vivax* are the most prevalent species and responsible for the majority of malaria cases recorded worldwide. In 2020, 95% of cases were in the World Health Organization African Region, and 99.7% of these were caused by *P. falciparum*. *P. falciparum* is also the predominant species in South-East Asia, the Eastern Mediterranean, and the Western Pacific (WHO 2021).

Plasmodium parasites are transmitted to humans by an infective mosquito bite leading to an asymptomatic liver infection lasting 6 – 18 days. From the liver, the parasites egress and infect red blood cells leading typically to flu-like symptoms, including headache, slight fever, muscle pain, anorexia, nausea, and fatigue as parasitemia rises in the blood. If not promptly treated, patients may develop cerebral or severe malaria. These life-threatening complications can result in coma, acute respiratory distress, and severe anemia (White et al 2014). In 2020, malaria was

responsible for an estimated 627,000 deaths with children under the age of five accounting for 67% of malaria-related deaths (WHO 2021).

Artemisinin derivatives remain the mainstay of antimalarial combination therapies, but a decade ago, resistance to artemisinin was reported in Southeast Asia (Dondorp et al 2009, Noedl et al 2009, Ashley et al 2014). Today, artemisinin combination therapies (ACT) such as Coartem® remain effective malaria treatments, but other combination therapies are failing in southeast Asia with no alternative treatment available (van der Pluijm et al 2019). So far, ACTs remain effective on the African continent although artemisinin resistance-conferring mutations have been identified in Rwanda. There is increased urgency and a strong medical need to develop new anti-malarials with new mechanisms of action (Uwimana et al 2021).

Research efforts have been focused on identifying drugs that display the appropriate pharmacologic properties to ensure potent, rapid, and sustained parasite killing with a simple and short treatment regimen in order to improve compliance and reduce the development of resistance. The target product profile for these new antimalarial agents is based on the requirements identified by the Medicines for Malaria Venture (MMV) and summarized as follows Burrows et al (2017): (1) highly efficacious, even against drug-resistant parasites (preferably with a new mechanism of action (MoA)); (2) safe, especially for young children and pregnant women; (3) administered orally in three daily doses or less, (4) inexpensive and (5) stable with a long shelf-life under tropical conditions; with the overarching goal to achieve a single-dose cure combination therapy.

2 Objectives, endpoints, and estimands

2.1 Objectives and Endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
Part A:	
• To assess the parasite clearance time (PCT) of oral doses of an anti-malarial agent administered as monotherapy in patients with uncomplicated *P. falciparum* malaria	• Parasite clearance time (hours) up to Day 7
Part B:	
• To assess the 28-day cure rate of an anti-malarial agent administered orally as combination therapy versus the standard of care (SoC) in patients with uncomplicated *P. falciparum* malaria	• Polymerase Chain Reaction (PCR)-corrected adequate clinical and parasitological response (ACPR) at Day 29 (i.e., 28 days post-dose)

Objective(s)	**Endpoint(s)**
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
Part A:	
• To assess the 28-day cure rate of an anti-malarial agent administered orally as monotherapy in patients with uncomplicated *P. falciparum* malaria	• PCR-corrected and uncorrected adequate clinical and parasitological response (ACPR) at Day 29 (i.e., 28 days post-dose)
Part B:	
• To assess the parasite clearance time (PCT) of oral combinations of anti-malarial agents versus the standard of care (SoC) in patients with uncomplicated *P. falciparum* malaria	• Parasite clearance time (hours) up to Day 7
• To assess the 28-day cure rate of an anti-malarial agent administered orally as combination therapy versus the SoC in patients with uncomplicated *P. falciparum* malaria	• PCR- uncorrected adequate clinical and parasitological response (ACPR) at Day 29 (i.e., 28 days post-dose)
For all parts:	
• To characterize PK of each anti-malarial agent administered orally as monotherapy [Part A] and/or as combination therapy [Part B] in patients with uncomplicated *P. falciparum* malaria	• PK parameters such as AUC0-t, AUClast, AUCinf, Cmax, Tmax, T1/2, Cl/F, V/F
• To assess the safety and tolerability of each anti-malarial agent administered orally as monotherapy [Part A] and/or as combination therapy versus SoC [Part B] in patients with uncomplicated *P. falciparum* malaria	• Adverse events, vital signs, ECG findings, safety laboratory assessments including chemistry, hematology, and urinalysis results up through EOS
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
CCI	

Objective(s)	Endpoint(s)
CCI	

2.2 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.

CCI


CCI

2.3 Secondary estimands

CCI [redacted]

The justification for both secondary estimands are identical as in Section 2.2.

The secondary estimand attributes in Part A are described as identical as the attributes in the primary estimand in Part B.

The secondary estimand attributes in Part B are described as identical as the attributes in the primary estimand in Part A.

Further details on the secondary analyses for part A and part B are provided in Section 9.4.1.

3 Study design

3.1 Overall design

This is a Phase 2, multi-part, multi-center, open-label platform study including CCI [redacted] This platform design allows the potential to investigate multiple therapies in the context of a single disease. Each anti-malarial agent entered into the trial at a given time will follow the same design as outlined in Parts A and/or B. More than one Part A and Part B cohort can be conducted at the same time. In addition, Part A and Part B cohorts can be conducted at the same time. Generally, one site will be enrolling into one cohort only at a given point in time; however, exceptions may be implemented if required and will be communicated with the site staff.

Figure 3-1 Study Design - Study Level View

- **Part A** is the open-label, randomized, multi-arm monotherapy part of this Phase 2 study evaluating a single oral administration of an anti-malarial agent at 3 parallel dose levels followed by optional adaptive sequential dose level(s).

CCI

- **Part B** is the open-label, randomized, two-arm combination therapy part of this Phase 2 study evaluating a single oral dose of up to three anti-malarial agents as a loose combination vs. standard of care (SoC), Coartem.

CCI

Each of the anti-malarial agents to be evaluated in this PLATINUM study must meet the following criteria:

For Part A:

CCI

For Part B:

CCI

If the above criteria are met, an anti-malarial agent may be included in Part B as combination therapy without having completed the monotherapy Part A. Cohort-specific DDI information can be found in Section 12.

Marketed anti-malarial agents and those for which safety, tolerability and efficacy data as monotherapy are already available may be directly investigated in combination therapy (Part B).

The decision to include future agents and cohorts is not dependent on performance of prior agents or cohorts. Each time a new agent is introduced, agent-specific information will be added to the protocol as a substantial amendment and submitted to Health Authorities and Ethic Committees, as required by local regulations.

Each cohort in the study will undergo a set of the same study evaluations and assessments but may also have cohort-specific evaluations/assessments that are outlined in Section 12.

Each cohort will include a screening period CCI [redacted]. Eligible patients will be dosed on Day 1 and remain at the site for inpatient follow-up for at least 3 days. Safety, efficacy, and PK assessments will be performed for the 3 days. Patients may remain inpatient longer at the investigator's discretion. CCI [redacted] A safety follow-up call will be performed on Day 31 for Part A. The visit structure at each cohort level for Parts A and B of the study is shown in Figure 3-2. Cohort-specific study designs are outlined in Section 12.

For a detailed outline of the core safety and other assessments, please refer to the assessment schedule in Table 8-1. Cohort-specific assessments are outlined in Section 12.

Figure 3-2 Study Design - Cohort Level View

Part A: Monotherapy

CCI [redacted]

Safety assessments will include physical examinations, triplicate ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), adverse event and serious adverse event monitoring.

CCI [redacted]

Multiple cohorts, each with a different anti-malarial agent, may be added. Each new anti-malarial agent evaluated will follow the same design.

Part B: Combination Therapy

In Part B, patients will be randomized to receive a single oral dose of a combination of up to three anti-malarial agents or the standard of care (Coartem). See Figure 3-1. Specific randomization ratios for each cohort will be specified in Section 12.

Doses for agents in Part B will be selected based on review by the Sponsor and the DMC of PK, safety, and efficacy data from Part A. Safety, efficacy and/or PK data may be evaluated in the first few patients (approximately 6 in each arm) in Part B and reviewed by the Sponsor for

safe use of combination in patients. The dose(s) may be adjusted based on these data in order to meet the desired exposure or to mitigate potential safety risks.

Safety assessments will include physical examinations, triplicate ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), adverse event and serious adverse event monitoring.

CCI [redacted]

Multiple cohorts with different anti-malarial agents may be added. Each new anti-malarial agent combination evaluated will follow the same design.

For subsequent cohorts in Part B, sample sizes for both SoC arm and the combination arm may be further refined by using the historical control data from Coartem, as well as using all already available SoC data in Part B (e.g., pooling strategy). Thus, the randomization ratio may change in subsequent cohorts in Part B. Any changes will be made via protocol amendment. Additionally, if inclusion and exclusion criteria might differ between cohorts in Part B, baseline covariate adjustment for SoC data may be considered.

4 Rationale

4.1 Scientific rationale for study design

The rationale of key design elements in this study includes the following:

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Duration of study	The design of the study within each cohort is assessing a 28-day cure rate. Twenty-eight days is the recognized duration to evaluate a cure for malaria per the World Health Organization (WHO) criteria. CCI [redacted]
Lack of control arm in Part A	CCI [redacted]
Inpatient period	Patients will remain inpatient initially to allow for close observation of safety and tolerability, and to ensure compliance with instructions for all patients
Multi-center	To enroll a diverse patient population in different regions
Platform design	CCI [redacted]
Randomization	To reduce risk of selection bias and also the risk of unequal distribution between arms
Parallel Arms (Part A) followed by optional dose level(s)	To allow for dosing of multiple dose levels of the same agent in an efficient manner with the flexibility to allow the addition of optional dose(s) based on the data from the parallel arms to further investigate optimum safety and efficacy as well as support dose selection for future studies
Open Label	The risk of bias arising out of the open label design is minimized due to the fact that the efficacy endpoints are objective in nature. The dosing regimens arms CCI [redacted]) for Part B and food requirements are different between the arms making it impractical to keep the blind. Measures will be taken to ensure that these objective endpoints are assessed in an unbiased way, and thus, the site microscopists must be blinded to the treatment.
Study population	This platform trial will include patients with uncomplicated malaria. Adults of 18 years or more will be included in Part A of the study, and adolescents and adults of 12 years or more will be included in Part B of the study. There is no expected difference in drug metabolism and dose response relationship in adolescents compared to adults. This will enable faster development of novel combination in target population (pediatric patients) for the disease under evaluation (uncomplicated malaria).

4.2 Justification for dose

Please refer to Section 12 for a detailed rationale for dose/regimen and duration of each cohort.

For Part A, multiple dose levels are chosen to select optimum safe and efficacious dose for patients. CCI [redacted]

In general, the dose of the agents to be studied will be chosen based on an evaluation of all available preclinical and/or clinical data to ensure acceptable safety and tolerability and will be detailed in the corresponding Section 12. The oral route of administration for the target indication of *P. Falciparum* uncomplicated malaria is considered the most convenient route for patients who can tolerate oral medication.

Dosing regimen for additional cohorts will be decided based on available clinical data of the anti-malarial of interest, at the time of inclusion of those cohorts in the study.

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

Choice of control drug

There is a control treatment only in Part B. The control treatment used in Part B of this study is Coartem, the artemisinin-based combination therapy artemether-lumefantrine. Coartem is widely used for *P. falciparum* malaria and has a well-characterized safety and efficacy profile (Hamed, Grueninger 2012). For these reasons, Coartem is considered the appropriate comparator treatment for this study.

Choice of combination drug(s)

This study is designed to test a number of different investigational anti-malarial agents (Part A) or combinations of anti-malarial agents (Part B). Agents must meet pre-specified criteria as outlined in Section 3.1 to be included in the study. In some cases, an investigational anti-malarial agent may also be combined with a marketed one. Each of the candidate agents to be studied will have rationale added in a substantial amendment. Refer to Section 12 for cohort-specific details.

4.4 Purpose and timing of design adaptations

Data Review Meetings

The design of this platform study will allow ongoing data review during study conduct for all available study data. As part of the ongoing data review, there will be a clinical decision point prior to dosing the optional dose level(s) in Part A, where available safety, efficacy, and PK data from the parallel dose levels from Part A will be reviewed by the Sponsor. Depending on the safety and efficacy results and PK data analysis emerging from these Data Review(s), the dose(s) for the optional dose level(s) of Part A may be adjusted, but the maximum tolerated dose established in previous cohorts or studies will not be exceeded.

Safety, efficacy and/or PK data may be evaluated in the first few patients (approximately 6 patients in each arm) in Part B by the Sponsor for safe use of combination in patients. The dose(s) may be adjusted based on these data in order to meet the desired exposure or to mitigate potential safety risks.

Interim Analyses

CCI [redacted] Additional details about the DMC can be found in Section 10.1.4. If cohorts complete around the same time, available data from separate cohorts may be included in the same IA. Other interim analyses may be performed as per Sponsor and DMC decision to assess efficacy and safety, to avoid unnecessary exposure of patients to agents that have no or marginal chances to be effective. Finally, additional interim analyses and/or DMC review may be conducted to support decision making concerning the current clinical study, the Sponsor's clinical development projects in general, or in case of any safety concerns. Additional information is presented in the interim analysis section (Section 9.7).

Addition of a new anti-malarial agent CCI [redacted] IAs may be done independently for each cohort, and new and ongoing cohorts may continue to be conducted. The clinical team may communicate interim results to relevant Novartis teams for information, consulting and/or decision purposes. Results from any particular IA may also be communicated beyond the Sponsor to groups including, but not limited to, individuals treating the study's patients, Health Authorities, and clinical registries.

4.5 Benefit/Risk assessment

Detailed descriptions of the expected risks and benefits of each investigational agent used in each cohort can be found in Section 12.

Procedural risks not specifically related to study drugs

Collecting a blood sample from a vein may cause pain, swelling, bruising, light-headedness, fainting, and very rarely, clot formation, nerve damage and/or infection at the site of the needle stick.

During cannulation, more than one attempt may be needed to insert the cannula in a vein of a patient, and it is possible that bruising and/or inflammation may be experienced at the site of cannulation.

Electrocardiogram (ECG) stickers on the patients' chests and limbs may cause some local irritation and may be uncomfortable to remove but patients will be closely monitored to ensure any local irritation does not persist.

Appropriate eligibility criteria and specific dose-limiting toxicity definitions, as well as specific dose modification and stopping rules, are included in this protocol.

The risk to patients in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring, and periodic data reviews of

available safety, efficacy, and PK data by an independent DMC. Refer to the respective anti-malarial agent's Investigator's Brochure.

Women of child-bearing potential and sexually active males 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 outlined in the exclusion criteria and/or in Section 12. If there is any question that the patient will not reliably comply, they should not be entered or continue in the study.

As is the case with any new compound in clinical development, there may be unknown risks of the study drugs that may be serious and unforeseen.

4.5.1 Blood sample volume

CCI [redacted] Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the assessment schedule (Table 8-1 and Section 12).

A summary blood log is available upon request. Instructions for sample collection, processing, storage and shipment information are also available in the laboratory manual.

