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COA566

Clinical Trial Protocol CCOA566B2307 / NCT04300309

A multicenter, open-label, single-arm study to evaluate the PK, safety, tolerability and efficacy of a new artemether-lumefantrine (2.5 mg:30 mg) dispersible tablet in the treatment of infants and neonates <5 kg body weight with acute uncomplicated *Plasmodium falciparum* malaria

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List of abbreviations

ACPR	Adequate Clinical and parasitological Response
ACT	artemisinin-based combination therapy
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ART	artemether
ARV	antiretroviral
ASAQ	artesunate-amodiaquine
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
b.i.d.	twice a day
BMI	Body Mass Index
BW	body weight
CFR	Code of Federal Regulation
CI	Confidence Interval
C_{max}	in the context of this study, C_{max} is meant as the higher concentration between those at 1 hour or 2 hours post first dose
CMO	Chief Medical Office (Novartis)
CNS	Central Nervous System
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTT	Clinical Trial Team
CV	coefficient of variation
DBP	Diastolic Blood Pressure
DHA	Dihydroartemisinin
DMC	Data Monitoring Committee
e.g.	For example
EC	Ethics committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
ETF	Early Treatment Failure
FAS	full analysis set
FCT	Fever clearance Time
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLDH	Glutamate dehydrogenase
HIV	Human Immunodeficiency Virus
i.e.	That is to say

IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMCI	Integrated Management of Childhood Illness
IN	Investigator Notification
INR	International normalized ratio of prothrombin time of blood coagulation
IRB	Institutional Review Board
IRT	Interactive Response Technology
LAR	Legally Acceptable Representative
LCF	Late Clinical Failure
LLOQ	lower limit of quantification
LPF	Late Parasitological Failure
MedDRA	Medical dictionary for regulatory activities
PBPK	Physiology-Based Pharmacokinetic modeling
PCR	polymerase chain reaction
PCT	time to parasite clearance
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PPS	per protocol set
PS	Patient Safety (Novartis)
QMS	Quality Management System
QT	QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QT_c	heart rate-corrected QT
RBC	red blood cell(s)
SAE	serious adverse event
SBP	Systolic Blood Pressure
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SMQ	Standardized MedDRA Query
[redacted]	[redacted]
SNPs	Single-Nucleotide Polymorphisms
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBIL/TBL	total bilirubin
ULN	upper limit of normal
WBC	white blood cell(s)
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the screening procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study
Investigational Product/ Investigational Medicinal product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference (such as an active comparator) in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Non-investigational medicinal Product (NIMP)	Products which are not the object of investigation (e.g. any background therapy administered to each of the clinical trial subjects, regardless of randomization group, rescue medication, active drug run-ins etc.)
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, treatment, follow-up, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Recruitment	Point/time of subject selection for the study: the point at which screening is completed and eligibility has been fully confirmed so that the patient can receive first dose of treatment.
Screen Failure	A subject who is screened but is not treated or randomized
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)

Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Amendment 1

Amendment Rationale

This study has completed enrollment for Cohort 1 (22 patients, > 28 days old) and Cohort 2.1 (3 patients, 15-28 days old). As of 29-Jun-2023, recruitment for Cohort 2.2 (patients 1-28 days old) is ongoing, 2 patients have been enrolled since recruitment for Cohort 2.2 has started in November 2022.

The protocol is being amended to enable additional optional PK checks for artemether and lumefantrine and additional interim assessments by the DMC to be able to read out and provide relevant clinical data as soon as possible for this difficult to recruit patient population. In addition, errors/inconsistencies have been corrected, clarifications provided, and text related to public health emergencies and safety reporting has been updated. The key changes include:

- To allow for a PK check during Cohort 2.2, after the first 9 patients in the 1-28 days age group have been recruited in Cohort 2 (from Cohort 2.1 and 2.2 combined)
- To allow for an additional optional PK check after the first 9 patients in the 15-28 days age group have been recruited in Cohort 2 (from Cohort 2.1 and 2.2 combined)
- To allow for additional interim assessments with DMC reviews throughout the study to assess PK, safety and efficacy to support identification of appropriate dose(s) for the population under study
- To allow for determination of appropriate dose(s) for the population under study using data from the ongoing study and PBPK modeling
- To update text about public health emergencies and safety reporting

Changes to the protocol

- **List of abbreviations:** has been updated based on the changes implemented in the amendment
- **Glossary of terms**: Definition of "Investigational medicinal product" and clarification of "Investigational drug" have been added.
- **Protocol Summary, Section 3, 10.2.1**: Population is clarified to include approximately 44 patients in the study (approximately 22 patients in each cohort).
- **Section 3, 4.2, 4,4, 6.5.1.2, 10.2.1; 12.5.3, 12.7**: Editorial changes have been done to streamline text in these sections to:
  - Clarify that PK check during Cohort 2.2 to occur when first 9 patients in the 1-28 days age group are recruited from Cohort 2.1 and 2.2. An additional optional PK check may occur after the first 9 patients in the 15-28 days age group are recruited from Cohort 2.1 and 2.2.
  - Clarify that two planned interim assessments will be done in the study.
- **Section 4.2, 4,4**: Language added to enable periodic update of PBPK model to support dose recommendation if data permits.
- **Section 4.5**: Text added for public health emergency mitigation procedure.
- **Section 5**:

  - Clarification added to enable use of PBPK modeling to support dose recommendation.
  - Number of sites and countries updated to reflect the current status of the study.
  - Text added in **Section 5.2** to clarify that Appendix 1 is an example for reference for electrolyte balance
- **Table 6-1:** Modified as per latest requirements
- **Section 6.1.3:** Editorial changes done to remove redundant duplicate text since details are already provided in Section 3.
- **Section 9.1.4**: Clarification added to reflect that early study termination may also occur on DMC recommendation
- **Section 10.1.3**: Additional clarification text added about SAE reporting in eCRF
- **Section 10.2.1, 12.7**: Clarification added about optional additional interim assessments along with DMC reviews to support decision making for dose recommendation.
- **Section 12.8.2**:
  - Typographical error rectified to reflect the correct probability calculation for power consideration for Day 8 lumefantrine concentration
  - Clarification added that enrolment may stop after 16 evaluable patients for PK analyses are recruited in any of the cohorts, as 16 evaluable patients are sufficient as per original protocol.
  - Clarification added about criterion for observed half width of 2 sided 90% CI for the log concentration in case of early readout of the study

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

IRBs/IECs
A copy of this amended protocol will be sent to the Institutional Review Boards (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein do not affect the Informed Consent.

Protocol summary

Protocol number	CCOA566B2307
Full Title	Multicenter, open-label, single-arm study to evaluate the PK, safety, tolerability and efficacy of a new **a**rtemether:**l**umefantrine (2.5 mg:30 mg) dispersible tablet in the treatment of **i**nfants and **n**eonates <5 kg body weight with **a**cute uncomplicated *Plasmodium falciparum* malaria. Acronym: CALINA
Brief title	Pharmacokinetics, safety, tolerability and efficacy of a new artemether-lumefantrine dispersible tablet in infants and neonates <5 kg body weight with acute uncomplicated *Plasmodium falciparum* malaria
Sponsor and Clinical Phase	Novartis Phase II/III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This study aims to evaluate PK, safety, tolerability and efficacy of a new formulation of artemether-lumefantrine dispersible tablet in neonates and infants <5 kg body weight with acute uncomplicated *Plasmodium falciparum* malaria. Malaria is a disease that has a much higher prevalence and severity in infants and children. Although relatively infrequent as compared to the number of cases in infants and children ≥5 kg, confirmed malaria in neonates and infants <5 kg does exist in certain endemic countries and calls for evaluation of appropriate treatment. It is still a significant unmet medical need as there are no approved treatments for this vulnerable group of patients. A previous clinical study with a similar design found that artemether exposure in patients <5 kg body weight following administration of dispersible tablets (artemether:lumefantrine 20 mg:120 mg; i.e. 1:6) was around 2-3 fold higher than anticipated safe exposures, whereas exposure to lumefantrine was as expected. Given the potential neurotoxicity of artemether at high exposures, this is undesirable and therefore, following detailed Physiology-Based Pharmacokinetic modeling (PBPK), new doses, using a dispersible tablet with a lower amount of artemether relative to lumefantrine (2.5 mg:30 mg, i.e.1:12) have been selected for investigation in this study.
Primary Objective(s)	The primary objective of this study is to assess the key PK parameter of artemether C_{max} (ART C_{max}; represents the higher concentration between the concentrations at 1 hour and 2 hours after first dose) in infants and neonates <5 kg body weight dosed with the new formulation of artemether-lumefantrine dispersible tablet
Secondary Objectives	Secondary objectives are: To determine efficacy by assessing: • PCR-corrected Adequate Clinical and parasitological Response (ACPR) at Days 15, 29, and 43, and uncorrected ACPR at Days 8, 15, 29, and 43. • Incidence rate of recrudescence and new infections at Days 15, 29 and 43. • Parasite and Fever clearance Times (PCT and FCT). To evaluate its safety and tolerability by collecting serious adverse events (SAEs), adverse events (AEs), and routine safety laboratory assessments.