See Section 8.7 and Section 8.8 on the potential use of residual samples.

4.6 Rationale for public health emergency mitigation procedures

In the event of a public health emergency as declared by local or regional authorities (i.e., pandemic, epidemic or natural disaster), mitigation procedures may be required to ensure patient safety and trial integrity and are listed in relevant sections of the study protocol (Section 8). Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures and permitted/approved by local or regional health authorities and ethics committees as appropriate.

4.7 End of study definition

The end of the study is defined as the date of the last visit CCI [redacted]

Study completion is defined as when the total number of primary events (collection of parasite clearance time for all patients) are obtained from all cohorts and when the last patient finishes their last study visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the investigator (e.g., Each patient will be required to complete the study in its entirety, and thereafter no further study treatment will be made available to them in the scope of the trial).

All randomized and/or treated patients should have a safety follow-up call conducted at least 30 days after last administration of study treatment. This follow-up may be a phone call or a

study site visit. The information collected is kept as source documentation. SAE reporting continues during this time period as described in Section 8.6.3. Documentation of attempts to contact the patient are required to be recorded in the source documentation.

5 Study Population

The study population will consist of adult and adolescent male and female patients.

IMPORTANT

The inclusion/exclusion criteria for the core protocol are located in these sections (Section 5.1 and Section 5.2). These criteria apply to all patients enrolled into this study. No additional criteria should be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients. However, there may also be additional agent specific inclusion/exclusion criteria for each of the investigational compounds, which are provided in Section 12.

5.1 Inclusion criteria

Part A:

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

1. Signed informed consent must be obtained prior to participation in the study. If the patient 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).
2. Male and female patients ≥18 years of age at screening.
3. Patients must have acute uncomplicated *P. falciparum* malaria mono-infection at screening confirmed by a parasite count between CCI [redacted] /µl of blood
4. Patients must weigh between 40 kg and 90 kg at screening.
5. Patients must be able to swallow oral medications.
6. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

Part B:

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

1. Signed informed consent must be obtained prior to participation in the study. If the patient 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). Patients younger than 18 years, who are capable of providing assent, must provide assent with parental/legal guardian consent or as per local ethical guidelines. The patient or parent/legal guardian 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.

2. Male and female patients ≥12 of age at screening.
3. Patients must have acute uncomplicated *P. falciparum* malaria mono-infection at screening confirmed by a parasite count between CCI /µl of blood.
4. Patients must weigh between 35 kg and 90 kg at screening.
5. Patients must be able to swallow oral medications.
6. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

5.2 Exclusion criteria

Part A:

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

1. Patients with signs and symptoms of severe/complicated malaria at screening
2. Mixed *Plasmodium* infection (i.e., infection with more than one malaria species) at screening
3. Use of any anti-malarial treatment or antibiotics with anti-malarial activity (or prohibited medication) in the preceding 14 days or at least 5 half-lives whichever is longer before screening
4. Moderate to severe anemia, chronic hemoglobinopathy (Hemoglobin level < 8 g/dL), or known chronic underlying disease such as sickle cell disease at screening
5. Active infections including tuberculosis, or history of taking anti-tuberculosis medications within 12 months prior to screening
6. History of, or current alcohol use disorder defined as five or more drinks on the same occasion on each of 5 or more days in the past 30 days prior to screening
7. Known clinically significant liver disease (e.g., chronic hepatitis, liver cirrhosis (compensated or decompensated), history of hepatitis B or C, hepatitis A or B vaccination in the last 3 months, known gallbladder or bile duct disease, acute or chronic pancreatitis.

   Clinical or laboratory evidence of any of the following at screening:

   - AST/ALT > 3 x the upper limit of normal range (ULN), regardless of the level of total bilirubin
   - AST/ALT > 1.5 and ≤ 2 x ULN and total bilirubin is > ULN
   - Total bilirubin > 2 x ULN, regardless of the level of AST/ALT
8. Any known/suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection at screening
9. Known disturbances of uncorrected electrolyte balance, e.g., hypokalemia, hypocalcemia or hypomagnesemia
10. Severe malnutrition (Body Mass Index (BMI) < 16.0) at screening
11. Severe vomiting, defined as more than 3 times in the 24 hours prior to screening or severe diarrhea defined as watery stools more than 3 times in the 24 hours prior to screening
12. Pregnant or nursing (lactating) women

13. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using methods of contraception defined in the cohort-specific sections (Section 12). Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age-appropriate history of vasomotor symptoms). Women are considered not of child-bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks prior to enrollment on study. 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 to be not of child-bearing potential.
14. Sexually active patients not willing to practice effective contraception. Sexually active males must use a condom during intercourse while taking treatment and for at least 30 days after stopping study treatment. A condom is required for **all** sexually active male patients to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male patients must not donate sperm for the time period specified above. If local regulations are more stringent than the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.
15. History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study such as:
    - Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
    - History of familial long QT syndrome or known family history of Torsades de Pointe
    - Resting heart rate (physical exam or 12 lead ECG) < 60bpm
16. Resting QTcF > 450 msec (males), QTcF > 460 msec (females) at screening
17. Use of agents known to prolong the QT interval unless they can be permanently discontinued for the duration of study
18. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the patient in case of participation in the study. The investigator should make this determination in consideration of the patient's medical history, clinical and/or laboratory result
19. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in situ* cervical cancer), treated or untreated, within the past 5 years of screening, regardless of whether there is evidence of local recurrence or metastases
20. Patients with serum creatinine ≥ 2 X ULN in the absence of dehydration at screening. In case of dehydration, patients with serum creatinine ≥2 X ULN after oral or parenteral rehydration
21. Patients taking drugs that are strong inducers of CYP3A4 such as rifampicin, carbamazepine, phenytoin, St. John's wort (*Hypericum perforatum*) at screening
22. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes
23. Use of herbal medication within one week of screening

24. Use of other investigational drugs within 5 half-lives of screening, or within 30 days or until the expected pharmacodynamic (PD) effect has returned to baseline, whichever is longer; **or longer if required by regulations.**
25. Previous participation in any malaria vaccine study or received malaria vaccine in any other circumstance
26. Previous participation in the same cohort within this study

Part B:

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

The same exclusion criteria from Part A apply in Part B with the addition of the following:

1. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using methods of contraception defined in the cohort-specific sections (Section 12). Additionally, for combination therapy in Part B, the more conservative contraception requirement will be used.

5.3 Restrictions for study participants

For the duration of the study, patients should be informed and reminded of the restrictions outlined in this section.

5.3.1 Dietary restrictions

Food restrictions for individual cohorts will be described in Section 12.

Patients taking Coartem in Part B should follow prescribing information. Coartem should be taken with food as per product label.

Patients can drink water *ad libitum;* however, to ensure adequate hydration for urine collection (if applicable), patients should have a fluid intake of at least 240 mL every 4 hours during waking hours on Day 1 in addition to fluid taken with meals and medication.

5.3.2 Other restrictions

- Contraception requirements are defined in Section 5.2 and Section 12
- Other restrictions are outlined in Section 12

5.4 Screen failures

A screen failure occurs when a patient who consents to participate in the clinical study is subsequently found to be ineligible and therefore not randomly assigned to treatment/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Patients who sign an informed consent form and are subsequently found to be ineligible prior to randomization will be considered as screen failures. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a serious adverse event during the screening period (see Section 8.6 for reporting details). If the patient fails to be randomized, the Interactive Response Technology (IRT) must be notified within 2 days of the screen fail that the patient was not randomized. Data and samples collected from patients prior to screen failure may still be analyzed.

Patients who are randomized and fail to start treatment, e.g., patients randomized in error, will be considered early terminators. The reason should be recorded on the appropriate Case Report Form.

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

Patients not meeting eligibility criteria at a particular malaria episode will receive an anti-malarial treatment as per local standards.

In the case where a safety laboratory assessment at screening is outside of the range specified in the eligibility criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified range, the patient must be excluded from the study.

5.4.1 Replacement policy

Additional patients may be enrolled in the study. If a patient is considered as non-evaluable in Part A or in Part B, enrollment of additional patients to the current treatment group will be considered if there are fewer than the required number of evaluable patients. Minimum numbers of evaluable patients per treatment group in Part A are defined in the guidelines for cohort progression and determination section (Section 6.5). Minimum numbers per treatment group in Part B are defined in the Cohort Specific Information outlined in Section 12.

Replacements of patients will be done on a case-by-case basis.

5.4.2 Participant numbering

Each patient is identified in the study by a Participant Number (Participant No.), that is assigned when the patient is enrolled for screening and is retained for the patient throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the patient is rescreened. The Participant No. consists of the Site Number (Site No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each patient's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Participant No. available.

A new ICF will need to be signed if the investigator chooses to rescreen the patient after a patient has screen failed, and the patient will be assigned a new Participant No.

6 Study treatment(s) and concomitant therapy

6.1 Study treatment(s)

The investigational compounds being evaluated in this study will be administered orally. Refer to compound-specific information in Section 12.

6.1.1 Additional study treatments

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

6.1.2 Treatment arms/group

In Part A, patients will be randomized at the screening visit to receive a single dose of an anti-malarial agent at one of the dose levels at equal ratios.

In Part B, patients will be randomized at the screening visit to receive a single dose of a combination of anti-malarial agents or the standard of care (Coartem).

See Section 12 for cohort specific information.

6.1.3 Treatment duration

For Part A, the planned duration of treatment is 1 day.

For Part B, the planned duration of treatment is 1 day for patients randomized to the active investigational medicinal products administered as a loose combination or 3 days for patients randomized to the standard of care arm. Patients may be discontinued from SoC treatment earlier at the discretion of the investigator or the patient.

6.2 Preparation, handling, storage, and accountability

Each study site will be supplied with study treatment(s) in packaging as described under the Investigational and control drugs in Section 12.

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

Investigator staff will identify the study medication kits to dispense to the patient by contacting the IRT and obtaining the medication number(s). The study medication provided by Novartis has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

6.2.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels.

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

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

The investigator or designated site staff must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by field monitors during site or remote monitoring visits, and at the completion of the trial. The investigator must provide accountability also for locally sourced materials used for administration as applicable.

The site may destroy and document destruction of unused study treatment, drug labels and packaging, as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the Investigator folder at each site.

6.2.2 Handling of other treatment

The following non-study treatment has to be monitored specifically:

- Coartem or other local standard anti-malarial agent per investigator discretion may be administered as rescue medication in case of treatment failure. Monitoring of rescue medication compliance and drug accountability will be performed by the field monitors during site or remote monitoring visits, and at the completion of the trial.

6.2.3 Instruction for prescribing and taking study treatment

Refer to Section 12 for compound specific instructions for prescribing and taking study treatment.

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

6.3 Measures to minimize bias: randomization and blinding

6.3.1 Treatment assignment, randomization

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

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient 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.

The randomization scheme for patients will be reviewed and approved by a member of the Randomization Office or by a designated member following CRO procedures.

6.3.2 Treatment blinding

In Parts A and B of the study, treatment will be open to patients, investigator staff, persons performing the assessments and the Novartis clinical trial team (CTT). Because the primary endpoint is an objective endpoint for Part A, blinding is not necessary except for the site microscopists who will be blinded. As the dosing regimens are different (i.e., CCI [redacted] vs. 3 day BID dosing for Coartem) for Part B, it would be impractical to blind the study, hence it will be unblinded except for the site microscopists who will be blinded. In addition, food requirements could be different for Coartem and investigational drug and thus preventing the blinding.

The study statistician, statistical programmer, data analysist (e.g., biomarker, PK) will be able to access the full randomization list from the start of the study and are allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision making. For example, unblinded summaries and unblinded individual data can be shared with the team whenever necessary.

At the time of safety review/interim analysis for efficacy, the Sponsor will create and review unblinded interim reports. These summaries/reports will be shared with the DMC for review and trial recommendations. More details will be provided in the DMC charter.

6.4 Study treatment compliance

In this study, the patients will be dosed at the investigator's center by qualified members of the site staff. Details of each dose of study drug will be recorded in the CRF.

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all patients treated with all anti-malarial agents, as detailed in the Cohort Specific Information section (Section 12).

6.4.1 Recommended treatment of adverse events

At present, there is insufficient information to provide specific recommendations regarding treatment of adverse events (AEs).

Medication used to treat adverse events (AEs) must be recorded on the appropriate CRF.

6.5 Cohort progression and dose modification

For Part A, available safety, efficacy, and PK data from the parallel dose levels will be reviewed to decide about the progression to the optional dose level(s). Additionally, available safety, efficacy, and PK data from Part A will be reviewed to decide about the progression to Part B of the study.

For Part A, investigational medicinal product dose adjustments are not possible; for Part B, the dose for investigational medicinal product(s) may be adjusted based on data from the first few patients (approximately 6 in each arm) in order to mitigate potential safety risks and to ensure adequate exposure to achieve desired efficacy (see Section 3).

6.5.1 Guidelines to start optional arm(s) in Part A

CCI

6.5.2 Guidelines to start Part B

CCI

Criteria for continuation from Part A to Part B

CCI

6.5.2.1 Starting dose

Please refer to the cohort specific information in Section 12 for starting doses of each investigational agent.

6.5.2.2 Provisional dose levels

Refer to cohort specific information in Section 12 for provisional dose levels for each investigational agent.

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

There will be no study treatment available to patients following the end of the study. This study includes Coartem or other local standard anti-malarial agent administered to all patients in Part A on Day 29 and in case of treatment failure in Part A or B. There are other treatment options for uncomplicated malaria.

6.7 Treatment of overdose

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- Closely monitor the patient for any AE/SAE and laboratory abnormalities for at least 5 half-lives of the investigational study drug.
- Document the quantity of the excess dose as well as the duration of the overdose.

6.7.1 Reporting of study treatment errors including misuse/abuse

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

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

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

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

6.8 Concomitant and other therapy

6.8.1 Concomitant therapy

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

Concomitant medication is defined as any medication, other than the study treatments being evaluated in this study, which is given at least once between the day of first dose of randomized study medication and the last day of study visit (including those which were started pre-baseline

and continued into the treatment period), including prescription and over-the-counter medicines, and any traditional or herbal remedies.

Paracetamol (daily total dose not to exceed 3g) as an antipyretic and metopimazine (or if not available, any other antiemetic which is not known to prolong QT and/or cause Torsades de Pointes) for repeated vomiting are recommended. If paracetamol or equivalent drug is given as an antipyretic up to 72 hours prior first dose, it must be reported as prior medication.

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including herbal therapy, physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the concomitant medications eCRF.

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

6.8.1.1 Permitted concomitant therapy requiring caution and/or action

Drugs permitted to use concomitantly with investigational medicinal products with caution are listed in Section 12.

6.8.2 Prohibited medication

IMPORTANT

The prohibited medications for the core protocol are located in this section. These apply to all patients enrolled into this study. However, there may also be treatment specific prohibited medications which are provided in Section 12 for the individual cohorts.

Use of following treatments is NOT allowed as per below recommendations in Parts A and/or Part B.

CCI

[redacted]

CCI


CCI

Prohibited medication for Part B cohorts with Coartem (SoC) arm

Coartem/Riamet prescribing information should be followed in general. Regarding prohibited medications for Coartem, refer to the current prescribing information. Some important prohibited medications are outlined below:

- Use of any prescription drugs known as strong inhibitors of CYP 3A4 (e.g., erythromycin, ketoconazole, itraconazole, etc.) or inducers of CYP 3A4 (e.g., rifampin, phenobarbital etc.) Drugs metabolized by CYP2D6 like flecainide, metoprolol, imipramine, amitriptyline, clomipramine, neuroleptics and those that increase QTc interval like terfenadine, astemizole, cisapride) are prohibited during study and within four (4) weeks prior to dosing.
- Herbal supplements with antimalarial activity and/or affecting CYP3A4, including St. John's wort (Hypericum perforatum), are also prohibited during study and within one week prior to dosing.

Other considerations for Part B cohorts with Coartem (SoC) arm:

- Medication which may be required to treat adverse events can be administered considering the potential interaction.
- Administration of paracetamol (daily total dose not to exceed 3g) / acetaminophen is acceptable, but dose and time of administration must be documented in the Concomitant medications / significant nondrug therapies section of the eCRF.

6.8.3 Rescue medication

The following rescue medications may be used per investigator discretion:

- Coartem (Artemether-Lumefantrine)

  or
- Other local standard anti-malarial agent

In Part A, Coartem (artemether-lumefantrine) or other local standard anti-malarial agent per investigator discretion will be administered on Day 29 in all patients in Part A of the study. If Coartem or other local standard anti-malarial agent is used as rescue medication prior to Day 29 due to treatment failure (see Section 8.3.4), then another course is not needed at Day 29.

In Part B, Coartem or other local standard anti-malarial agent per investigator discretion will be used as rescue medication only for patients not randomized to the SoC in Part B if they meet the treatment failure criteria (see Section 8.3.4). An alternative rescue medication should be used for patients assigned to the SoC arm if they met treatment failure criteria.

Although the use of the above rescue medication is allowable at any time during the study when there is treatment failure in Part A or B, the use of rescue medication should be used at the discretion of the PI following the failure criteria as outlined in Section 8.3.4. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

7 Discontinuation of study treatment and participant discontinuation/withdrawal

7.1 Discontinuation of study treatment

Since only one dose is administered in Part A, discontinuation of study treatment is not applicable.

Since only one dose of a combination of anti-malarials is administered in non-SoC arm of Part B, discontinuation of study treatment of the active arm is not applicable. However, discontinuation of the SoC in Part B may occur.

Discontinuation of study treatment for a patient occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study treatment administration, if any) and can be initiated by either the patient or the investigator.

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

Discontinuation from study treatment is required under the following circumstances

- Patient/guardian decision
- Pregnancy
- Any situation in which continued study participation might result in a safety risk to the patient
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the patient's overall status, prevents the patient from safely continuing participation in the study

Prohibited medications that require discontinuation of the study treatment are listed in Section 6.8.2 and Section 12.

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

Patients who discontinue from study treatment (Coartem arm in Part B) but agree to complete the study should return for the remaining visits and end-of-study visit indicated in the Assessment Schedule Table 8-1.

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

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

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

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

7.2 Participant discontinuation from the study

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

If the patient agrees, a final evaluation at the time of the patient's study discontinuation should be made following the assessments of the EOS visit as detailed in the Assessment Schedule Table 8-1.

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

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

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment

and

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

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

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

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

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

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

If the patient agrees, a final evaluation at the time of the patient's withdrawal of consent/exercise data privacy rights should be made following the assessments of the EOS visit as detailed in the Assessment Schedule Table 8-1.

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

7.4 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other patients' data privacy rights), the investigator must show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc. A patient should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

7.5 Study stopping rules

Dependent on regional guidance, any restart following a temporary hold due to stopping rules being met will require an evaluation by the Sponsor and the DMC, and approval to proceed.

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[redacted]

The severity of adverse events will be graded by the study investigators based on the mild, moderate, severe grading scale and captured in the CRF. This information will be used to quantify events that may lead to a patient's discontinuation or stopping cohort progression.

7.6 Early study termination by the Sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination (include but are not limited to):

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

In taking the decision to terminate, Novartis will always consider patient welfare and safety. Should early termination be necessary, patients must be seen as soon as possible and treated as a patient who discontinued from study treatment: EOS procedures should be performed, and the patient should be transferred to SoC. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator or Novartis depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Study Assessments and Procedures

The Assessment Schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

Patients should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Patients who discontinue from study treatment are to attend the follow-up visits as indicated in the Assessment Schedule.

Patients who discontinue from study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the applicable assessments listed for the final EOS visit Day 29 will be performed. At this final visit, the adverse event and concomitant medications not previously reported must be recorded on the CRF.

When the following assessments are scheduled to be performed at the same time point, the order of priority will be as follows: ECG, vital signs, blood sampling (safety, followed by PK blood sampling from opposite arm). Every effort will be made to take the pharmacokinetic sample at the protocol specified time.

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

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowed by local Health Authority and depending on operational

capabilities, phone calls, virtual contacts (e.g., tele consult) or visits by site staff/ home nursing staff to the patient´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the patient to visit the site again.

Table 8-1 Assessment Schedule


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8.1 Screening

Screening

Procedures conducted as part of the patient's routine clinical management/standard of care (e.g., blood count) and obtained before signing of the ICF may be utilized for screening purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the Assessment Schedule Table 8-1.

8.2 Participant demographics/other baseline characteristics

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

Patient demographics: age, sex, race, predominant ethnicity (if permitted) and relevant medical history/current medical conditions (until date of signature of informed consent) will be recorded in the eCRF. Where possible, the diagnosis and not symptoms should be recorded.

All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented. See the core protocol Section 6.8 Concomitant and other therapy and cohort-specific Section 12 for further details on what information must be recorded on the appropriate page of the eCRF.

8.3 Efficacy assessments

Pharmacodynamic samples will be collected at the timepoints defined in the Assessment Schedule (Table 8-1). Follow instructions outlined in the Laboratory manual regarding sample collection, numbering, processing, and shipment.

In order to better define the PD profile, the timing of the sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will remain under the limits recommended in the population considered.

Pharmacodynamic (PD) samples will be obtained and evaluated in all patients at all dose levels.

8.3.1 Clinical signs and symptoms of malaria

A full assessment of malaria signs and symptoms will be made according to the time points in the assessment schedule (Table 8-1) for all patients.

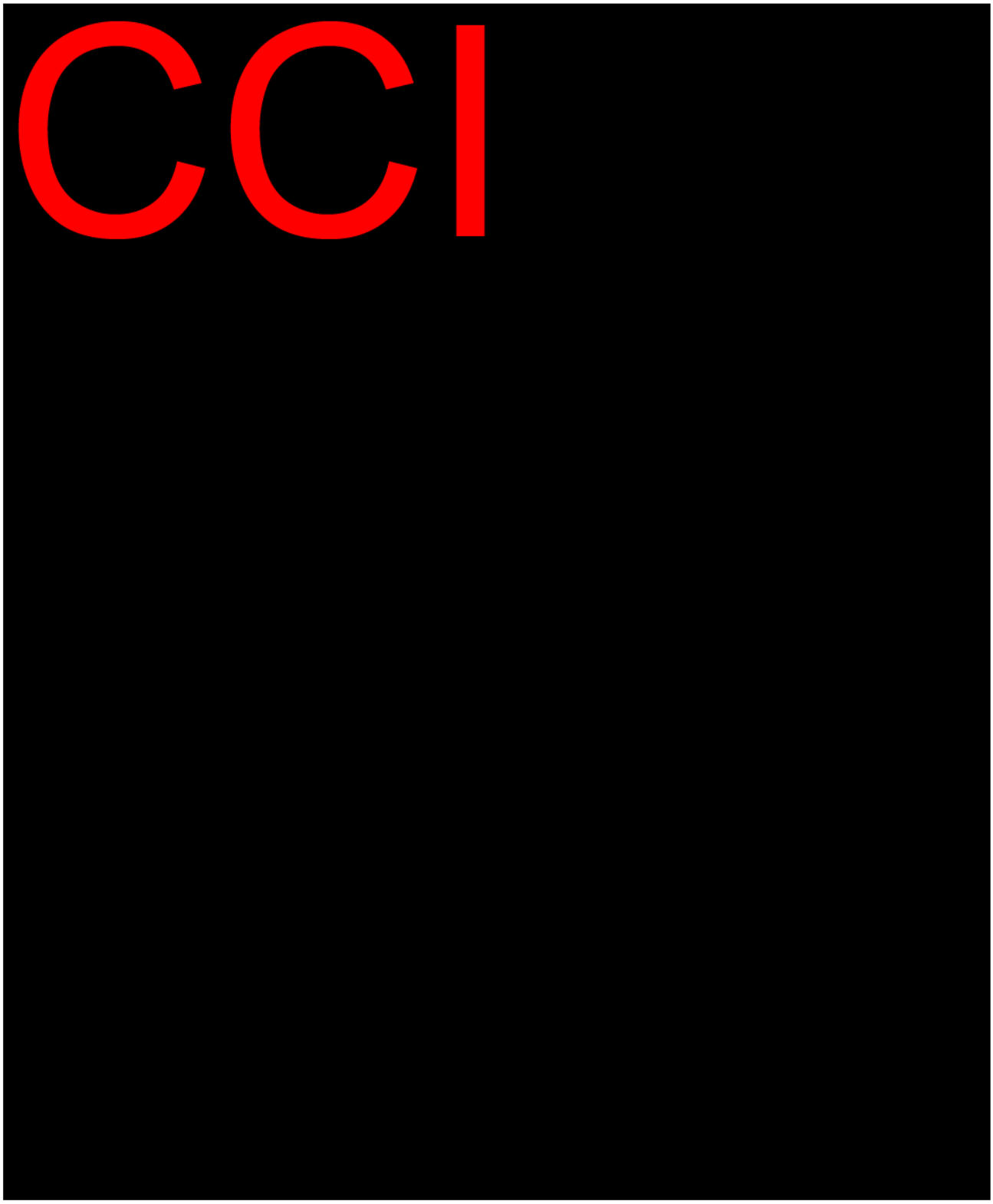
The following signs and symptoms of malaria are to be assessed:

8.3.3 Parasitemia and parasite clearance time

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

Parasite counts

- Giemsa stained thick and thin films will be examined. Thin films will be examined only if identification of species is needed after malaria (*Plasmodium)* parasite is detected in a thick film
- Examination with binocular microscope and with oil immersion lens at 1,000 magnification
- Screening examination (prior to patient inclusion into the trial), thick film: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Note: The first day of treatment with study medication is defined as Day 1 while the day prior to the first day of treatment is defined as Day -1. Compared to WHO (2015) which defined Day 0 as the first day of treatment with study medication, days after treatment referred to in this protocol are 1 day greater. For example, Day 29 in this protocol corresponds to Day 28 by WHO (2015).

8.3.5 Incidence rate of recrudescence and reinfection

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

Recrudescence is defined as appearance of asexual parasites after clearance of initial infection with a genotype of at least one allele identical to that of parasites present at baseline.

Reinfection and Recrudescence must be confirmed by PCR analysis.

Time to event (recrudescence or reinfection) will be calculated from the time of first study medication to the date of first event if a patient experiences the event and be censored at the time of last parasite assessment if a patient does not experience the event due to whatever reason.

A participant who was already treated in one cohort who experiences a subsequent malaria episode may be enrolled into a different cohort provided they meet eligibility criteria, but may not be recruited within the same cohort.

8.3.6 Blood sample for molecular diagnostic purpose

Blood will be sampled for parasite genotyping and phenotyping as indicated in the assessment schedule. At screening, a blood sample will be collected from all patients fulfilling eligibility criteria for inclusion in the study. A second blood sample collected as per assessment schedule will be analyzed only in patients showing treatment failure. This will be used to distinguish between recrudescence and new infection. Molecular analysis will be done by an analytical laboratory.

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

8.3.7 Appropriateness of efficacy assessments

The efficacy assessments are standard for this patient population.

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8.4 Safety assessments

Safety assessments are specified below with Assessment Schedule Table 8-1 detailing when each assessment is to be performed.

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

As per Section 4.6, during a public health emergency as declared by local or regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur for safety monitoring and discussion of the patient´s health status until it is safe for the patient to visit the site again.

8.4.1 Physical examinations

- A **complete** physical examination will be performed by the investigational staff at screening and include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Malaria signs and symptoms, body weight, and body weight will also be recorded at screening as part of the complete physical examination. 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 timepoints as described in Table 8-1. Body mass index (BMI) will be calculated using the following formula:

- BMI = Body weight (kg) / [Height (m)]2

Rounding should be done to the nearest tenth of a decimal place.

- A **short** physical exam will be performed at all other visits starting from Day 1 including the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse).
- A full assessment of ***malaria signs and symptoms*** will be made alongside the physical examinations at timepoints described in the assessment schedule for all patients (Table 8-1).

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 included in the appropriate CRF that captures medical history. Significant findings after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.4.2 Vital signs

Vital signs will include the collection of oral body temperature (recorded in °C), blood pressure (BP) and pulse measurements.

After the patient has been sitting for 5 minutes, with back supported and both feet placed on the floor, systolic and diastolic BP will be measured using an automated validated device, e.g., OMRON with an appropriately sized cuff. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

Body temperature will be monitored as indicated in the study assessment schedule table (Table 8-1) and recorded on the clinical database. Fever monitoring will be done every 6 hours until resolution of fever, defined as being afebrile for 24 hours.

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

In case of repeated vital sign assessments, the eCRF should contain the qualifying results.

8.4.3 Electrocardiograms

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

Figure 8-1 Timing of study procedures

8.4.4 Clinical safety laboratory tests

As per Section 4.6, during a public health emergency as declared by local or regional authorities' i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if patients cannot visit the site for protocol-specified safety lab assessments, an alternative lab (local) collection site may be used.

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

In the case where a laboratory range is not specified by the protocol, but a value is outside the reference range for the laboratory at screening, a decision regarding whether the result is of clinical significance or not shall be made by the investigator (in consultation with the Sponsor) and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once prior to randomization.

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

In all cases, the investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the patient to continue in the study.

Local laboratories will be used for analysis of safety specimens.