	To assess other key PK parameters, i.e. Lumefantrine Day 8 concentration (C_{168h}), Artemether AUC, DHA and Lumefantrine C_{max} and AUC as appropriate.
Study design	This will be a multicenter, open-label, single-arm, adaptive study with two sequential and age-descending cohorts in infants and neonates <5 kg body weight with acute uncomplicated *P. falciparum* malaria. There will be a core study period of 43 days followed by a long term safety follow up at one year of age.
Population	This study will consist of male and female patients <5 kg body weight with acute uncomplicated *P. falciparum* malaria. Cohort 1: infants >28 days of age, and Cohort 2: neonates ≤28 days of age. The plan is to enroll and treat a minimum of approximately 44 patients (approximately 22 in each of the two sequential cohorts). Additional patients may be enrolled if the artemether/lumefantrine exposure is inadequate according to the periodic PK checks as per the protocol (with a maximum of 98 patients overall).
Key Inclusion criteria	1. Male or female neonates/infants 2. Body weight <5 kg but ≥ 2 kg 3. In Cohort 1, infants aged >28 days; in Cohort 2, neonates aged 1 to ≤28 days (3 subgroups: 1-7 days; 8-14 days; 15-28 days) 4. Microscopically confirmed diagnosis of *P. falciparum* malaria (or mixed infections): • in Cohort 1 of ≥500 and <100,000 parasites/µL asexual *P. falciparum parasitemia* • in Cohort 2 of ≥100 and <100,000 parasites/µL asexual *P. falciparum parasitemia* • in Cohort 2, either congenital or neonatal • either symptomatic or asymptomatic
Key Exclusion criteria	1. Head circumference < - 2 SD z-score in cm following WHO age and sex-specific reference curves (suspicion of microcephaly) 2. Presence of severe malaria (according to WHO 2015 definition) 3. HIV status: • in Cohort 1, patient's or patient's mother's current treatment with ARV • in Cohort 2, mother's known HIV positive status at patient's birth or mother's current treatment with ARV 4. Presence of the following signs of a critical condition: apnea-bradycardia, sustained bradycardia, tachycardia, desaturation, hypotension, hypothermia; or other severely deteriorated general condition (based on IMCI criteria in sick infants) (WHO 2005) 5. Presence of any clinically significant neurological condition: • any episode of convulsion during the present illness (in keeping with the IMCI list of general danger signs) • known neurological disorders (e.g. chronic seizure disorders, cerebral palsy) 6. Presence of clinically significant abnormality of the hepatic and renal systems 7. Patients unable to swallow or whose drinking is impaired

	8. Known hypersensitivity of the patient or either patient's parent to artemether, lumefantrine, any of the excipients of Coartem®/Riamet® Dispersible tablet, or to drugs of similar chemical classes 9. History of malabsorption or previous gastrointestinal surgery, or history of radiation therapy that could affect drug absorption or metabolism, or any other disorder or history of a condition that could interfere with drug absorption, distribution, metabolism, or excretion 10. Known family history of congenital prolongation of the QTc interval or sudden death or with any other clinical condition known to be associated with prolongation of the QTc interval such as history of symptomatic cardiac arrhythmias, with clinically relevant bradycardia or with severe cardiac disease 11. Disturbances of electrolyte balance (e.g. hypokalemia or hypomagnesaemia) 12. Presence of any age-adjusted clinically or hematologically relevant laboratory and blood chemistry abnormalities 13. Patients who received any antimalarial drug, including antibiotics with antimalarial activity, within 14 days of trial start, or any other prohibited drug (see Table 6-2) 14. Patients who received an investigational drug within 5 half-lives of enrollment or participated in an investigational study or within 30 days, whichever is longer NOTE: Where information is either not available or insufficient (e.g. from medical history, charts, etc.) to assess whether a patient meets a specific exclusion criterion, the study site team shall use its best medical judgement to make an inclusion/exclusion decision for the patient.
Study treatment	artemether:lumefantrine 2.5 mg:30 mg dispersible tablet
Efficacy assessments	Parasitemia determinations in peripheral blood and body temperature measurement, as well as signs and symptoms of early treatment failure.
Pharmacokinetic assessments	5 blood samples (500 µL each) will be obtained from each subject at the scheduled time points indicated in one of the 2 possible sample schemes in order to assess artemether, dihydroartemisinin and lumefantrine in every sample.
Key safety assessments	Adverse event monitoring, Physical examinations, Vital signs, monitoring of hematology and blood chemistry.
Other assessments	Follow up of liver events. [redacted]
Data analysis	Artemether C_{max} (ART C_{max}; higher concentration between the concentrations at 1 hour and 2 hours after first dose) is the primary endpoint. Day 8 (168 h) lumefantrine concentration is a key secondary endpoint. Ninety percent (90%) confidence intervals for artemether C_{max} and Day 8 (168 h) lumefantrine concentration will be calculated based on the log normal distribution by cohort and treatment group using the PK analysis set. For PCR corrected ACPR rates at Days 15, 29, and 43 and uncorrected ACPR rates at Days 8, 15, 29, and 43, 95% confidence intervals will be provided using the Pearson-Clopper method for each treatment group by cohort using PPS for PCR-corrected ACPR and FAS for uncorrected ACPR. For PCT and FCT, descriptive statistics (mean, standard error, median, quartiles) will be presented for each treatment by cohort using the Kaplan-Meier method based on the FAS.

Key words	Plasmodium falciparum, malaria, artemether, lumefantrine, dispersible, neonates, infants, PK, pharmacokinetics.

1 Introduction

1.1 Background

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

In 2017, an estimated 219 million cases of malaria and 435 000 deaths occurred worldwide: 92% of malaria cases and 93% of malaria deaths were in the African Region; and about half of all malaria deaths (49%) came from six countries (Nigeria, Democratic Republic of the Congo, Burkina Faso, Tanzania, Sierra Leone and Niger) (WHO 2018). Children aged under 5 years are the most vulnerable group affected by malaria, which accounted for 61% (266 000) of all malaria deaths worldwide in 2017 (WHO 2018).

Artemisinin (ACT) combination products are recommended by worldwide experts for the treatment of malaria (WHO 2018). Coartem dispersible tablet (artemether:lumefantrine 20 mg:120 mg) contains a fixed dose combination of two anti-malarial agents, artemether (an artemisinin derivative) and lumefantrine. Artemether has a rapid onset of antiparasitic activity and is rapidly metabolized. Lumefantrine has a slower onset of activity and a half-life of around 5 days. The pharmacokinetic properties of the two anti-malarial agents correlate with antiparasitic activity in which artemether is able to effect early parasite reduction while lumefantrine is effective in preventing recrudescence.

Riamet®/Coartem® dispersible tablet is administered over 3 days using an initial dose, a second dose after 8 hours, and then twice daily (morning and evening) for the following 2 days for a total of 6 doses. The total number of tablets administered per dose depends on body weight. However, Riamet®/Coartem® is not approved for infants less than 5 kg body weight (BW), whereas neonates and infants <12 months of age constitute one of most vulnerable groups affected by malaria (WHO 2018). Although relatively infrequent, confirmed malaria in neonates and infants <5 kg does exist in certain endemic countries and calls for evaluation of appropriate treatment (Alao et al 2013). Recent reports from sub-Saharan Africa suggest that malaria is more common in neonates and young infants than previously thought, with an incidence ranging from 3.7-22% (Ceesay 2015, Ameade 2018). However, no consistent treatment guidelines are available for uncomplicated *P. falciparum* malaria in patients <5 kg BW and national treatment guidelines vary significantly across countries (Alao et al 2013), WHO itself recommends "*an ACT at the same BW target dose as for children weighing 5 kg*" (WHO 2015), but as there are no approved treatments, this vulnerable group of patients is treated with undocumented doses of anti-malarials including quinine, potentially posing a safety risk (Mbonye et al 2015).

In 2010, as part of an EU pediatric development plan associated with the Riamet®/Coartem®dispersible tablet formulation, a clinical study, Study B2306 (COA566B2306), with a design similar to the present study B2307 (COA566B2307), was conducted. That study found that, in around 20 patients <5 kg body weight and >28 days of age, artemether exposure following administration of dispersible tablets (artemether:lumefantrine 20 mg:120 mg) was around 2-3 fold higher than anticipated safe exposures, whereas exposure to lumefantrine was as expected.

Pre-clinical studies have shown neurotoxic effects of high artemether exposures in dogs. Monkeys were less susceptible to artemether-induced neurotoxicity while human clinical data

so far do not suggest that artemether C_{max} values exceeding those associated with neurotoxicity in dogs have resulted in neurological findings in patients.

Nevertheless, given the potential neurotoxicity of artemether at high exposures, and because the fixed artemether relative to lumefantrine ratio (1:6) in the Coartem dispersible tablet does not allow to reduce the amount of artemether alone, it was decided not to proceed with the second cohort of study B2306 (infants ≤28 days of age). This decision was endorsed by the study's Data Monitoring Committee (DMC).

Detailed Physiology-Based Pharmacokinetic modeling (PBPK modeling) was subsequently performed to estimate the exposure of artemether and lumefantrine in different age groups of patients (from full term birth to 6 months of age) receiving different doses. As a result, a new dose ratio, with a lower amount of artemether relative to lumefantrine (1:12) has been selected for investigation in this population (<5 kg).

This adaptive PK/safety/tolerability/efficacy clinical trial is therefore designed in order to identify the appropriate dose of the newly formulated artemether-lumefantrine dispersible tablet in neonates and infants < 5 kg with acute uncomplicated *P. falciparum* malaria.

1.2 Purpose

This Phase II/III study aims to evaluate PK, safety, tolerability and efficacy of a new formulation of artemether-lumefantrine dispersible tablet in infants and neonates <5 kg body weight with acute uncomplicated *Plasmodium falciparum* malaria.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the key PK parameter of artemether in infants and neonates < 5 kg body weight dosed with the new formulation of artemether-lumefantrine dispersible tablet	• Artemether C_{max} (represents the higher concentration between the concentrations at 1 hour and 2 hours after first dose)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess other key PK parameters of artemether, DHA and lumefantrine in infants and neonates <5 kg body weight dosed with the new formulation of artemether-lumefantrine dispersible tablet	• Lumefantrine Day 8 concentration (C_{168h}) Artemether AUC, DHA and Lumefantrine C_{max} and AUC as appropriate
• To evaluate the safety and tolerability of the new formulation of artemether-lumefantrine dispersible tablet in infants and neonates <5 kg body weight with acute uncomplicated *P. falciparum* malaria	• Serious adverse events (SAEs), adverse events (AEs), and routine safety laboratory assessments
• To determine the efficacy of the new formulation of artemether-lumefantrine dispersible tablet for treatment of acute uncomplicated *P. falciparum* malaria in infants and neonates <5 kg body weight	• PCR-corrected Adequate Clinical and parasitological Response (ACPR) at Days 15, 29, and 43 Uncorrected ACPR at Days 8, 15, 29, and 43

Objective(s)	Endpoint(s)
	Incidence rate of recrudescence and new infections at Days 15, 29 and 43 Parasite and Fever clearance Times (PCT and FCT)
[redacted]	

3 Study design

This will be a multicenter, open-label, single-arm, adaptive design with dose adaptation (de-escalation or escalation) study in infants and neonates <5 kg body weight with *P. falciparum* malaria.

A total of approximately 44 male and female infant/neonate patients (<5 kg) are planned to be recruited in the study. There will be two sequential and age-descending cohorts of approximately 22 patients each (see Figure 3-2), all <5 kg: Cohort 1 of infants >28 days of age, and Cohort 2 of neonates ≤ 28 days of age. Cohort 2 will include 3 age subgroups (15-28, 8-14 and 1-7 days), starting with the highest age subgroup in Cohort 2.1. The two lower age subgroups (i.e., 8-14 and 1-7 days) will be recruited in parallel. These two subgroups will be optional, depending on recruitment feasibility.