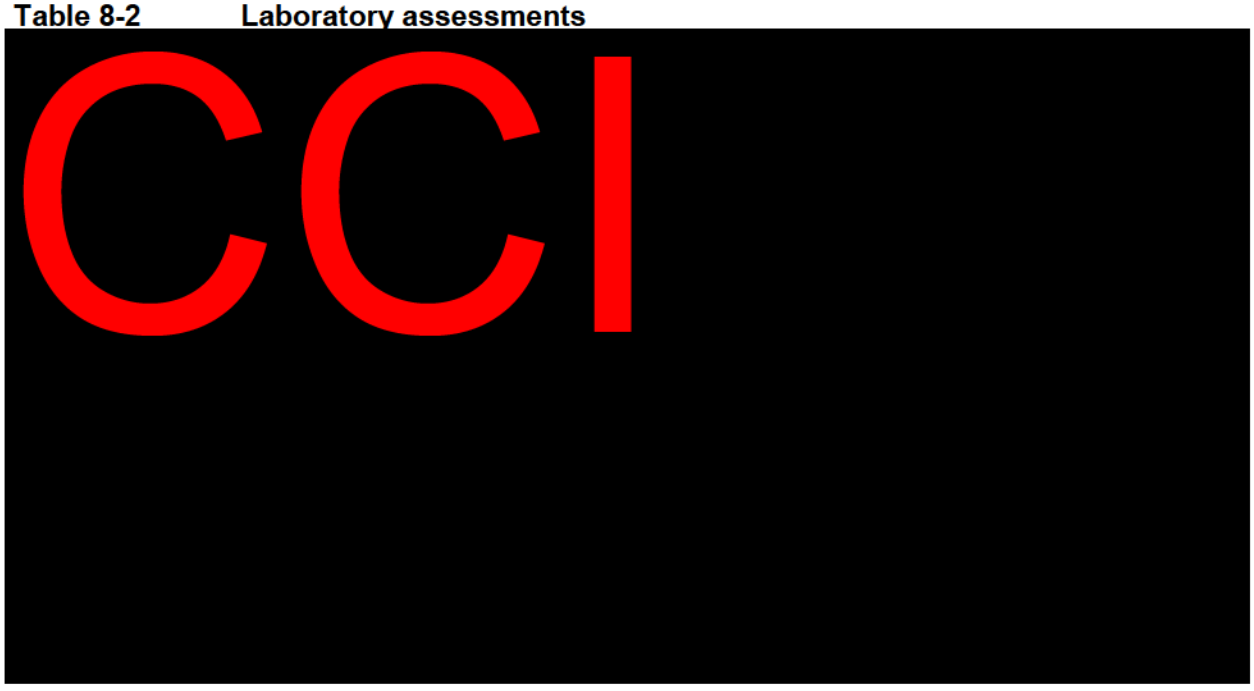
Urinalysis

A midstream urine sample (approx. 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments.

Special clinical laboratory evaluations

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

Table 8-2 Laboratory assessments



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8.4.5 Pregnancy testing

Condom use is required for all sexually active male patients to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male patients should not donate sperm for the time period specified above.

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

A serum or plasma pregnancy test will be performed at the screening visit and/or pre-dose and urine pregnancy test will be performed at study completion. All female patients in this study must undergo obligatory pregnancy testing as per schedule of assessment. Local pregnancy test and associated results will not be collected on CRF.

Assessments of fertility

A woman is considered of childbearing potential from menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents.

A post-menopausal state is defined as no menses for 12 months without an alternative medical cause and an appropriate clinical profile.

In absence of the medical documentation confirming permanent sterilization, or if the post-menopausal status is not clear, the investigator should use his medical judgment to appropriately evaluate the fertility state of the woman and document it in the source document.

8.4.6 Other safety evaluations

Signs and symptoms of severe malaria

Danger signs:

- not able to drink
- vomiting > twice within preceding 24 hours
- one convulsion within preceding 24 hours
- unconscious state
- unable to sit or stand

Signs of severe malaria:

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

- Impaired consciousness (Glasgow coma score < 11 in adults)
- Prostration (generalized weakness i.e., unable to sit, stand or walk without assistance)
- Multiple convulsions (more than two episodes within 24 hours)
- Acidosis (a base deficit of > 8 mEq/L or if not available a plasma bicarbonate level of < 15 mmol/L or venous plasma lactate ≥ 5 mmol/L. Severe acidosis manifests clinically as respiratory distress i.e., rapid, deep, labored breathing)
- Hypoglycemia (blood or plasma glucose < 2.2 mmol/L; < 40 mg/dL)
- Severe malarial anemia (hemoglobin concentration ≤ 5 g/dL or a hematocrit of ≤ 15% in children < 12 years of age (< 7 g/dL and < 20% respectively in adults) with a parasite count > 10,000/µL)
- Renal impairment (plasma or serum creatinine > 265 µmol/L (3 mg/dL) or blood urea > 20 mmol/L)
- Jaundice (plasma or serum bilirubin > 50 µmol/L (3 mg/dL) with a parasite count > 100,000/µL)
- Pulmonary edema (radiologically confirmed or oxygen saturation < 92% on room air with a respiration rate > 30/min, often with chest indrawing and crepitation on auscultation)
- Significant bleeding (including recurrent or prolonged bleeding from the nose, gums of venipuncture sites, hematemesis or melena)
- Shock (compensated shock i.e., capillary refill ≥ 3s or temperature gradient on leg but no hypotension; decompensated shock i.e., systolic blood pressure < 70 mm Hg in children or < 80 mm Hg in adults with evidence of impaired perfusion)
- Hyperparasitemia (*P. falciparum* parasitemia > 10%)

If a patient experiences and danger signs / signs of severe malaria, the investigator should report the event as an SAE following the guidance provided in Section 8.6.3. Local guidance should be followed for the treatment of these danger signs / signs of severe malaria.

8.4.7 Appropriateness of safety measurements

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

8.5 Additional assessments

As per Section 4.6, during a public health emergency as declared by local or regional authorities' i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if patients cannot visit the site for protocol-specified PK and CCI [redacted], an alternative lab (local) collection site may be used.

8.5.1 Meal Records

Meal records are required for domiciled meals on the day(s) indicated in the assessment table (Table 8-1).

For domiciled meals on days indicated in the Assessment Schedule Table 8-1, the date and start and end time and percentage of meal consumption will be recorded in the appropriate section of the eCRFs.

8.5.2 Other assessments

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

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

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

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

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

8.6.1 Adverse events

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

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

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 8.6.2):

1. The severity grade
    - mild: usually transient in nature and generally not interfering with normal activities
    - moderate: sufficiently discomforting to interfere with normal activities
    - severe: prevents normal activities

2. Its relationship to the study treatment and other investigational treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e., progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single patient
3. Its duration (start and end dates or ongoing) and the outcome must be reported
4. Whether it constitutes a SAE (see Section 8.6.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

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

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/permanently discontinued

6. Its outcome

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

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 for at least 30 days (or 5 half-lives or end of study visit, whichever is longer) following the last dose of study treatment.

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

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

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

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

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

8.6.2 Serious adverse events

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

- fatal
- life-threatening

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

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

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

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

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

8.6.3 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days following the last administration of study treatment if there are post-treatment follow-up visits with no required procedures must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

SAEs occurring after the patient has provided informed consent until the time the patient is deemed a Screen Failure must be reported to Novartis.

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

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

Suspected Unexpected Serious Adverse Reactions (SUSARs) and SAEs 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 after the 30-day period following the last administration of study treatment should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

Protocol specific SAEs to be reported to Novartis within 24 hrs:

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8.6.4 Pregnancy Reporting

- Details of all pregnancies in female patients and, if indicated, female partners of male patients will be collected after the start of study treatment and until 30 days after administration of study drug or for 5 half-lives, whichever is longer.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- Any post study pregnancy-related SAE considered reasonably related to the study treatment by the investigator will be reported to Novartis as described in Section 8.6.3. While the investigator is not obligated to actively seek this information in former study patients/pregnant female partners, he or she may learn of an SAE through spontaneous reporting.

Any female patient who becomes pregnant while participating in the study will discontinue the study.

Pregnancies

If a female trial patient becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial patient. The patient must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy. To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy 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 investigational medicinal product in any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

If a female partner of a male trial patient who took study treatment in this study becomes pregnant, pregnancy outcomes should be collected. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

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

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

There are no disease-related events and/or disease-related outcomes that would not qualify as an AE or SAE.

8.7 Pharmacokinetics

PK samples will be collected at the visits defined in the cohort specific assessment schedules (Section 12). Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing and shipment. CCI [redacted]

In order to better define the PK profile, the timing of the PK sample collection may be altered based on emergent data. Pharmacokinetic (PK) samples will be obtained and evaluated in all patients treated with the anti-malarial agents and combinations included in this study at all dose levels. A bioanalyst will only analyze samples from the patients on investigational drug(s). The parent drug(s) will be determined by a validated LC-MS/MS method. CCI [redacted]

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. In case of missing drug concentrations, impact of this on PK parameter calculation and interpretation will be considered.

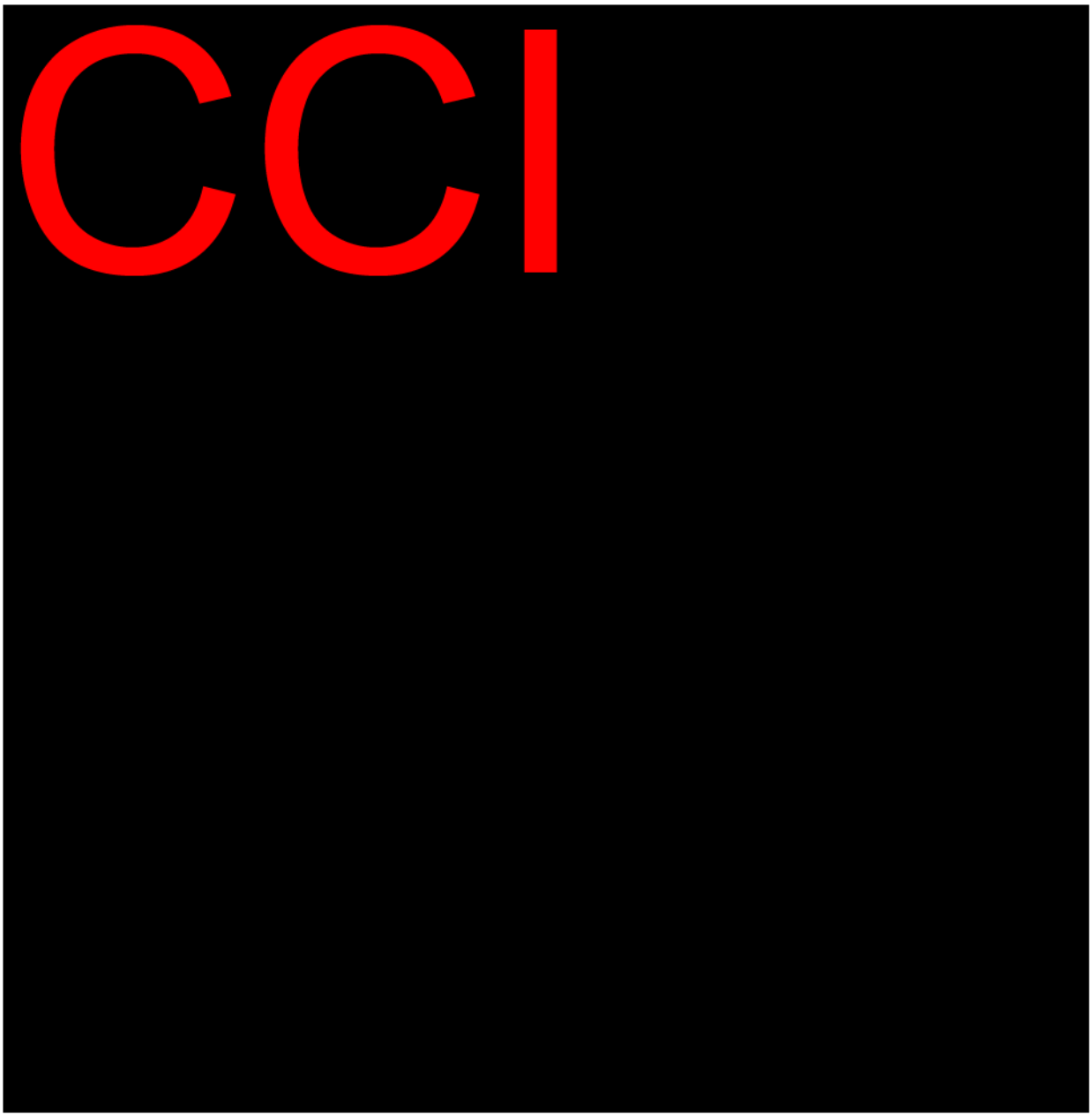
For standard pharmacokinetic abbreviations and definitions, see the List of Abbreviations.

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): Cmax, Tmax, AUClast, AUCinf, T1/2, Vz/F and CL/F from the plasma concentration-time data.

The linear trapezoidal rule will be used for AUC calculation. Regression analysis of the terminal plasma elimination phase for the determination of T1/2 will include at least 3 data points after Cmax. If the adjusted R2 value of the regression analysis of the terminal phase will be less than 0.75, no values will be reported for T1/2, AUCinf and Cl/F.

8.8 Biomarkers


CCI



8.9 Health economics

Health economics parameters are not evaluated in this study.

9 Statistical considerations

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

For each single anti-malarial agent, statistical analyses for Part A and Part B will be performed separately for efficacy and safety outcomes.

For statistical analyses and clinical study reporting, treatment group name, instead of cohort number, will be used for both parts and the pooled analysis. The treatment group will be labeled to include the full dose level of both study drugs for the combination therapy.

For SoC in Part B, pooling across compounds may be considered. Further details will be provided in the statistical analysis plan (SAP).

9.1 Analysis sets

The following analysis sets are considered for the study:

- Randomized analysis set (RAS): all patients who are randomized.
- Full analysis set (FAS): the FAS will be comprised of all patients that have baseline *P. falciparum* count > 0 and take at least one dose of the study treatment during the treatment period. Following the intent-to-treat principle, patients will be analyzed according to the treatment group assigned at randomization.
- The Safety analysis set (SAF) includes all patients who received at least one dose of the study treatment. Patients will be analyzed according to the study treatment received.
- PK analysis set: All patients 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). In general, SAF will be used for safety analysis, RAS for demographics, FAS for efficacy analyses and PK analysis set for all PK analyses, unless otherwise stated.

9.2 Statistical analyses

9.2.1 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by single anti-malarial agent, study part, and treatment group for the RAS set.

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

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by single anti-malarial agent, study part, and treatment group.

9.2.2 Treatments

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

The duration of exposure in number of doses to each treatment will be summarized by means of descriptive statistics for the SoC in Part B.

Concomitant medications, rescue and other anti-malarial medications as well as significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized by anti-malarial agent, study part, and treatment group.

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

9.3.1 Definition of primary endpoint(s)

The primary efficacy endpoint of the study in Part A is the time to parasite clearance (PCT), as defined as the time (in hours) from the first dose until the first total and continued disappearance of asexual parasite forms which remained at least a further 48 hours. PCT, will be calculated based on uncorrected *P. falciparum* asexual parasite counts. The FAS will be used for the analysis.

The primary efficacy endpoint in Part B is the PCR corrected Adequate Clinical and Parasitological Response (ACPR) at Day 29 as defined in Section 8.3.4. The FAS will be used for the analysis.

PCT and PCR corrected ACPR will be used for the primary estimand analyses in Part A and Part B, respectively.

9.3.2 Statistical model, hypothesis, and method of analysis

For Part A, descriptive statistics (mean, standard deviation, median, quartiles) will be provided by treatment group. Individual plots will be provided, and Kaplan-Meier curves will be presented by study part and treatment group. The primary analysis tests whether the upper limit of two-sided 90% CI for the median PCT using Kaplan-Meier estimates for a treatment group is lower than 96 hours.

For Part B, the primary endpoint will be calculated at Day 29 by computing the percent of patients with PCR corrected ACPR for each treatment group. The primary analysis will test for non-inferiority of the combination therapy versus SoC based on the dual efficacy criteria as specified below, CCI [redacted] Informative priors for the SoC will be used, while for the combination treatment prior information may be vague or informative depending on whether relevant prior information is available.

Table 9-1 shows the historical data about the 28-day cure rate observed in historical trials for the SoC.

Further details on the prior used for the combination therapy will be specified in the Cohort Specific Information in Section 12 and details of the statistical methodology will be outlined in the SAP.

The dual efficacy criteria are the following:

9.3.3 Handling of intercurrent events of primary estimand

The primary analysis in Part A will account for below mentioned inter-current events using a hypothetical strategy. If a patient receives any rescue anti-malarial medication or receives other concomitant medication having an effect on malaria for any reasons, the time-to-event PCT will be set to Day 7 from the day of the occurrence of the event.

The primary analysis in Part B will account for the below mentioned inter-current events using a principal stratum strategy. Data will be handled as follows:

9.3.4 Handling of missing values not related to intercurrent event

For handling missing values in the primary analysis in Part A, the following strategies will apply:

- If the parasite is not cleared and the last parasite count is missing but not related to intercurrent event, the time-to-event PCT will be censored at Day 7.
- If an intermediate parasite count is missing between 2 existing measures (e.g., such as missing sample, technical reason, etc.):
  - If both previous and following measures are quantifiable and above the limit of quantification, the intermediate value will be considered as presence of parasite.
  - If both previous and following measures are below the limit of quantification, the missing value will be considered as no presence of parasite.
  - If the previous measure is quantifiable and above the limit of quantification, but not the following measure, the intermediate value will be considered as presence of parasite.

In Part B no imputation of data will be performed.

9.3.5 Sensitivity analyses

In Part B, 2-sided 80% confidence intervals for the difference to SoC will be constructed using the Wilson uncorrected method.

9.3.6 Supplementary analysis

Supplementary analyses are not planned for Part A. For Part B, the computation of percent of patients with PCR uncorrected ACPR (using the FAS) and 95% confidence intervals for each treatment group will be computed, such as described in Section 9.3.2. PCR-corrected ACPR rate and PCR-uncorrected ACPR rate will be also calculated and plotted using the Kaplan-Meier method for each single anti-malarial agent, study part and treatment group in the FAS.

9.4 Secondary endpoint(s)/estimand(s) analysis

The secondary efficacy variable in Part A is the PCR corrected ACPR, at Day 29 as defined previously in Section 9.3.1.

The secondary efficacy variable in Part B is the PCT as defined previously in Section 9.3.1.

The secondary estimand will be used to analyze the PCR corrected ACPR in Part A and PCT in Part B.

In addition, pharmacokinetics and safety and tolerability will also be assessed.

9.4.1 Efficacy and/or Pharmacodynamic endpoint(s)

The secondary analysis for Part A will be the computation of percent of patients with PCR corrected (using the RAS) and uncorrected ACPR (using the FAS) and 95% confidence intervals for each treatment group as described in Section 9.3.2. No hypothesis testing will be performed.CCI [redacted]

At each visit, the percent of patients with PCR corrected and uncorrected ACPR and 95% confidence intervals will be provided using Clopper-Pearson method for each single anti-malarial agent and for each treatment group. 2-sided 80% confidence intervals for the difference to SoC at each visit will be constructed using the Wilson uncorrected method. At each visit, PCR uncorrected failure will be classified into, ETF before Day 4, LCF before Day 8, recrudescence, new infection, negative PCR, missing PCR, or missing assessment. The classification will be tabulated using the FAS.

CCI [redacted]

If relevant, key efficacy endpoints will be summarized by treatment group for subgroups of participants with or without relevant resistance mutations.

9.4.2 Safety endpoints

For all safety analyses, the SAF will be used. All listings and tables will be presented by single anti-malarial agent, study part, and treatment group.

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

Adverse events

All information obtained on adverse events will be displayed by each single anti-malarial agent, study part, treatment group and patient.

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

- by each single anti-malarial agent, study part, treatment group, primary system organ class and preferred term.
- by each single anti-malarial agent, study part, treatment group, primary system organ class, preferred term and maximum severity.
- by each single anti-malarial agent, study part, treatment group, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation, and adverse events leading to dose interruption in the SoC of Part B.

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

Vital signs

All vital signs data will be listed by single anti-malarial agent, study part, treatment group, patient, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by single anti-malarial agent, study part, treatment group, and visit/time.

12-lead ECG

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

Categorical Analysis of QT/QTc interval data based on the number of patients meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these patients will be produced (by each single anti-malarial agent, study part and treatment group).

All ECG data will be listed by each single anti-malarial agent, study part, treatment group, patient and visit/time, abnormalities will be flagged. Summary statistics will be provided by each single anti-malarial agent, study part, treatment group, and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by each single anti-malarial agent, study part, treatment group, patient, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by each single anti-malarial agent, study part, treatment group, and visit/time. Shift tables for each single anti-malarial agent and study part using the low/normal/high classification will be used to compare baseline to the worst post-treatment value.

9.4.3 Pharmacokinetics

The PK analysis set will be used for the pharmacokinetics analyses.

Table 9-2 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})
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (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)
Lambda_z	Smallest (slowest) disposition (hybrid) rate constant (time^{-1}) may also be used for terminal elimination rate constant (time^{-1})
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
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)

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9.4.5 PK/PD relationships

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

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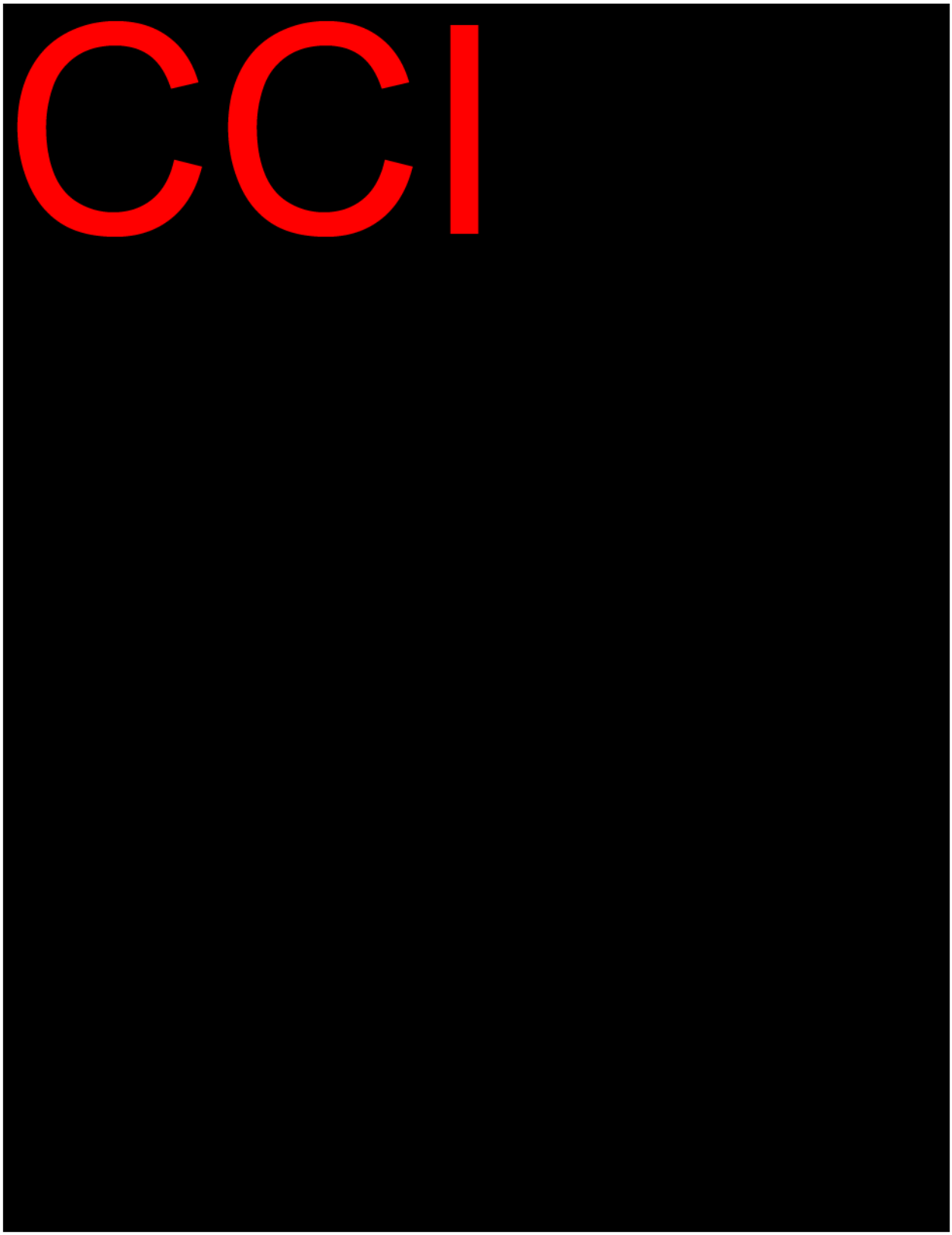
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9.6 (Other) Safety analyses

Not applicable.

9.7 Interim analyses

Data Reviews and dose modifications between each part will be conducted by reviewing available data as described in Section 4.4 and Section 6.5.

Interim analyses are planned for the monitoring of safety data and will be performed approximately after each cohort during the course of the study.

The decision to continue to Part B of the study will be made by the Sponsor and the DMC. If notable adverse events or safety concerns are found at one of the planned dose levels in Part A, the planned dose level in Part B may be adjusted.

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9.8 Sample size calculation

9.8.1 Primary endpoint(s)

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9.8.2 Secondary endpoint(s)

10 Supporting documentation and operational considerations

10.1 Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

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

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

- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

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

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

The investigator will be responsible for the following:

- Signing a protocol signature page confirming 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
- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, and all other applicable local regulations
- Inform Novartis immediately if an inspection of the clinical site is requested by a regulatory authority

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, and with the ethical principles laid down in the Declaration of Helsinki.

10.1.2 Informed consent process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the patient or their legally authorized representative and answer all questions regarding the study.

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

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

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

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

A patient who is rescreened is not required to sign another ICF if the rescreening occurs within 6 hours from the previous ICF signature date. The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional additional research. The investigator or authorized designee will explain to each patient the objectives of the additional research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a patient's agreement to allow any remaining specimens to be used for additional research. Patients who decline to participate in this optional additional research will document this.

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

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

Information about common side effects already known about the investigational treatment can be found in the Investigator's Brochure (IB) (or Core Data Sheet for marketed drugs). This information will be included in the patient informed consent and should be discussed with the patient upon obtaining consent and also during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the patient.

The following informed consents are included in this study:

- Main study consent, which also includes:
  - 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
- As applicable, Pregnancy Outcomes Reporting Consent for female patients or the female partners of any male patients who took study treatment
- Patient information sheet for female partners of any male patient who took study treatment
- CCI

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10.1.3 Data protection

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

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

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

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

10.1.4 Committees Structure

10.1.4.1 Data monitoring committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site Investigators participating in the study. The DMC will review the available clinical trial data in the following situations:

- To decide on the transition of an agent between study Parts
- Planned IAs and unplanned IAs
- If study stopping criteria are met

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

10.1.5 Data quality assurance

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

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the

retention period without the written approval of Novartis. No records may be transferred to another location or party without written notification to Novartis.

10.1.5.1 Data collection

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

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 will receive copies of the patient data for archiving at the investigational site.

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

10.1.5.2 Database management and quality control

Novartis personnel (or 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.

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

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

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to

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

10.1.6 Source documents

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

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

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

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

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

10.1.7 Publication policy

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

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

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

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

10.1.8 Protocol adherence and protocol amendments

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

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

10.1.8.1 Protocol amendments

This study uses a platform type design with the potential to investigate multiple therapies in the context of a single disease. Each time a new agent is introduced, agent-specific information will be added to the protocol as a substantial amendment and submitted to Health Authorities and Ethical Committees, as required by local regulations.

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

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

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

11 Appendices

11.1 Appendix 1: Liver Safety Monitoring

Liver safety monitoring

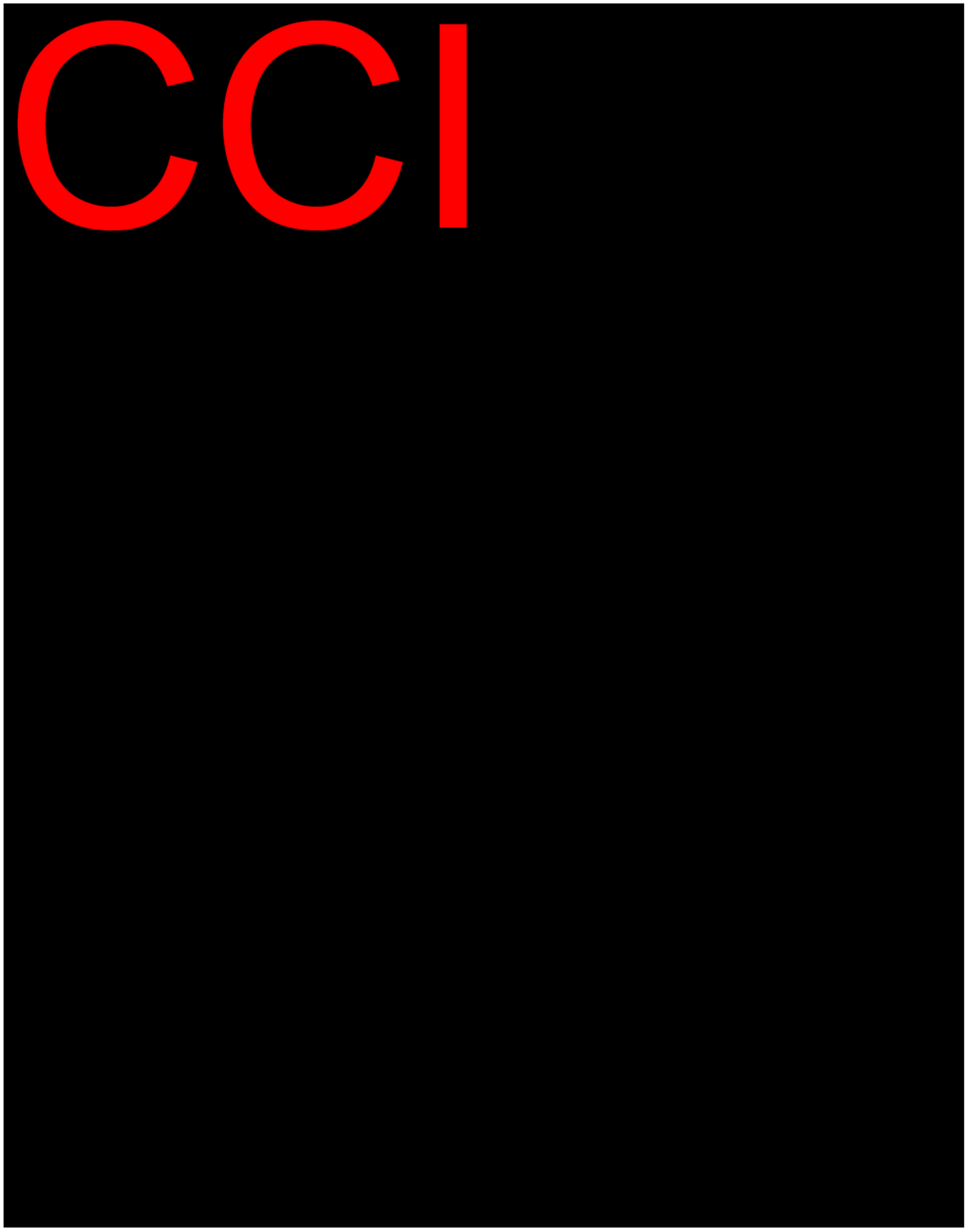
To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Once a patient is exposed to study treatment, every liver event defined in Table 11-1 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 11-2 and Table 11-3. Repeat liver chemistry tests (i.e., ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

- These liver chemistry repeats will be performed a local laboratory to monitor the safety of the patient. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.
- If the initial elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 7 Discontinuation of study treatment section), if appropriate
- Hospitalization of the patient if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should 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.