In the event of inadequate exposure (Section 4.2), determined at predefined PK checkpoints (i.e., after the first 9 patients in Cohort 1, and after the first 3 patients and then the first 9 patients of Cohort 2 (1-28 days of age)), additional patients may be recruited up to a total of 98 patients across the 2 cohorts (Figure 3-2). An additional PK check may be performed after the first 9 patients of the 15-28 days age group in Cohort 2 have been recruited. For Cohort 2, if an adequate dose cannot be determined or if recruitment is not feasible in any age subgroup, the cohort may be closed and 22 additional patients may be recruited in Cohort 1 up to a total of approximately 44 patients treated with the same dose (instead of the planned 22 patients). Cohort 2.3 will start recruitment after the dose used in Cohort 2.2 has been assessed to be appropriate.

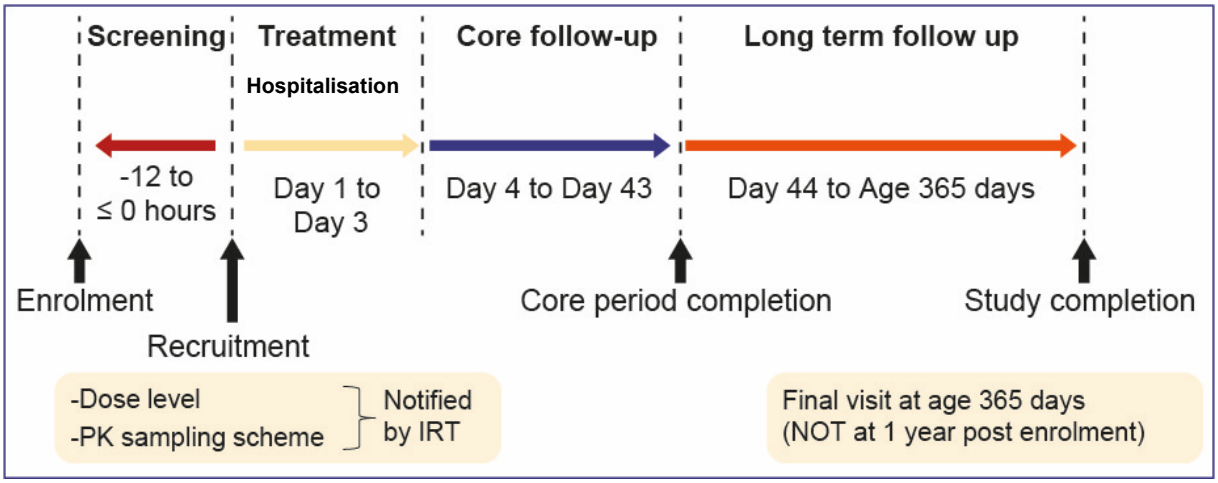
Patients will be admitted to the hospital on or before Day 1 (see Figure 3-1). After meeting all the inclusion and exclusion criteria in the study, they will receive study drug. The starting dose regimen in Cohort 1 will be two dispersible tablets twice daily for three consecutive days. The

dose must be preceded and/or followed as much as possible by food/drinks rich in fat, e.g. breast milk, or formula milk.

Patients will remain in the hospital under close supervision until they are discharged by the investigator or designee on Day 4. At the discretion of the investigator, patients may stay for a few additional days if needed. The patients will be then followed up at regular intervals until Day 43 (core follow-up), in order to assess study drug exposure, safety, tolerability and efficacy (See Visit schedule in Table 8-1). If symptoms re-emerge outside the scheduled study visits, parents/legal guardians of the patients will be instructed to contact the investigator. In case of treatment failure (as per WHO definition), rescue treatment according to local clinical practice will be provided.

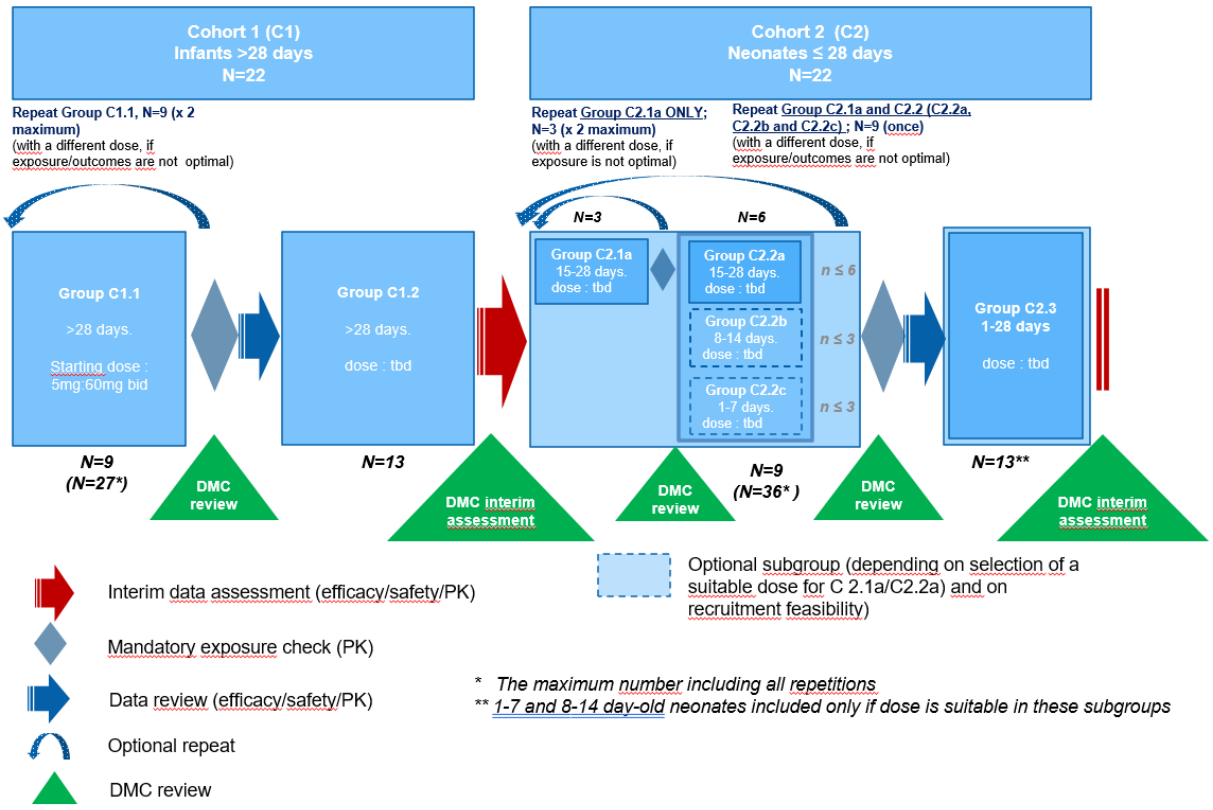
Patients will then attend a long term safety follow-up visit [redacted]

Figure 3-1 Patient participation overview



In this study, a stepwise and sequential approach will be adopted in order to minimize the risk for patients (Figure 3-2).

Figure 3-2 Study flow chart



PK exposure checks (together with safety and efficacy data review as available) will be performed on a periodic basis to assess the dose included at the following timepoints:

1) once the first 9 patients in Cohort 1 have been dosed and followed up to Day 15,

2) once the first 3 patients in Cohort 2 (15-28 days age subgroup) have been dosed and followed up to Day 15,

3) once the first 9 patients in Cohort 2 (1-28 days age subgroup) have been dosed and followed up to Day 15. In case exposure data in the 9 patients from the 1-28 day subgroup are not sufficient to make a decision on dose selection (e.g., due to a significantly different exposure across age subgroups), as many additional patients as needed to reach a total of 9 (across Cohort 2.1 and 2.2) in the 15-28 day subgroup specifically will be recruited in Cohort 2.2 and treated with the same dose. An additional PK check will then be performed after these additional patients will have been followed up to Day 15.

A total of 9 patients in a defined age group should allow to confirm with reasonable confidence if ART C_{max} is within approximately 2-fold (safety interval) of the C_{max} which has been found to be safe and efficacious in previous studies; a total of 3 patients will however allow to check at an early stage if the ART C_{max} range is within the expected safety interval (Cohort 2 only).

An Independent Data Monitoring Committee (DMC) will review the PK, efficacy and safety data at these checks, and also at two planned interim data assessments, one between the two cohorts, and another one after all patients in Cohort 2 have completed Day 43 (Figure 3-2).

The interim data assessment based on Cohort 1 data will serve to determine the starting dose level for Cohort 2 (for further details see Section 10.2.1).

Based on these checks, the dose being considered will be assessed as suitable or not for the subgroup of patients treated.

In Cohort 1:

- if the dose is deemed adequate in the first 9 patients (based on PK, safety and efficacy data review as available), additional patients will be recruited up to approximately 22 treated with the same dose level (expansion phase).
- if the dose is not adequate, the first set of 9 patients will be repeated, up to twice, using a different dose level, until a dose level is determined as suitable.

In Cohort 2:

- if the dose is deemed adequate in the 3 patients from the highest age subgroup (15-28 days), recruitment of 6 additional patients in the 1-28 day subgroup will be attempted.
- if the dose is not adequate, the first set of 3 patients from the highest age subgroup (15-28 days) will be repeated, up to twice, using a different dose level, until a dose level is determined as suitable. Then, recruitment of 6 additional patients in the 1-28 day subgroup will be attempted.
- Another PK check (together with safety and efficacy data as available) will then be performed when a total of 9 patients have been treated with the same suitable dose in the 1-28 day subgroup. In case exposure data from these 9 patients (1-28 day subgroup) is not sufficient to make a decision on dose selection, as many additional patients as needed to reach a total of 9 (across Cohort 2.1 and 2.2) in the 15-28 day subgroup specifically will be recruited in Cohort 2.2 and treated with the same dose. An additional PK check will then be performed after these additional patients will have been followed up to Day 15. If the former PK check shows that the dose is suitable for all subgroups, expansion of Cohort 2 will include all age subgroups. If it is unsuitable for any of the two lower age subgroups, no further patients will be recruited in this/these lower age subgroup(s), and further expansion of Cohort 2 will only include patients from the 15-28 day subgroup. In the case the dose is not confirmed as suitable for the highest age subgroup, a repeat run with 9 patients (3+6 patients) will be performed using a different dose.

In Cohort 2, if through the steps above, no suitable dose has been determined in the higher age subgroup (15-28 days), recruitment will be stopped in that cohort and an additional 22 patients will instead be recruited in Cohort 1 and treated with the dose that was deemed adequate in that cohort.

Once either cohort's expansion has been completed with approximately 22 patients treated with the same, suitable dose, or any or the alternative scenarios described above, patients will be followed up to Day 43, when the complete set of key efficacy and safety parameters and PK exposures will be assessed.

Note: Patients treated with dose levels deemed not suitable will also be closely followed up to Day 43 and at one year of age.

In the unlikely case when all the iterations described above would have to be implemented, a maximum of 98 patients would be recruited.

4 Rationale

4.1 Rationale for study design

This will be a multicenter, open-label, single-arm, adaptive dosing study in infants and neonates <5 kg body weight with acute uncomplicated *P. falciparum* malaria.

The objective of this Phase II/III study design is to test the new artemether-lumefantrine dispersible tablet formulation to determine exposure to artemether, DHA and lumefantrine as well as its safety, tolerability and efficacy in patients <5 kg with uncomplicated *P. falciparum* malaria.

The open-label, adaptive, sequential-group design used in the study aims to minimize the risk by studying first a cohort of infants (>28 days of age, <5 kg) that is similar to the population already evaluated in previous clinical trials (i.e., infants ≥5 kg body weight, irrespective of age). The risk of bias arising from an open-label design is minimized as objective endpoints have been chosen for the study.

Patients will be enrolled at sites experienced in managing the population targeted in the present study (neonates and infants <5 kg BW) and they will be hospitalized during the treatment period in order to ensure close monitoring.

The planned periodic pharmacokinetic exposure check after dosing a limited number of patients (as specified in Section 3 of this protocol), along with the review of the available efficacy and safety data by the DMC, aims to minimize the risk for patients, and it will also allow to adjust the dose in case of inadequate outcome.

The design of the core follow-up (up to Day 43) within each cohort is well established for malaria trials and follows WHO guidelines.

[redacted] Since central nervous system (CNS) toxicity with artemisinin derivatives has been reported in animal studies, the neurological safety of artemether-lumefantrine has been a subject of much attention (Adjei et al 2009). However, CNS toxicity has not been reported in well designed clinical trials (Chattopadhyay et al 2007), including ototoxicity (Carrasquilla et al 2012), nor in the previous clinical study (COA566B2306 in infants >28 days and <5 kg) with a similar design to the current study's (Tiono et al 2015).

4.2 Rationale for dose/regimen and duration of treatment

Dose selection in this study is based on extensive safety and efficacy experience with artemether:lumefantrine 20 mg:120 mg and also specifically based on data from the controlled clinical trial in infants and children ≥5 kg BW, study B2303 (COA566B2303) as well as on the results of a previous study, study B2306 (COA566B2306) in this very young population (infants < 5 kg BW and > 28 days) (See Table 4-1).

In Study B2306, exposure to artemether and DHA was around 2-3 fold higher in 20 infants <5 kg BW and >28 days compared to infants ≥5 kg BW, irrespective of age (Study B2303), whereas the exposure to lumefantrine was comparable between these two studies (Tiono et al 2015). The dose regimen administered to infants <5 kg body weight (study B2306) and to those

5-<15 kg BW (study B2303) was the same (a 6-dose regimen of artemether:lumefantrine 20 mg:120 mg of over 3 days). The higher artemether exposure at a lower age and weight could result from immature metabolic enzymes mainly CYP3A4 and CYP2B6 (Lin et al 2016). The safety profile associated with a higher systemic artemether exposure, could not be fully supported by preclinical data:

- in dogs, pathological evidence of neurotoxicity was noted with intramuscular doses of artemether administered daily for 8 days.
- monkeys were less susceptible to artemether-induced neurotoxicity (Li and Hickman 2011).

Although difficult to interpret, available clinical data do not suggest that artemether C_{max} values exceeding those associated with neurotoxicity in dogs have resulted in neurological effects in infants. Given the highly vulnerable patient population in this study, it is nevertheless imperative to bring the exposure of artemether within the limits which have been clinically proven to be safe (See Table 4-1 below).

On the other hand, lumefantrine exposure was generally comparable between Study B2306 and Study B2303 except for the Day 8 exposure which was more than 2-fold higher in Study B2306. A potential reason for this observation was a reduced intestinal absorption combined with reduced clearance in patients <5 kg BW leading to a comparable exposure during the dosing period between the two groups of infants /children.

Table 4-1 Historical exposure values from previous studies

Study	Body weight (age)	ART Dose (mg)	n	First dose Artemether C_{max} (ng/mL)	LUM C_{max} (µg/mL)	LUM $C_{168\ h}$ (ng/mL)
B2306	<5kg >28days	20	18	509 ± 309	6.38	815
B2303	≥5 - <15	20	55	196 ± 204	5.16	386
B2303	≥15 - <25	40	29	150± 106	8.03	
B2303	≥25 - <35	60	8	134 ± 56.7	12.3	

ART: artemether; LUM: lumefantrine

Based on the above data and on ontogeny data (course of development of the human organism), a full PBPK model was developed and validated. This model was used to simulate exposures to artemether and lumefantrine corresponding to different doses and at different neonate and infant ages (Report DMPK R1809279) (See Table 4-2 below).

While selecting the doses for the present study, the following considerations were taken into account:

- due to artemether's potential neurotoxicity (based on animal data), it is hypothesized that its exposure should be contained within the range that has been found to be well tolerated and efficacious in children ≥5 kg.
- Exposure to lumefantrine should also be adequate, especially the Day 8 plasma concentration (which is a surrogate efficacy marker), i.e., it should be ≥ 200 ng/mL on

Day 8 based on an extensive meta-analysis, (WWARN 2015) to achieve long-term parasite clearance.

- within the exposures which were found to be well tolerated in children ≥5 kg BW, while kept on the higher side, due to lower immunity and potential lower exposure in pediatric patients (Kloprogge et al 2018, WWARN 2015).

Table 4-2 PBPK modeled exposures based on a 5:60 mg (A:L) dose regimen

	Neonates (≤28 days, <5 kg)	Infants (>28 days (1-7 months), <5kg)
Artemether (5 mg)		
First dose C_{max} (ng/mL)	234	78.5
Lumefantrine (60 mg)		
Full regimen C_{max} (µg/mL)	5.1	5.4
C_{168h} (ng/mL)*	530	270

Based on PBPK simulations, with an individual artemether dose of 10 mg, C_{max} in infants <5 kg BW is expected to be in the range of the C_{max} observed in infants ≥5 kg BW, but at the high end. Because of the neurotoxicity risk, an individual artemether dose of 5 mg was selected in order to remain conservative. This dose is expected to provide a C_{max} that is still efficacious but at least two fold lower than the highest exposures observed in infants/children ≥5 kg BW. C_{max}, not AUC, was targeted because only two data points around C_{max} can be captured in this population, due to limitation in blood draws. Due to the same limitation, a reliable estimate of AUC could not be established in study B2306 (COA566B2306). For lumefantrine, a 60 mg individual dose was selected which would provide a total exposure within the observed safe exposures. This dose is expected to provide a C_{max} >10 fold of an effective concentration of 200 ng/mL if patients are well fed.

This leads to doses of 5 mg and 60 mg (ratio 1:12) respectively for artemether and lumefantrine that will be assessed in the present study. The ratio is therefore different from the 1:6 ratio (artemether:lumefantrine 20 mg:120 mg dispersible tablet) used in the rest of the population (≥5 kg BW), but it is not expected to adversely impact treatment outcome. The confidence in the prediction is moderate as the physiology affecting the exposure to these two compounds is not fully known and variability does exist, especially in the youngest patients (Cohort 2, ≤28 days). As a consequence, in order to minimize the risk, an early exposure check will be performed in a staggered fashion:

- in the first 9 patients in Cohort 1 (>28 days) where the risk is lower
- in Cohort 2, in the first 3 patients in the highest age subgroup (15-28 days, Cohort 2.1), and only then in the lower two age subgroups (1-7 and 8-14 days, Cohort 2.2), to further decrease the risk
- in the first 9 patients in Cohort 2 (1-28 days subgroup. Cohort 2.1 and 2.2), once the step directly above has been completed
- in case exposure data in the 1-28 day subgroup in the step right above is not sufficient to inform about the optimal dose for this population, an additional PK check may be performed after 9 patients of the 15-28 day subgroup have been recruited at the same dose across Cohort 2.1 and 2.2 (additional patients will then be recruited in Cohort 2.2 to this effect)

The dose used in Cohort 1 and in the highest age subgroup in Cohort 2 may be modified as required, either upwards or downwards before including further patients. In the event the dose deemed suitable in the highest age subgroup in Cohort 2 is not suitable for either or both lower age subgroups in Cohort 2, recruitment will be stopped and no further doses will be evaluated in the concerned subgroup(s). If no dose at all can be determined as suitable in Cohort 2, the cohort will be stopped.

The PBPK model will be updated and qualified periodically with the available PK data from Cohort 1 and/or Cohort 2 and PBPK simulations may be used to support the recommendation of an appropriate dose for this population.

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

Not applicable.

4.4 Purpose and timing of interim analyses/design adaptations

There will be two planned interim assessments performed:

1. after all patients in Cohort 1 have completed Day 43 (core study period), when key efficacy and safety parameters and PK exposure data will be assessed in order to determine whether to proceed to Cohort 2 and if so, to select the starting dose for that Cohort.
2. after all patients in Cohort 2 have completed Day 43 (core study period), when efficacy and safety parameters and PK exposure data from both cohorts will be assessed

PK exposure checks (including safety and efficacy data review as available) will also be performed as described in Section 3, Section 4.2 and Section 12.7.

The PBPK model will be updated and qualified periodically with the available PK data from Cohort 1 and/or Cohort 2 and additional interim assessments including PBPK simulations may be used to support a recommendation of an appropriate dose for this population.

4.5 Rationale for public health emergency mitigation procedures

During a public health emergency as declared by local or regional authorities e.g., pandemic, epidemic, or natural disaster, mitigation procedures to ensure participant safety and trial integrity may be implemented. Notification of the public health emergency as declared by local or regional authorities should be discussed among investigators and Novartis. All procedures adapted to the situation must be submitted, if required as per local regulations, through a protocol amendment for approval by local or regional Health Authorities and Ethics Committees prior to implementation of mitigation procedures.

4.6 Risks and benefits

The safety and efficacy of Coartem®/Riamet® has been characterized in adults and pediatric patients ≥5 kg BW.