Potential Hy's Law cases (defined as ALT or AST $> 3 \times$ ULN and Total bilirubin $> 2 \times$ ULN [mainly conjugated fraction] without notable increase in ALP to $> 2 \times$ ULN) need to be reported as SAE to Novartis within 24 hrs.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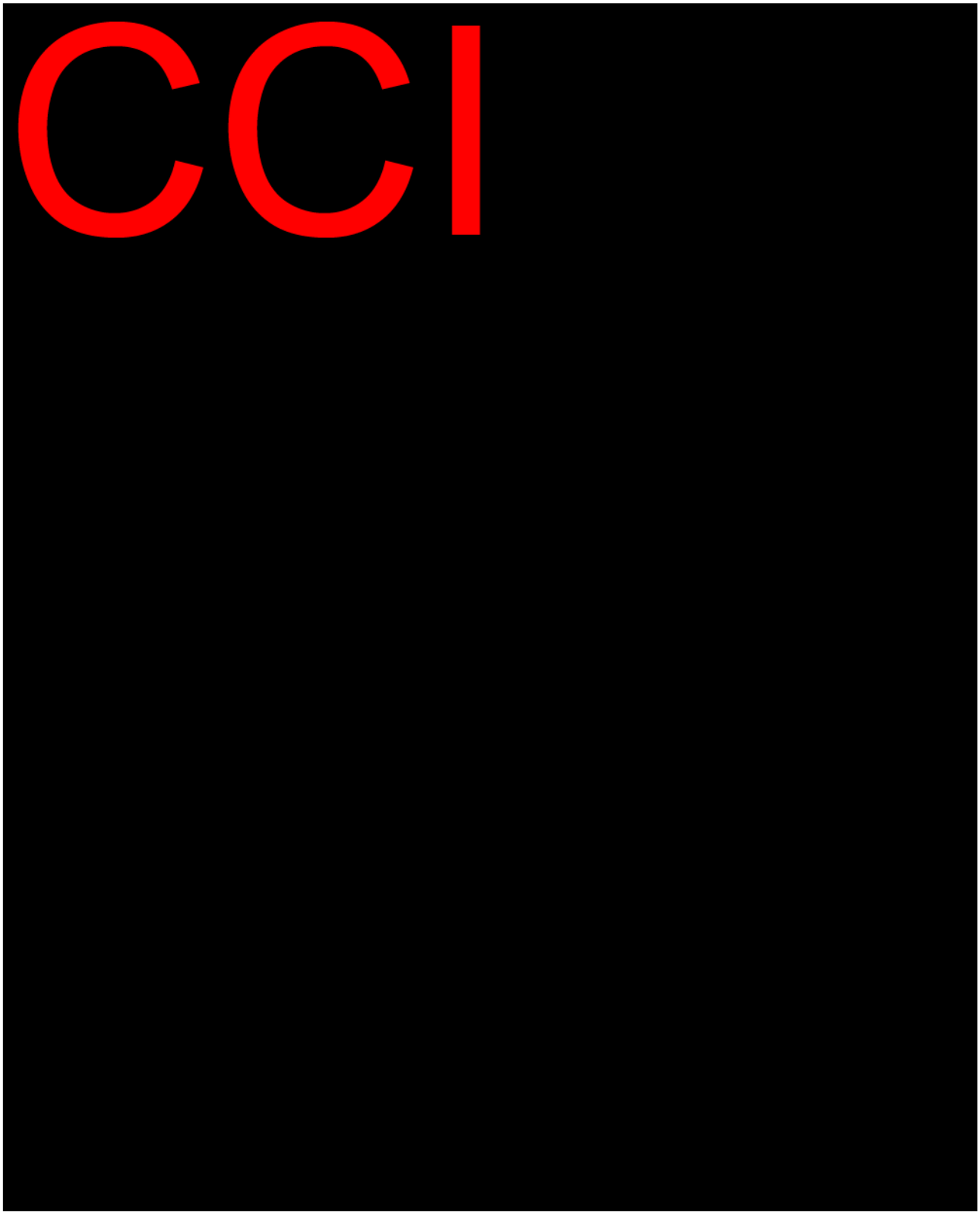
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12 Cohort Specific Information

This section contains details that pertain to specific cohorts and anti-malarial agents and should be considered as supplementary to information presented in the preceding core protocol sections and respective Investigator Brochures. If there are no treatment-specific details presented for a given topic (e.g., cohort- or treatment-specific eligibility criteria, study restrictions, food effects, etc.), then the information in the corresponding section in the core protocol for that topic should be implemented without further adjustment.

12.1 Cohort A1: INE963

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12.1.1 INE963 Background

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12.1.2 Cohort A1 Study Design

As mentioned in Section 3, this is a multi-part platform study. Part A evaluates anti-malarial agents as monotherapy, and Part B evaluates anti-malarial agents as combination therapy

In Cohort A1, patients will receive a single dose of INE963.

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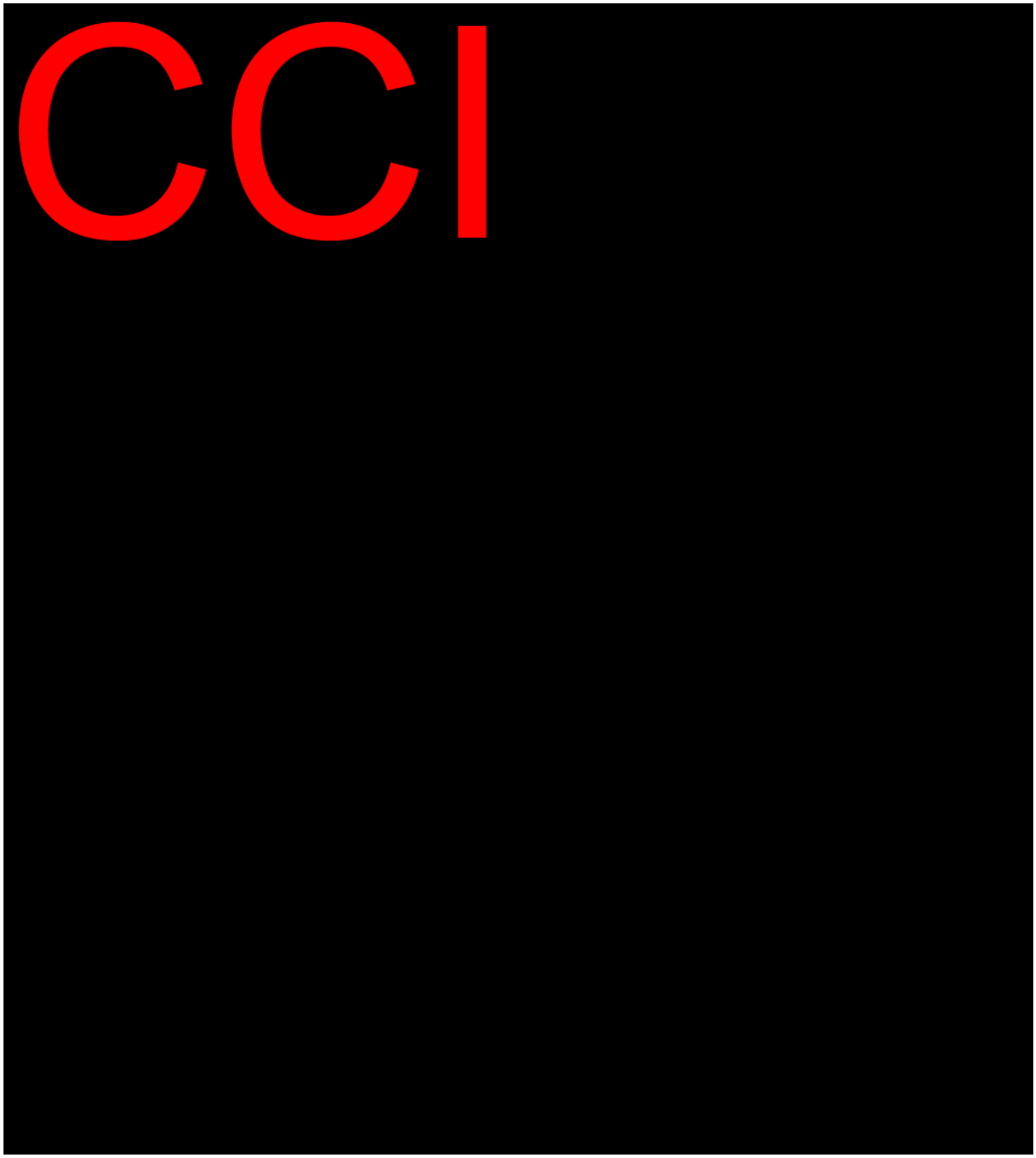
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12.1.4 Cohort A1 Risks and Benefits

INE963 is expected to reduce the number of circulating malaria parasites in the blood of patients and consequently improve their clinical symptoms.

INE963 IMP Related Risk

Against the background of the COVID-19 pandemic, the potential risk of a patient developing COVID-19 has been considered in terms of the risk-benefit evaluation. The mode of action of this anti-malarial agent has been considered alongside available pre-clinical and clinical data (including class effects) and it is considered that a patient would not be at increased risk of either becoming infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; the virus that causes COVID-19) or experiencing a more severe illness. That is, this agent has no known immunomodulatory effect that would confer an increased risk to patients enrolled in the study.

12.1.5 Cohort A1 Study Population and Special Restrictions

Additional Exclusion Criteria

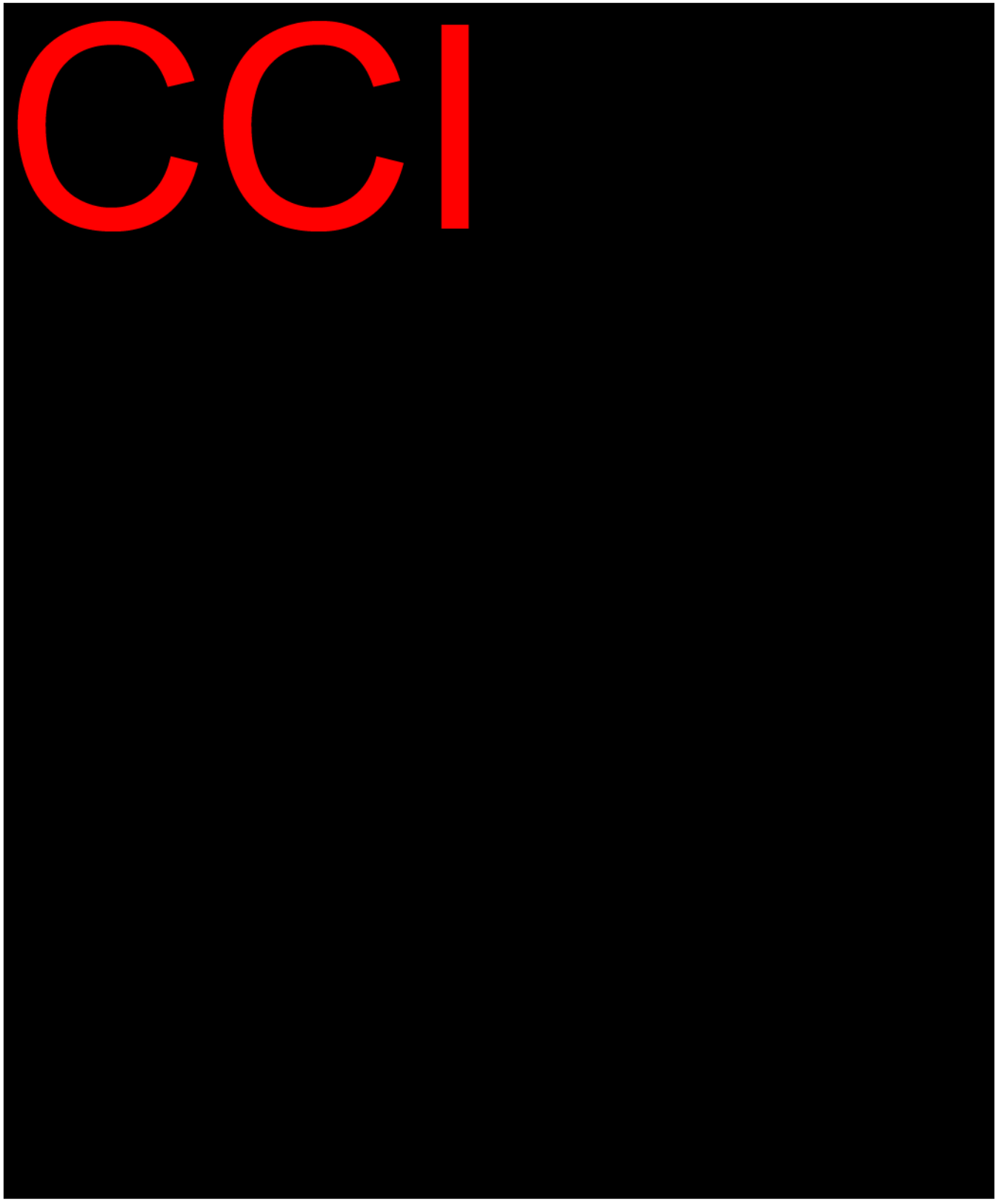
Patients meeting any of the following criteria are not eligible for inclusion in this cohort:

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 5 half-lives. Highly effective contraception methods include:

- Total abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female bilateral tubal ligation, female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), or total hysterectomy at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.