The safety profile of the current Coartem®/Riamet® 6-dose regimen has been well-characterized in approximately 6000 patients in Novartis-sponsored clinical trials (almost 500 of them having received the dispersible tablet). There have been two pooled safety analyses of randomized clinical trials data performed, one including 712 adolescent/adult patients (i.e., patients >12 years of age and ≥35 kg BW) and another including 1262 infants and children (i.e., patients <12 years of age and ≥5 kg to <35 kg BW) treated with the standard tablet or dispersible tablet formulation according to the 6-dose regimen. Overall, Coartem®/Riamet® is well tolerated in both pediatric and adult patients. The profile and frequency of adverse events seems comparable between these patient populations. A majority of the adverse events reported in these studies could also have been attributed to malaria: they were rated mild to moderate in intensity and not necessarily related to artemether-lumefantrine. Furthermore, extensive post-marketing experience confirmed that Coartem®/Riamet® (artemether:lumefantrine 20 mg:120 mg) has a well characterized risk-benefit profile. Currently, clinical data available in patients <5 kg were collected in study B2306 in 20 patients >28 days of age. In that study, artemether exposure following administration of the 6-dose regimen of Coartem® (one artemether:lumefantrine 20 mg:120 mg dispersible tablet/dose) was around 2-3 fold higher than anticipated safe exposures, whereas exposure to lumefantrine was as expected. Given the potential neurotoxicity of artemether at high exposures, and based on preclinical data, it was decided not to proceed with the second cohort of the same study (infants ≤28 days of age).

The safety profile associated with a higher systemic artemether exposure could not be fully supported by preclinical data:

- in dogs, pathological evidence of neurotoxicity was noted with intramuscular doses of artemether administered daily for 8 days.

- monkeys were less susceptible to artemether-induced neurotoxicity (Li and Hickman 2011).

Although difficult to interpret, available clinical data do not suggest that artemether C_{max} values exceeding those associated with neurotoxicity in dogs have resulted in neurological effects in infants. Given the highly vulnerable patient population in this study, it is nevertheless imperative to bring the exposure of artemether within the limits which have been clinically proven to be safe (See Table 4-1).

However, there were no new or changing safety signal observed in study B2306 compared to the ≥5 kg population. Most AEs reported during the core period reflected the underlying disease of the patients, with the most commonly reported AE being malaria (55%), with anemia reported for 35% of patients, bronchitis reported for 30% of patients, pyrexia for 25% of patients and vomiting for 20% of patients. Most reported AEs were moderate in severity (55% of patients), with mild events reported for 15% of patients and severe events also for 15% of patients – severe AEs (anemia, diarrhea, cerebral malaria, meningitis, and death of unknown etiology) were all SAEs reported during the long-term follow-up period and none of them was attributed to the study medication. AEs suspected to be related to the study drug by the investigator were reported for 5 (25% of patients), including anemia and vomiting (each reported for 3 patients, 15%). One patient discontinued study medication during the core study

period for an AE (vomiting of moderate severity). Laboratory parameters did not show clinically meaningful changes from baseline during the study. A large proportion of patients had notable vital signs at baseline (55% with high systolic blood pressure (SBP), 40% with high Diastolic blood pressure (DBP) and pulse rate). There was no meaningful change in this over the course of the study. There were no deaths or SAEs reported during the core follow-up period of the study. Two patients died during the long-term follow-up period up to 12 months of age (one patient from dehydration due to acute diarrhea, the second of unknown etiology but [redacted] later reported that the subject had experienced a one day history of anorexia on the day of death). Finally, there were no findings following the neurodevelopment assessment at 1 year of age.

In the present B2307 study, a lower ratio of artemether relative to lumefantrine (1:12) has been selected for investigation, in order to minimize the risk of neurotoxicity.

The risk to subjects in the present trial will be minimized by excluding neonates/infants with critical conditions, through ensuring close clinical monitoring, and in-patient status (during the treatment period). Regular safety laboratory measurements will be used including hematology and blood chemistry tests, in order to ensure a close monitoring beyond the hospitalization period.

Furthermore, pain and fever control methods will be implemented at the investigator's discretion including appropriate use of antipyretics (e.g., during and after a painful procedure such as venipuncture). In terms of PK assessments, a sparse blood sampling strategy (Djimdé et al 2011) will be used. The total blood volume drawn over 6 weeks in this population will not exceed the limit of 2.4 to 2.7 mL per kg BW, following WHO recommendations (Howie 2011). In case of severe anemia developing during the study, the total blood volume drawn should be adjusted downwards as necessary at the investigator's discretion.

Finally, a DMC will be established to safeguard patient safety (see Section 10.2.1). The DMC will meet at regularly scheduled time points to review the PK, efficacy and safety data collected. The responsibilities and specific aspects of the DMC are described in the DMC charter.

Hence, based on the risk-benefit profile and unmet medical need, Novartis has considered justified to explore the use of artemether:lumefantrine (1:12) in acute, uncomplicated *P. falciparum* malaria-infected infants and neonates <5 kg BW through the present study (B2307).

5 Population

The study population will consist of a representative group of neonates and infants of both sexes with a BW <5 kg and a confirmed diagnosis of acute uncomplicated *P. falciparum* malaria or mixed infections by microscopy with asexual *P. falciparum* parasitemia of ≥500 and <100,000 parasites/µL in Cohort 1 and of ≥100 and <100,000 parasites/µL in Cohort 2.

The study population will be enrolled in two sequential cohorts, infants >28 days of age (Cohort 1) and term neonates ≤28 days of age (Cohort 2). Cohort 2 is further divided into 3 age subgroups (15-28; 8-14; 1-7 days). In order to obtain for the primary endpoint approximately 16 evaluable neonates/infants exposed to an adequate dose in each cohort, it is planned to have approximately 22 neonates/infants entering the study and exposed to an adequate dose in each cohort. In the event no suitable dose can be determined in the highest age subgroup (15-28 days)

of Cohort 2 or recruitment is not feasible, the cohort will be closed and an additional 22 patients will instead be recruited in Cohort 1 and treated with the dose that was deemed adequate. Additionally, PBPK modeling may be explored with existing data from Cohort 1 to support the dose recommendation in the study population.

Patients will be recruited at approximately 10 sites across 8 countries in Sub-Saharan Africa. Reflecting the local legal and cultural context, effective community engagement will be sought and ensured by the clinical site team.

5.1 Inclusion criteria

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

1. Male or female neonates / infants
2. Body weight <5 kg but ≥ 2kg
3. In Cohort 1, infants aged >28 days; in Cohort 2, neonates aged 1 to ≤28 days (3 subgroups: 15-28 days; 8-14 days; 1-7 days)
4. Microscopically confirmed diagnosis of *P. falciparum* malaria (or mixed infections)
   - in Cohort 1: of ≥500 and <100,000 parasites/µL asexual *P. falciparum parasitemia*
   - in Cohort 2: of ≥100 and <100,000 parasites/µL asexual *P. falciparum parasitemia*
   - either congenital or neonatal
   - either symptomatic or asymptomatic
5. Parental/legal guardian informed consent obtained and signed prior to any study related procedure. If the parent/legal guardian is unable to read or write, then a witnessed consent according to local ethical standards is permitted (formally documented and witnessed, via an independent trusted witness)
6. The 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

5.2 Exclusion criteria

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

1. Head circumference < - 2 SD z-score in cm following WHO age and sex-specific reference curves (suspicion of microcephaly) (See Section 16.1 Appendix 1)
2. Severe malnutrition (body mass index (BMI) less than 70% of median normalized WHO reference weight)
3. Presence of severe malaria (according to WHO 2015 definition - See Section 16.4 Appendix 4)
4. Hemoglobin < 7 g/dL
5. HIV status:
   - in Cohort 1 : patient’s or patient's mother's current treatment with ARV
   - in Cohort 2 : Mother’s known HIV positive status at patient's birth or mother's current treatment with ARV
6. Presence of the following signs of a critical condition: apnea-bradycardia, sustained bradycardia, tachycardia, desaturation, hypotension, hypothermia; or other severely

deteriorated general condition (based on IMCI criteria in sick infants, WHO 2005 - See Section 16.5 Appendix 5)

7. Presence of any clinically significant neurological condition:
   - any episode of convulsion during the present illness (in keeping with the IMCI list of general danger signs)
   - known neurological disorders (e.g. chronic seizure disorders, cerebral palsy)
8. Presence of clinically significant abnormality of the hepatic and renal systems
9. History of malabsorption or previous gastrointestinal surgery, or history of radiation therapy that could affect drug absorption or metabolism, or any other disorder or history of a condition that could interfere with drug absorption, distribution, metabolism, or excretion
10. Patients unable to swallow or whose drinking is impaired
11. Known hypersensitivity of the patient or either patient's parent to artemether, lumefantrine, any of the excipients of Coartem®/Riamet® Dispersible tablet, or to drugs of similar chemical classes
12. Known family history of congenital prolongation of the QT_c interval or sudden death or with any other clinical condition known to be associated with prolongation of the QT_c interval such as history of symptomatic cardiac arrhythmias, with clinically relevant bradycardia or with severe cardiac disease
13. Disturbances of electrolyte balance (e.g. hypokalemia or hypomagnesemia) - See Section 16.1 Appendix 1 as an example for reference
14. Presence of any age-adjusted clinically or hematologically relevant laboratory and blood chemistry abnormalities
15. Patients who received any antimalarial drug, including antibiotics with antimalarial activity, within 14 days of trial start, or any other prohibited drug (see Table 6-2)
16. Patients who received an investigational drug within 5 half-lives of enrollment or participated in an investigational study or within 30 days, whichever is longer.

NOTE: Where information is either not available or insufficient (e.g. from medical history, charts) to assess whether a patient meets a specific exclusion criterion, the study site team shall use its best medical judgement to make an inclusion/exclusion decision for the patient.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Novartis will supply artemether:lumefantrine 2.5 mg:30 mg (COA566 2.5 mg:30 mg) as an investigational product in the form of open label patient specific supplies (see Table 6-1).

Table 6-1 Investigational and control drug

Treatment Title	COARTEM/RIAMET, COA566
Treatment Description	dispersible tablet, 2.5 mg artemether / 30 mg lumefantrine, 1 to 4 tablets per dose, BID for 3 days, open label

Type	drug
Dose Formulation	dispersible tablet
Unit Dose Strength(s)	2.5 mg artemether / 30 mg lumefantrine
Dosage Level(s)	1 to 4 tablets per dose, BID for 3 days
Route of Administration	oral
Use	experimental
IMP	yes
Sourcing	provided centrally by the sponsor
Packaging and Labeling	Study treatment will be provided in blisters. Each blister will be labeled as required per country requirement.

6.1.2 Additional study treatments

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

6.1.3 Treatment arms/group

Patients will receive artemether:lumefantrine 2.5 mg:30 mg dispersible tablet. Although it is anticipated to have one dose level assessed in the study, four possible dose levels (1 to 4 tablets per dose) may be used (See Section 6.5.1.2).

In Cohort 1, a regimen of two dispersible tablets (i.e., 5 mg:60 mg artemether:lumefantrine) twice daily for 3 consecutive days will be administered as a starting dose to the first 9 patients. Following a PK check (including safety and efficacy data review as available), the dose level may be adjusted and administered to another 9 patients (up to two re-runs, see Figure 3-2 and Table 6-3). Once a suitable dose has been determined in 9 patients, about 13 additional patients will be recruited and administered the same dose.

Cohort 2 will be further divided into 3 age subgroups. A PK check will be performed after 3 patients have been treated in the highest age subgroup (15-28 days). In the event the exposure is not considered adequate (see Section 4.2), the dose may be adjusted and administered to another 3 patients of that age subgroup (up to two re-runs, see Figure 3-1 and Table 6-3).

For more details, see Section 3.

In case the suitable dose would not be the same across the 2 cohorts, or within Cohorts, treatment groups will be defined based on dose level.

6.1.4 Treatment duration

After inclusion in the study, each patient will be dosed b.i.d. with study drug for 3 days (at the following time points: 0, 8, 24, 36, 48 and 60 hours) under hospital supervision.

Patients may be discontinued from treatment at the discretion of the investigator or of the parents/legal guardian or due to:

- Disease progression (see Section 6.2.3)
- Use of prohibited treatment (see Table 6-2)

- Any situation in which study participation might result in a safety risk to the patient and/or any adverse events that in the judgement of the investigator, taking into account the patient's overall status, prevent the patient from continuing participation in the study
- Deviation from the planned dose regimen for the study drug, for instance, if the patient vomits a dose within 1 hour of intake, as well as its replacement dose within 1 hour of intake.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

Concomitant medication is defined as any medication, other than the study drug, which is given at least once between the day of first dose of study medication and the last visit of core follow-up period (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.

The investigator should instruct the patient's legal guardian to notify the study site about any new medications the patient takes after the start of the study drug. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be recorded on the appropriate CRF.

Similarly, all medications and significant non-drug therapies administered during the core follow-up period to a mother breastfeeding a patient after the patient starts treatment with study drug must be listed on the appropriate CRF.

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 entering a subject in the study or allowing a new medication to be started during the study. If the subject is already recruited, the investigator should also contact Novartis to determine if the subject should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

The following should be used with caution, i.e. with staggered dosing (unless already listed in Section 6.2.2) during the core follow-up period (6 weeks)

- **CYP3A4 inhibitors**: The concurrent oral administration of ketoconazole with artemether-lumefantrine 20 mg:120 mg led to a modest increase (≤2-fold) in artemether, DHA, and lumefantrine exposure in healthy adult subjects. This was not associated with increased side effects. However, there is a potential for increased concentrations of lumefantrine which could lead to QT prolongation,
- **Weak to moderate inducers of CYP3A4**: When artemether:lumefantrine 20 mg:120 mg is co-administered with weak to moderate inducers of CYP3A4, it may result in decreased concentrations of artemether and/or lumefantrine and lower the antimalarial efficacy. Patients can experience this interaction even while they or the mother/breastfeeding person stops treatment around 2 weeks before the patient starts taking artemether-lumefantrine.

These restrictions result from potential interactions with study drug.

6.2.2 Prohibited medication

For the period(s) specified, use of the treatments displayed in Table 6-2 is not allowed in:

- patients
- the person providing breastmilk to the patients (as the prohibited drug is known to be secreted significantly in breastmilk), except for antimalarials or antimicrobials with antimalarial activity.

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

Table 6-2 Prohibited medication

Medication*	Prohibition period**	Action taken***
Drugs that are known to prolong the QTc interval such as: • antiarrhythmics of classes IA and III • neuroleptics, antidepressant agents • certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents • certain non-sedating antihistaminics (terfenadine, astemizole) • cisapride	At least 5 times their half-life before study entry and at least for 28 days after last AL dose	Discontinue prohibited medication, monitor patient closely for any cardiac event, discontinue the study treatment in case of cardiac event
Drugs which are metabolized by the cytochrome enzyme CYP2D6 especially those with a narrow therapeutic index e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine	At least for 28 days after last AL dose	Discontinue prohibited medication, monitor for potential effects of overexposure of impacted drug. However patients taking one of these drugs should stay in the study and follow-up visits for efficacy should be performed according to the visit schedule, i.e. remaining visits for the entire core study period (until Day 43), and the follow-up visit at 12 months of age

Medication*	Prohibition period**	Action taken***
inducers of CYP3A4 Strong inducers of CYP3A4 like rifampicin and St. John's wort can reduce the exposure of artemether and lumefantrine to a clinically significant level	At least 5 times their half-life plus two weeks before study entry and during entire core study period (until Day 43)	Discontinue prohibited medication. However patients taking one of these drugs should stay in the study and follow-up visits for efficacy should be performed according to the visit schedule, i.e. remaining visits for the entire core study period (until Day 43), and the follow-up visit at 12 months of age
Herbal medication	Entire core study period (until Day 43) except as rescue medication	Discontinue study treatment. However, patients taking one of these drugs should stay in the study and follow-up visits for efficacy should be performed according to the visit schedule, i.e. remaining visits for the entire core study period (until Day 43), and the follow-up visit at 12 months of age
Antimalarials other than the study drug	At least 5 times their half-life before study entry and during entire core study period (until Day 43) except as rescue medication	Discontinue study treatment. However, patients taking one of these drugs should stay in the study and follow-up visits for efficacy should be performed according to the visit schedule, i.e. remaining visits for the entire core study period (until Day 43), and the follow-up visit at 12 months of age
other ACTs: e.g. artesunate-amodiaquine (ASAQ), artesunate-pyronaridine, DHA-piperaquine		
chloroquine, amodiaquine		
quinine, quinidine		
mefloquine, halofantrine, lumefantrine as monotherapy		
artemisinin and its derivatives used as monotherapy: artemether, arteether, artesunate, dihydroartemisinin		
proguanil, chlorproguanil, pyrimethamine		
sulfadoxine, sulfalene, sulfamethoxazole, dapsone		
primaquine		
atovaquone		

Medication*	Prohibition period**	Action taken***
Other antimicrobials with antimalarial activity	entire core study period (until Day 43) except as rescue medication	Discontinue study treatment. However patients taking one of these drugs should stay in the study and follow-up visits for efficacy should be performed according to the visit schedule, i.e. remaining visits for the entire core study period (until Day 43), and the follow-up visit at 12 months of age
antibiotics: tetracycline****, doxycycline, erythromycin, azythromycin, clindamycin, rifampicin, trimethoprim		
pentamidine		

* applicable to the patient AND the person breastfeeding the patient
** based on the patient's time point of inclusion in the study
*** applicable to the patient (except for prohibited drug discontinuation)
****Topical tetracycline can be used.

6.2.3 Rescue medication

The following circumstances warrant discontinuation of study treatment (during the treatment period) and the implementation of rescue medication by the investigator (Commencement of rescue medication may occur after the start of study drug and up to Day 43):

Early Treatment Failure (ETF)

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

Late Clinical Failure (LCF)

- Development of danger signs or severe malaria on any day from Day 5 to Day 43 in the presence of parasitemia without previously meeting any of the criteria of Early Treatment Failure.
- Presence of parasitemia and axillary temperature ≥37.5° on any day from Day 5 to Day 43 without previously meeting any of the criteria of Early Treatment Failure.

Late Parasitological Failure (LPF)

- Presence of parasitemia on any day from Day 8 to Day 43 and axillary temperature <37.5° without previously meeting any of the criteria of Early Treatment Failure or Late Clinical Failure.

Rescue treatment involves therapy with an effective antimalarial available locally as per local medical practice or National Treatment Guidelines. Administration may be oral or parenteral depending on the subject's clinical condition. Rescue treatment will not be considered study medication. The exact rescue regimen and route of administration must be recorded on the appropriate CRF.

Patients will be monitored, either in clinic, or via home visits for the duration of treatment to ensure adherence to the rescue medication therapy. These patients will not discontinue the study (i.e., all the examinations as per the assessment schedule and all CRF for this patient will need to be completed), and they will not be replaced (unless the PK data cannot be properly analyzed due to treatment schedule discontinuation).

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is uniquely identified in the study by a Subject Number (Subject No.), that is assigned when the subject enters screening and it is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Once assigned to a subject, the Subject Number will not be reused.

Upon their parent/legal guardian signing the informed consent form, the subject is assigned to the next sequential Subject No. available. The investigator or his/her staff will then contact the Interactive Response Technology (IRT) and provide the requested identifying information for the subject to register them into the IRT. The site must select the CRF book with a matching Subject Number from the electronic data capture (EDC) system to enter data.

6.3.2 Treatment assignment, randomization

No randomization will be performed in this study. All eligible subjects will be assigned to one of the treatment packs via Interactive Response Technology (IRT). The investigator or their delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a unique medication number for the package of study treatment and the dose level to be dispensed to the patient.

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the appropriate disposition CRF.

6.4 Treatment blinding

This study is open label and treatment as well as the dose level will be open to the subjects' parents/legal guardian, investigator staff, persons performing the assessments, and the CTT.

6.5 Dose escalation and dose modification

6.5.1 Dose escalation guidelines

6.5.1.1 Starting dose

The starting dose in Cohort 1 in this trial is artemether:lumefantrine 5 mg:60 mg, i.e., 2 tablets bid for 3 days.

6.5.1.2 Provisional dose levels

Table 6-3 describes the starting dose and the dose levels that may be evaluated during this trial.

Table 6-3 Provisional dose levels

Dose level	Proposed dose*	Number of tablets per dose**
1	2.5 mg:30 mg	1
2	**5 mg:60 mg (starting dose in Cohort 1)**	2
3	7.5 mg:90 mg	3
4	10 mg :120 mg	4

*administered bid over 3 days.

**Dose level number 1 represent treatment regimen if a dose reduction is required from the starting dose level number 2 (used in Cohort 1) while Dose level numbers 3 and 4 represent treatment regimens if a dose increase is required. No dose reduction below dose level number 1 nor dose increase above dose level number 4 is permitted for this study.

Dose modification in a particular subject is not permitted. However, each cohort will be divided into sequential groups (see Figure 3-2 and Table 6-3). A pharmacokinetic exposure check (together with a review of efficacy and safety data as available) will be performed as described in Section 3 and Section 4.2. Based on the outcome of these checks, the dose may be adjusted between dose levels 1-4 in further patients recruited, following a pattern specific to each cohort. For more details, see Section 6.1.3.

6.5.2 Dose modifications

Dose level modification may not occur in an individual patient's 6-dose regimen, but the dose level may be adjusted between patients after each PK exposure check (See Section 6.5.1.2).