- Use of oral (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception. Coartem/Riamet may reduce the effectiveness of hormonal contraceptives. Therefore, patients randomized to Coartem using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control.
- In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

12.1.5.1 Permitted concomitant therapy requiring caution and/or action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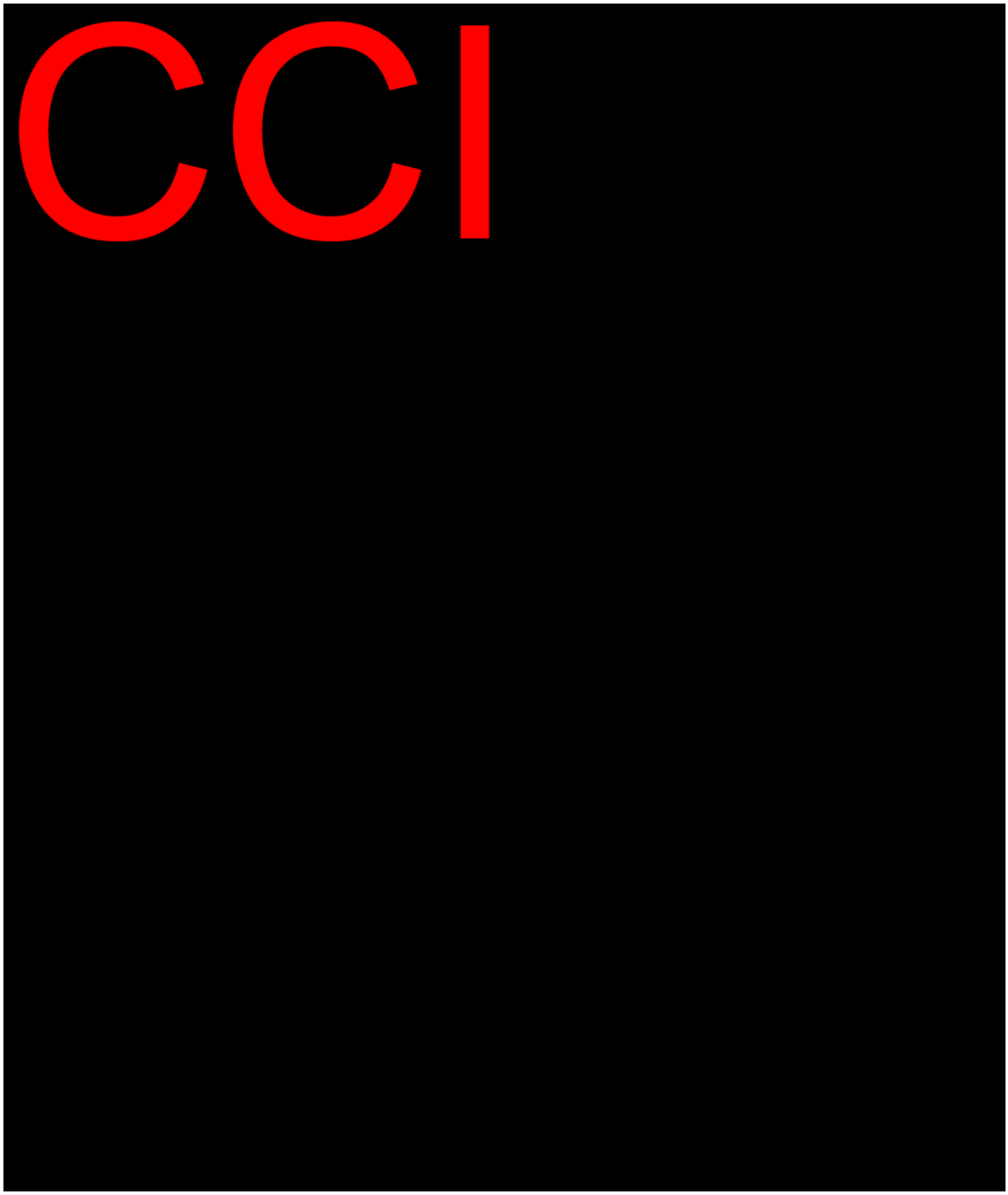
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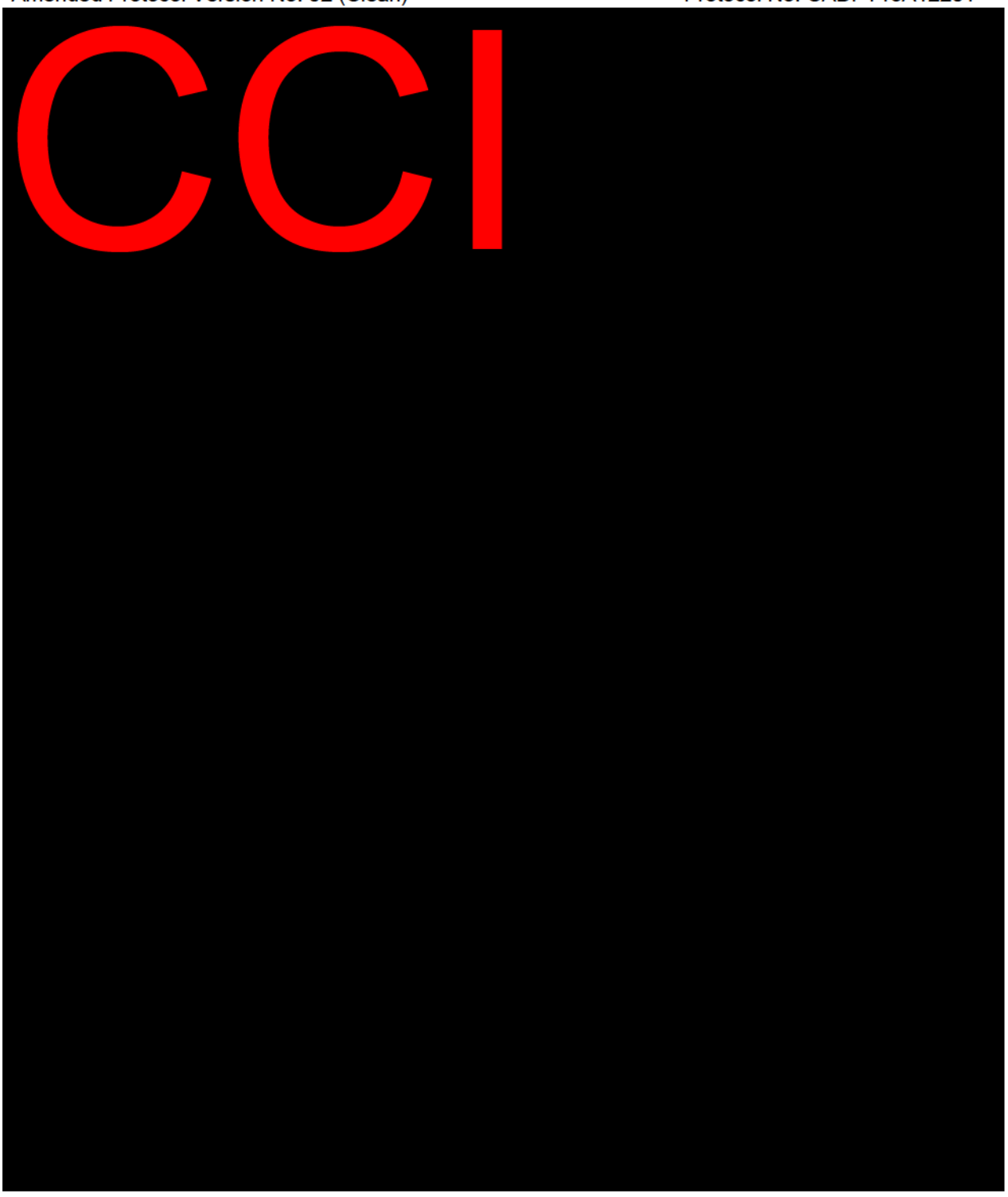
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12.2 Cohort B1: INE963 + Cipargamin

Cohort B1 will start after the completion of Cohort A1. Cohort B1 will evaluate the use of INE963 and KAE609 (cipargamin) in combination vs the SoC (Coartem) in patients with uncomplicated *P. falciparum* malaria.

INE963 background information can be found in Section 12.1.1.

12.2.1 Cipargamin Background

Cipargamin, a spiroindolone, represents a new class of potent, fast-acting, schizonticidal anti-malarial. It appears to exert its antiplasmodial activity through deregulatation of Na^+ homeostasis in the parasite cytosol through inhibition of a P-type nonSERCA ATPase, PfATP4.

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12.2.2 Cohort B1 Study Design

In Cohort B1, INE963 and cipargamin will be evaluated as combination therapy vs the SoC (Coartem).

Table 12-9 Treatment Arm(s) for Cohort B1 – INE963 + Cipargamin

Arm Title	INE963 + Cipargamin	Standard of Care
Arm Type	Experimental	Standard of Care control - Coartem
Arm Description	CCI	BID for 3 days (at the following time points: 0, 8, 24, 36, 48, and 60 hours) and must be received with a standard meal or drink rich in fat, as per label.

12.2.3 Cohort B1 Sample Size


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12.2.6 Cohort B1 Study Population and Special Restrictions

Additional Exclusion Criteria

Patients meeting any of the following criteria are not eligible for inclusion in this study:

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 5 half-lives. Highly effective contraception methods include:

- Total abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female bilateral tubal ligation, female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), or total hysterectomy at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.

- Use of oral (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception. Coartem/Riamet may reduce the effectiveness of hormonal contraceptives. Therefore, patients randomized to Coartem using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control.
- In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

In addition to the below special restriction(s) specific to cipargamin, the special restrictions specific to INE963 can be found in Section 12.1.5.

- Patients are advised to use commonly recommended precautions when in the sun (e.g., sunscreen, hat, protective clothing) from first dosing until study completion evaluation.

12.2.6.1 Permitted concomitant therapy requiring caution and/or action

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12.2.8 Cohort B1 PK/PD and Biomarker Assessments


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12.2.9 Cohort B1 Compound Specific Assessments

12.3 Cohort B2: KLU156 + cipargamin

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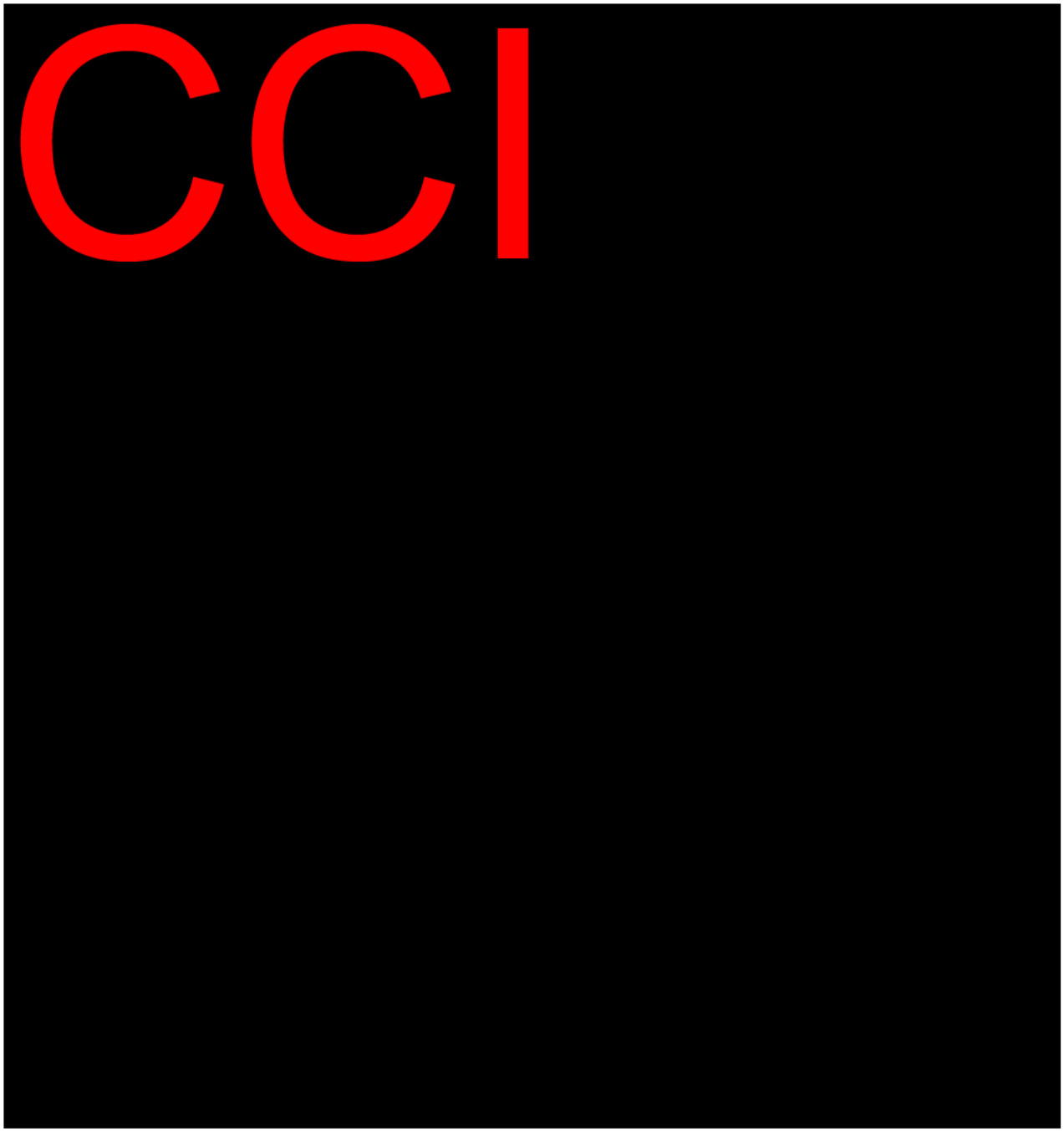
12.3.1 KLU156 Background



12.3.2 Cohort B2 Study Design

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12.3.3 Cohort B2 Sample Size

12.3.4 Cohort B2 Dose Rationale

12.3.4.1 Rationale for choice of KAE609 as combination drug with KLU156

Selection of cipargamin as partner drug with KLU156 for Cohort B2:

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[redacted]

12.3.4.2 Rationale for dose/regimen and duration of treatment

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12.3.5 Cohort B2 Risks and Benefits

Risks and benefits relating to cipargamin

Risks and benefits relating to cipargamin can be found in Section 12.2.5.

KLU156 and cipargamin IMP Related Risk

Against the background of the COVID-19 pandemic, the potential risk of a patient developing COVID-19 has been considered in terms of the risk-benefit evaluation. The mode of action of this anti-malarial agent has been considered alongside available pre-clinical and clinical data (including class effects) and it is considered that a patient would not be at increased risk of either becoming infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; the virus that causes COVID-19) or experiencing a more severe illness. That is, this agent has no known immunomodulatory effect that would confer an increased risk to patients enrolled in the study.