In addition, a replacement dose may be given to a patient in case of vomiting of a dose within 1 hour of administration (see Section 6.7.2). In case this repeat dose is vomited within 1 hour of intake, rescue treatment should be immediately provided.

6.5.3 Follow-up for toxicities

See Appendix 2 - Section 16.2

6.6 Additional treatment guidance

6.6.1 Treatment compliance

A limited number of qualified individuals, will be designated as appropriate by the investigator in order that two of these people ensure compliance by direct observation of both preparation

and administration of all doses of study medication for each patient. The exact dosages administered will be recorded on the Dosage Administration Record CRF, along with any comments about whether the patient swallowed all or only part of the medication, whether and when vomiting occurred, and whether replacement medication had to be initiated.

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

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

6.6.2 Recommended treatment of adverse events

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

(see Section 6.2.1).

6.6.3 Emergency breaking of assigned treatment code

Not applicable.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described in Table 6-1.

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

Investigator staff will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s) as well as the appropriate dose level.

The study medication has a 2-part label (base plus tear-off label). Immediately before preparing and dispensing the medication kit to the subject, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

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

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis/ CO Quality Assurance.

Medication labels will be in the appropriate 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 subject except for the medication number.

The investigator 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 monitors during site visits or remotely and at the completion of the trial.

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

6.7.1.2 Handling of additional treatment

Rescue medication will be handled as per Section 6.2.3.

6.7.2 Instruction for prescribing and taking study treatment

Two qualified individuals (from a limited number of people designated by the investigator for this task) will directly observe preparation and administration of all doses of study medication. They should promote compliance by ensuring that the patient take the study drug exactly as prescribed and by stating to the patient's legal guardian that compliance is necessary for the patient's safety and the validity of the study.

The study drug (dispersible tablets) should be administered as follows: the appropriate number of dispersible tablets composing 1 dose should be completely dispersed in a small amount of clean water (approximately 3 mL per dose) using a syringe for oral use and its content should be shaken gently and administered immediately to the subject (i.e., within 10 min). The syringe should then be rinsed with an additional small amount of clean water (approximately 3 mL) and given immediately to the subject (further details can be found in the Pharmacist intruction manual). The dose should be preceded and/or followed as much as possible by food/drinks rich in fat such as breast milk, or formula milk, in order to enhance absorption as well as to avoid dehydration.

In the event of vomiting of a dose within 1 hour of administration a repeat dose should be administered. In case this repeat dose is vomited within 1 hour of intake, rescue treatment should be immediately initiated and the infant discontinued from the study medication. The exact rescue regimen and route of administration (see Section 6.2.3) is to be recorded on the appropriate CRF.

For Dose 2 (at Hour 8), the administration time window should not be greater than ± 1 hour to achieve effective plasma level as soon as possible after start of treatment. For the following doses at Hours 24, 36, 48 and 60 (twice daily), the time window should not be greater than ± 2 hours. During the 3-day treatment period, study medication will be given under hospital supervision.

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

7 Informed consent procedures

Eligible subjects may only be included in the study after IRB/IEC-approved informed consent (witnessed, where required by law or regulation) has been provided by their legally acceptable representative (LAR), i.e. parent or legal guardian.

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 subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the informed consent and should be discussed with the subject's LAR 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 subject.

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

8 Visit schedule and assessments

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 subject’s source documentation.

Table 8-1 Schedule of assessments

Day*	1			2		3		4	5	8	15	29	43	Age 365 days
Hours	-24 to <0h	0h	8h	24h	36h	48h	60h	72h	96h	168h				
Informed Consent	X													
Inclusion/Exclusion criteria	X													
Demography	X													
Medical history	X													
Prior or concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	
Malaria Blood Film	X		X	X	X	X	X	X	X	X	X	X	X	
IRT contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug administration		X	X	X	X	X	X							
Meal Record		X	X	X	X	X	X	X						
Weight/Height (length)	X			X		X		X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	
Head circumference	X													X
Physical Exam	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Blood chemistry/ Hematology	X			X			X			X	X		X	
Sample for PCR	X									(X)	(X)	(X)	(X)	
Neuro-devt. Safety FU								X						X
PK sample	According to separate PK sampling scheme (See Section 16.3, Appendix 3)													
Adverse events	←	—	—	—	—	—	—	—	—	—	—	—	—	
Serious Adverse events	←	—	—	—	—	—	—	—	—	—	—	—	—	→

*To conform with Novartis internal standards, Day 1 is considered baseline (as opposed to Day 0 following WHO terminology); as visits should be scheduled in full 24-hour periods, days after Day 1 Visit, say Day 7 visit should occur 7 full days after Day 1 visit, i.e. often on the 8th day

Subjects 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 study discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit of the core follow-up period (Day 43) will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse events and concomitant medications recorded on the CRF.

8.1 Screening

The investigator or their delegate will contact the IRT when a patient enters screening. It is permissible to re-screen a subject if they fail the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

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

8.1.1 Information to be collected on screening failures

Subjects whose legal guardian sign an informed consent form and who are subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the applicable CRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event during the screening phase (see SAE section for reporting details).

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

8.2 Subject demographics/other baseline characteristics

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

Patient demographic and baseline characteristic data to be collected on all patients include: age (in days), sex, race, ethnicity, birth weight, current body weight, height, temperature, and malaria blood smears/parasite counts. Relevant medical history/current medical condition data and concomitant medication significant non-drug therapies prior to start of study drug consist in data up to the start of study drug. Where possible, diagnoses and not symptoms will be recorded.

In addition, all medications and significant non-drug therapies administered to a mother (or the person) providing breastmilk to a patient before the patient enters the study and starts treatment with study drug must be listed on the specific Concomitant medications/Significant non-drug therapies prior to start of study drug (e)CRF.

8.3 Efficacy

Efficacy assessments will consist of parasitemia determinations in peripheral blood and body temperature measurement, as well as signs and symptoms of early treatment failure.

Methods of parasitemia assessment

- Giemsa stained thick (and thin) films will be examined. Thin films are only required in the case of confirmation of species other than *P. falciparum*.
- Examination will be done using a light binocular microscope fitted with an oil immersion lens.
- Thick film screening examination (prior to patient inclusion into the trial):
- At least 200 thick film fields are examined. If there is no *P. falciparum*, the slide is declared negative, and the patient is not suitable for inclusion.

- If asexual forms of Plasmodia are found, a total of 200 thick film fields are to be screened for *Plasmodium* species other than *P. falciparum*.
- When it has been ascertained that *P. falciparum* is present, a count is made of the asexual forms against leukocytes, using a tally counter. Counting needs to be done based on at least 200 leukocytes according to the WHO standards. If less than 100 parasites, counting will be extended to 500 leukocytes.
- The parasite density will be calculated according to the following formula:

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

* WBC at screening or the latest available one

- Blood examination during the 43-day core trial period:
- A total of 200 thick films **fields** are examined (tally counter) before a slide can be pronounced negative.
- If asexual forms of *P. falciparum* are present, a parasite count is required
- If *Plasmodium* species other than *P. falciparum* are found, note species
- If *P. falciparum* gametocytes are seen, perform a gametocyte count against 1000 leukocytes

The count should be made for each species and for the *P. falciparum* gametocytes. Thick (and thin blood) films will be taken at each visit and evaluated by standard techniques (Giemsa stain). This will be the definitive test for a positive *P. falciparum* infection. The parasite counts can also be quantified in ‰ (per 1000) of red cells in the thin film.

For quality control purposes, all slides will be double read by two independent microscopists (as per each site's laboratory standard procedure and quality control measures).

In addition, central reading of all slides will be performed at a central reference laboratory. The results of the local reading will be entered in the (e)CRF and results of the central readings will be sent electronically by the central laboratory to Novartis (or a designated CRO). Results from the central reading will be used for the derivation of primary and secondary efficacy endpoints.

Blood samples for molecular diagnostic purposes

Blood will be sampled for parasite genotyping (PCR) as indicated in the assessment schedule (Table 8-1). At screening, a blood sample will be collected in all patients fulfilling eligibility criteria for inclusion in the study. A second blood sample will be analyzed only in patients showing treatment failure. This will allow to distinguish between recrudescence and a new infection. Sample analysis will be performed at a pre-selected reference laboratory.

Microscopic species identification (parasitemia) will be confirmed and determined with PCR-based methods on blood retained from samples collected at the time of treatment failure.

All parasite samples at baseline will also be screened for specific genes/single-nucleotide polymorphisms (SNPs) that are known as markers for *P. falciparum* resistance.

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

8.3.1 Appropriateness of efficacy assessments

The microscopy examination methods to quantify the malaria parasite and gametocyte in blood are validated methods (Sinden et al 2012; White et al 2014).

8.4 Safety

Safety assessments are specified in Table 8-2 with the assessment schedule (Table 8-1) detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section.

Table 8-2 Assessments & Specifications

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. At further visits an abbreviated one will include general appearance. At all visits, patients will be examined for signs of dehydration. At selected visits, head circumference will be measured in cm Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded as medical history. Significant findings made after signing informed consent which meet the definition of an adverse event must be recorded as an adverse event.
Vital signs	Vital signs will include systolic and diastolic blood pressure, temperature and pulse rate. After the patient has been still for five minutes (as much as possible), systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. Dynamap/Denshi, with an appropriately sized cuff. Repeat measurements will be made at 1-2 minute intervals and the mean of the three measurements will be used. 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. Temperature will be taken using a standard clinical thermometer, for 5 minutes before reading. Clinically notable vital signs are defined in Section 16.1 - Appendix 1 .

Assessment	Specification
Height and weight	Height in centimeters (cm) and body weight (in [g] to the nearest 10 g). Whenever available, birth weight (g) will also be collected at baseline visit. Infants should preferably be weighed and measured nude, alternatively wearing clean disposable diapers (weighing infants with too much clothing is one of the most frequent sources of error in infant weight measurements).

8.4.1 Laboratory evaluations

At each site, a local laboratory (validated/accredited) will be used for analysis of all specimens collected, i.e., for hematology and blood chemistry (for either PCR [parasite identification and resistance markers], or PK measurements, a central reference laboratory will be used).

All specimens will be processed and analyzed in the local laboratory. If any results are of clinical concern, a repeat sample will be collected at the next scheduled visit, while remaining within the overall blood volume limit for the patient (Howie 2011).

Test Category	Test Name
Hematology	Hemoglobin, hematocrit, red cell count (RBC and reticulocytes), white blood cell (WBC) count with differential (absolute value preferred, %s are acceptable) (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other), and platelet count
Chemistry	sodium, potassium, magnesium, glucose, creatinine, AST (SGOT), ALT (SGPT), and total bilirubin will be measured
Urinalysis	Not applicable

8.4.2 Other safety evaluations

A specific follow up of liver events will be performed as per Section 16.2 - Appendix 2.