Related Risk and Benefits Related to KLU156 (KAF156 i.e., ganaplacide/LUM-SDF i.e., lumefantrine-SDF)

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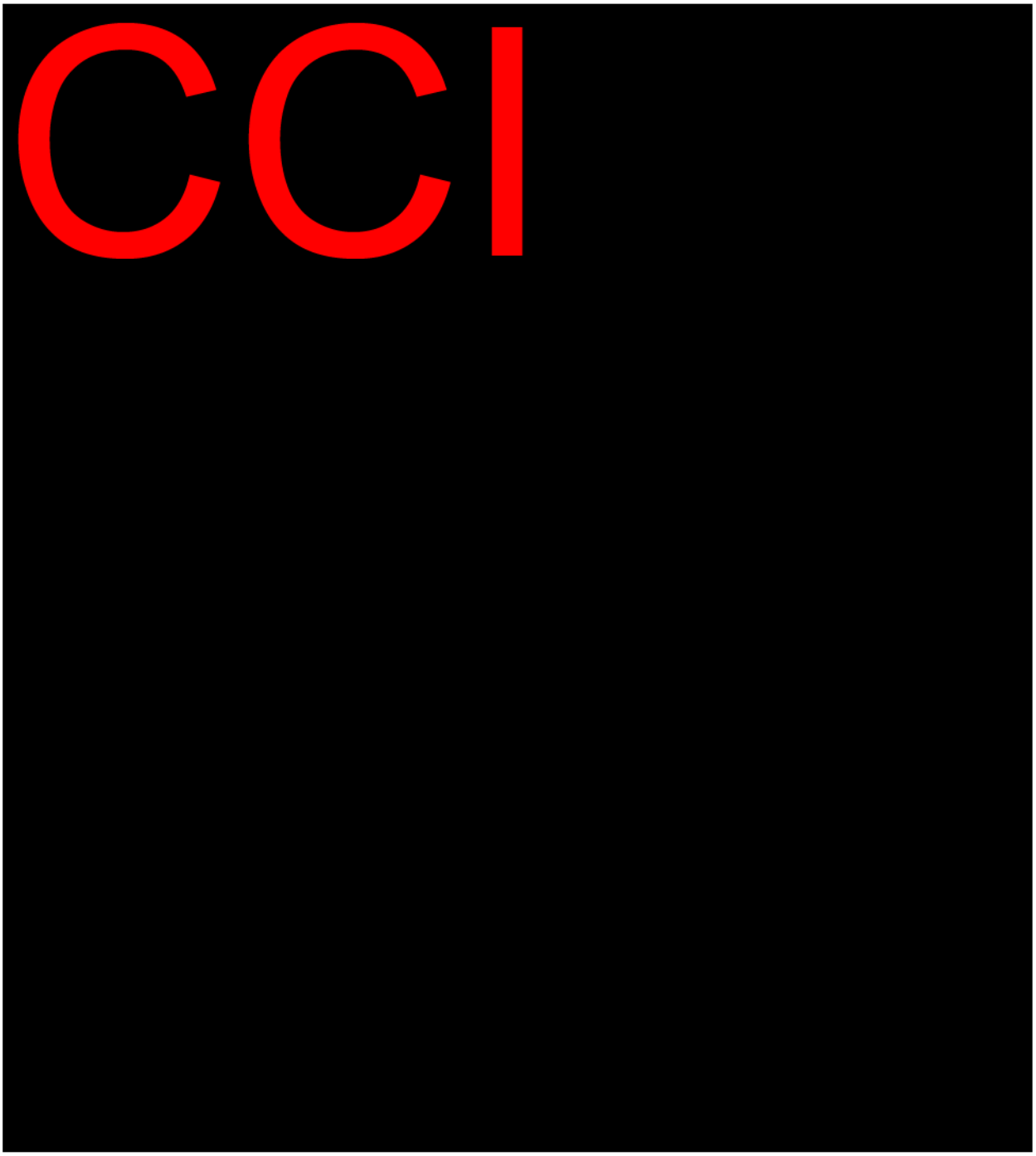
Risks and benefits relating to cipargamin and KLU156 co-administration



12.3.6 Cohort B2 Study Population and Special Restrictions

Additional Exclusion Criteria

Patients meeting any of the following criteria are not eligible for inclusion in this study:

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 5 half-lives. Highly effective contraception methods include:

- Total abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female bilateral tubal ligation, female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), or total hysterectomy at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.
- Use of oral (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception. Coartem/Riamet may reduce the effectiveness of hormonal contraceptives. Therefore, patients randomized to Coartem using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control.
- In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

12.3.6.1 Permitted concomitant therapy requiring caution and/or action

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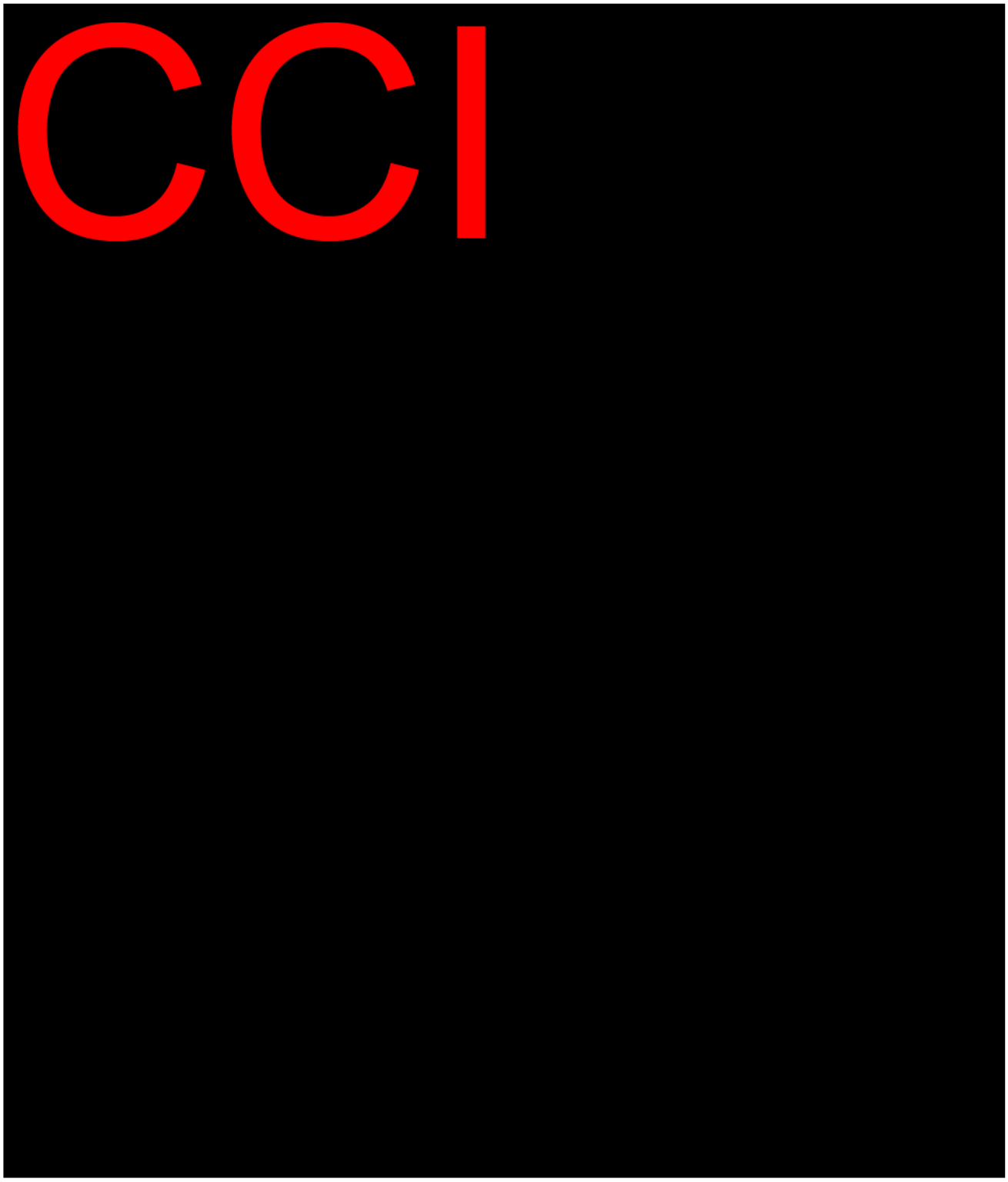
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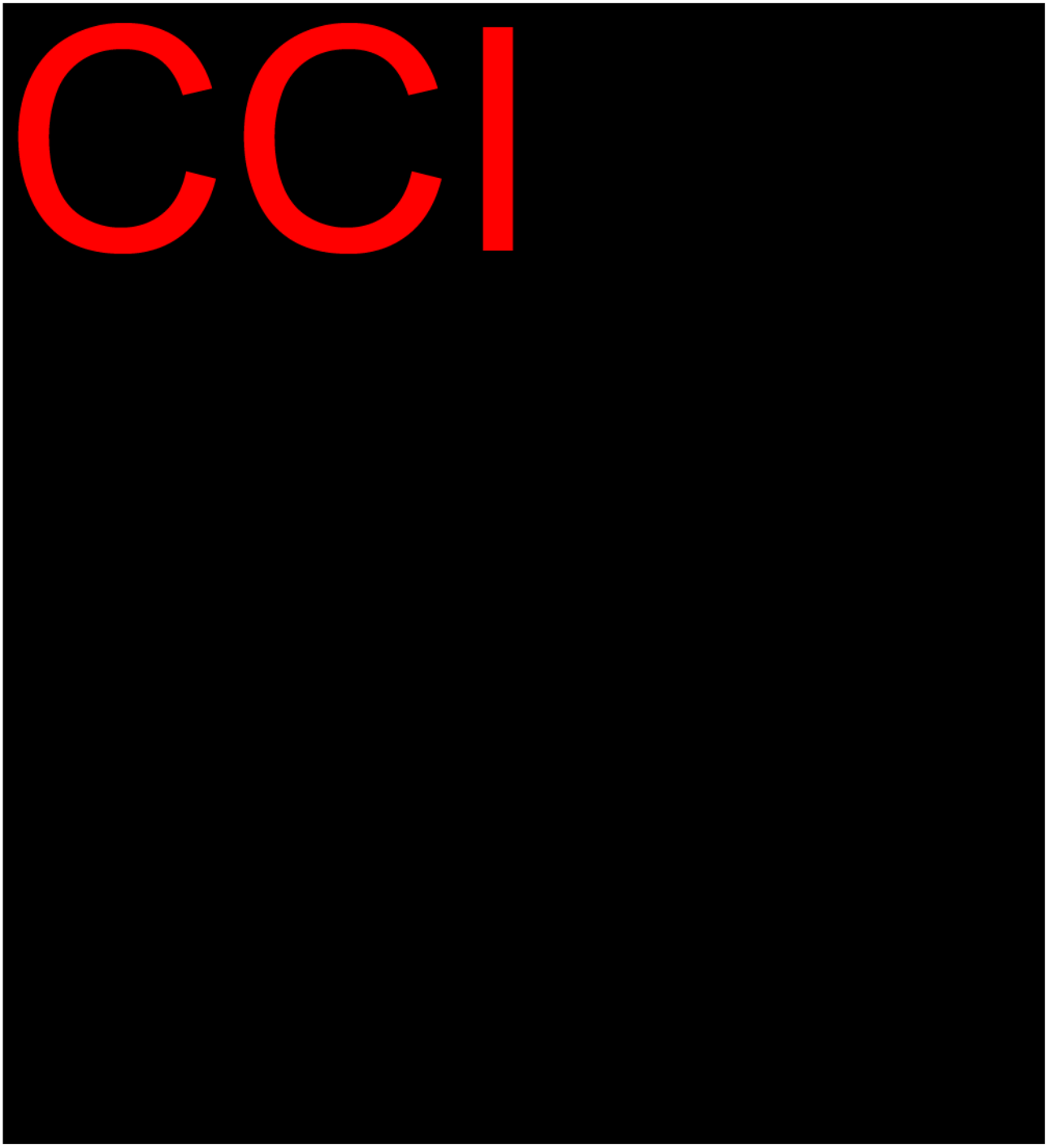
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12.3.7 Cohort B2 Study Treatment

- Patients should be instructed to swallow whole capsules and not to chew or open them.
- Each subject's mouth must be checked to ensure that the medication was swallowed.
- Subjects should be administered KLU156 under fed conditions with light meal (estimate of 100-300 calories, 5-10 g of fat). Cipargamin can be administered irrespective of food intake
- In case of Coartem, medication should be followed by a normal diet or a drink rich in fat (including broth, sweetened condensed milk, etc.) within 30 min of dosing as per label.

- In case that vomiting occurs
  - KLU156+ cipargamin: In the case that the patient vomits within 1 hour of intake a replacement dose will be given to the patient and the investigator or designee will notify IRT. If the replacement dose is vomited, the patient has to be given Coartem as rescue medication or another suitable rescue medication as per local guidelines.
  - Coartem: In the case that the patient vomits within 1 hour of intake a replacement dose will be given to the patient and the investigator or designee will notify IRT. If the replacement dose is vomited, the patient has to be given non-lumefantrine standard of care.

12.3.8 Cohort B2 PK/PD and Biomarker Assessments


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Pharmacokinetic assessments will be performed as described in Section 8.7. In addition to PK parameters mentioned in Section 8.7, C168h (concentration at 168h) and AUC0-168h (Area under the plasma concentration time curve from zero to 168h) will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher).

12.3.9 Cohort B2 Compound Specific Assessments

13 References

References are available upon request

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

Burrows JN, Duparc S, Gutteridge WE, et al (2017) Erratum to: New developments in anti-malarial target candidate and product profiles. Malar J; 16(1):151.

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

CCI

Food and Drug Administration (2016) Clinical Trial Design Considerations for Malaria Drug Development. https://www.fda.gov/drugs/news-events-human-drugs/clinical-trial-design-considerations-malaria-drug-development. Accessed 29-Nov-2022.

CCI

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

CCI

Noedl H, Socheat D, Satimai W (2009) Artemisinin-resistant malaria in Asia. N Engl J Med; 361(5):540-1.

Uwimana A, Legrand E, Stokes BH, et al (2021) Author Correction: Emergence and clonal expansion of in vitro artemisinin-resistant Plasmodium falciparum kelch13 R561H mutant parasites in Rwanda. Nat Med; 27(6):1113-5.

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

Woodcock J, LaVange L (2017) Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. N Engl J Med; 377(1):62-70.

World Health Organization (2015) Guidelines for the treatment of malaria. https://apps.who.int/iris/handle/10665/162441. Accessed 17-Sep-2021.

World Health Organization (2021) World malaria report 2021. https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2021. Accessed 08-Apr-2022.

World Health Organization (2022) WHO Guidelines for Malaria. https://app.magicapp.org/#/guideline/5701. Accessed 29-Nov-2022.