[redacted]

8.4.3 Appropriateness of safety measurements

Safety measurements used in the 43-day follow-up are standard for this indication/subject population and follow WHO guidelines (WHO 2009; 2018)

All safety measurements, [redacted] were implemented in the previous study B2306 (Tiono et al 2015; EMA 2011).

8.5 Additional assessments

No additional tests will be performed on subjects entered into this study.

8.5.1 Clinical Outcome Assessments (COAs)

Not applicable.

8.5.2 Pharmacokinetics

Rationale for Artemether C_{max} (ART C_{max}) as primary endpoint

The previous study B2306 targeting the same population was stopped prematurely because the exposure to artemether and DHA was 2-3 fold higher in the first cohort (>28 days of age and <5 kg body weight) than what had been observed in earlier studies in children ≥5 kg body weight. There were no specific safety or efficacy related observations, however, absence of toxicity associated with the higher exposure, especially of neurotoxicity, could not be supported, by historical clinical or non-clinical data nor by the small sample size of study B2306 itself. Therefore, in the present B2307 study, it is hypothesized that if the exposure to artemether and lumefantrine is contained within the range of exposures which have been established to be safe and efficacious in children ≥5 kg, a dosing recommendation can be made with reasonable confidence in this vulnerable population. Due to limitations in recruiting the target population, the sample size remains limited and similar to that of Study B2306. Based on available information (Beckman et al 2013) it is anticipated that a higher artemether exposure remains a major concern of potential neurotoxicity so that monitoring artemether exposure remains critical in this population. Due to the limited number of sampling time points (and limitation of the overall blood volume drawn) in this population, the exposure reference in infants is available only in terms of ART C_{max}, achieving the target maximum concentration (C_{max}) for initial rapid parasitemia reduction (efficacy), ART C_{max} is also an appropriate measure of artemether exposure as artemether PK is described by a one compartment model ; ART C_{max} was therefore selected as the primary endpoint in this study. Nevertheless, other exposure parameters for artemether, DHA and lumefantrine will also be measured, wherever possible, along with safety and efficacy assessments in order to reach a conclusion in this study.

Pharmacokinetic Assessments

Blood samples will be collected for PK at the scheduled time points indicated in one of the 2 possible sample schemes (See Section 16.3-Appendix 3). When the investigator or their delegate contacts the IRT to confirm that the subject is eligible, the IRT will assign one of the 2 possible sample schemes to the patient (following a 1:1 ratio in each cohort). Due to the limitation in volume and in the number of samples which can be drawn from patients in this study, a total of 5 samples (500 µL each) will be obtained from each subject. Each subject will be assigned to either of the 2 sampling schemes by the IRT. In every sample, artemether, DHA and lumefantrine will be assessed. The sample points are selected in such a way that will allow

comparison with historical data (concentration at specific time points and ART C_{max}) and also collect useful information about AUC as appropriate.

For artemether, ART C_{max} is determined by collecting samples at 1h and 2h after first dose (as determined in study B2303 and study B2306) and ART C_{max} represents the higher concentration between the concentrations at 1 hour and 2 hours after first dose.

Further details on collection, labeling and shipment of the PK samples can be found in Section 16.3-Appendix 3 and the laboratory manual.

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

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the subject's parent/legal guardian or the investigator.

The investigator must discontinue study treatment for a given subject if they believe that continuation would negatively impact the subject's well-being.

Study treatment must be discontinued under the following circumstances:

- Subject's parent/legal guardian decision
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the subject
- Adverse events, abnormal laboratory values, or abnormal test result that indicate a safety risk to the subject (see Section 16.1-Appendix 1). For liver, see Section 16.2-Appendix 2.
- Unsatisfactory therapeutic effect
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study

Subjects who discontinue study treatment or whose parent/legal guardian decide they do not wish their child to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see 'Withdrawal of Informed Consent' section). **Where possible, they should return for the assessments indicated** in the Assessment Schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g., home visit) should be made to contact the subject's pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the parent/legal guardian cannot or is unwilling to have the subject attend any visit(s), the site staff should maintain regular contact with them, or with a person pre-designated by them. This contact should preferably be done according to the study visit schedule.

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

9.1.1.1 Replacement policy

Escalation/de-escalation part

Subjects will not be replaced in the study. However, if the dose is considered as unsuitable in the first few patients of the current cohort, enrollment of another set of new subjects to the current cohort to be treated with a different dose will be considered (for further details, see Section 3 and Figure 3-2).

Expansion part

During the dose expansion part of each cohort, no replacements will be needed.

9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject's legal guardian:

- Does not want the infant to participate in the study anymore, and
- Does not allow further collection of personal data from the infant

In this situation, the investigator should make a reasonable effort (e.g., telephone or any other suitable means) to understand the primary reason for the subject's legal guardian's decision to withdraw his/her consent and record this information.

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

Further attempts to contact the subject's legal guardian are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in Table 8-1.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until the time of withdrawal), as provided for in the ICF and according to applicable law.

All biological samples not yet analyzed at the time of withdrawal will no longer be used, as provided for in the ICF, and they will be destroyed according to applicable legal requirements.

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without their legally acceptable representative stating an intention to discontinue or withdraw their child, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject's LAR, e.g. dates of home visits, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including slow enrollment), a DMC recommendation or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject's welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. 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 subject's interests. Specifically, the investigator will inform the subject's legal guardian about the reasons for study termination. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

All treated subjects will have a safety follow-up visit at Day 43, and at 12 months of age. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the subject's parent/legal guardian should be recorded in the source documentation.

Study completion is defined as when the last subject finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision (Each subject will be required to complete the study in its entirety, including the safety follow up at the age of 12 months).

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems and the relevant contact details will be provided to each site.

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

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

2. 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
3. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
4. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment. All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Dose Reduced/increased
   - Drug interrupted/withdrawn
6. its outcome (i.e. recovery status or whether it was fatal)

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

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

Adverse event monitoring should be continued until the Day 43 Visit (end of the core follow-up period).

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

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (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 subjects with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Sections 16.1-Appendix 1 and 16.2-Appendix 2.

10.1.2 Serious adverse events

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

- fatal
- life-threatening

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

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the informed consent was signed
  - social reasons and respite care in the absence of any deterioration in the subject'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 subject 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 subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

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

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

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

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject's parent/legal guardian has provided informed consent and until the last core follow-up study visit must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs will be collected and recorded on the eCRF Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

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

If the SAE is not previously documented in the Investigator's 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) 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 last core follow-up study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Not applicable.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the

safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness (See Table10-1).

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

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

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

10.2 Additional Safety Monitoring

10.2.1 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be established (EMEA 2005, FDA 2006 , EMA 2018), who will monitor at regular time points PK, safety and efficacy data collected, i.e. once the first 9 patients in Cohort 1 , 3 and 9 patients (1-28 days old) and/or optionally 9 patients 15-28 days old in Cohort 2 treated with one same dose in each cohort have completed Day 15 (See Figure 3-2): Cohort 1 (infants >28 days of age) and Cohort 2 (neonates ≤28 days of age).

In addition the DMC will meet for 2 planned interim assessments:

Interim assessment 1

At the completion of Cohort 1's core period (Day 43), i.e. in 22 patients minimum to discuss and evaluate analyses of the PK data, as well as safety and efficacy data collected in the full cohort. The DMC will make a recommendation on whether to proceed with Cohort 2, and if so, either with the same dose regimen that was deemed suitable in Cohort 1 or an alternative one.

Interim assessment 2

At the completion of Cohort 2's core period (Day 43) to discuss and evaluate analyses of the PK data, as well as safety and efficacy data collected in both cohorts, i.e. in approximately 44 patients.

Optional interim assessment

Additional interim assessments along with DMC reviews may be conducted to support decision making for dose recommendations.

Additional ad-hoc safety reviews may be requested by the DMC or Novartis if needed (e.g. in case of SAEs).

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

11 Data Collection and Database management

11.1 Data collection

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

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

After final database lock (including long term safety follow up data), the investigator will receive copies of the subject data for archiving at the investigational site.

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

11.2 Database management and quality control

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

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

Data about all study treatment (s) dispensed to the subject and all dose level administered 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 at specific timelines.

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

11.3 Site monitoring

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

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of effective informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

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

Although there is only one study drug form (artemether 2.5 mg-lumefantrine 30 mg dispersible tablet), there are 4 possible dose levels (see Table 6-3). Therefore, treatment group in this study means study drug dose level and treatment group label will always include the study drug level even if there is only one study drug dose level in the whole study. In case that the dose level that passed the exposure check for the first 3 patients in the highest age subgroup in Cohort 2 is not appropriate for either or both the lower age subgroup(s) after the exposure check in 3 patients, the recruitment in these subgroup(s) will be stopped, they will be separated out from Cohort 2 and analyzed separately as needed.

12.1 Analysis sets

The Full Analysis Set (FAS) comprises all subjects that received any study drug. Subjects will be analyzed according to the treatment(s) received.

The Safety Set includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment received. The Safety set will be used for safety analyses while FAS will be used for other analyses.

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

- did not have important protocol deviations affecting efficacy
- took at least 80% of study medication
- PCR corrected cure status at Day 29 can be defined.

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

The PK set is a subset of the Full Analysis Set who had evaluable PK parameter data.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by cohort and treatment group for the FAS.

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

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

12.3 Treatments

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

The duration of exposure in number of study drug doses taken will be summarized by means of descriptive statistics using the Safety Set.

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

12.4 Analysis of the primary endpoint(s)

A pharmacokinetic parameter for artemether after the first dose, artemether C_{max} (ART C_{max}) will be assessed as the primary endpoint. The ART C_{max} will be compared with historical data especially from children ≥5-<15 kg BW in Study B2303.

12.4.1 Definition of primary endpoint(s)

ART C_{max} (artemether C_{max}) will be calculated using the peak plasma concentration of artemether following the first dose. For artemether, ART C_{max} is determined by collecting samples at 1h and 2h after first dose (as determined in study B2303 and study B2306) and

ART C_{max} represents the higher concentration between the concentrations at 1 hour and 2 hours post first dose.

12.4.2 Statistical model, hypothesis, and method of analysis

Ninety percent (90%) confidence intervals for ART C_{max} will be calculated based on the log normal distribution by cohort and treatment group using the PK analysis set. The study objective will be considered to be met if 90% CIs for ART C_{max} contain the desired values based on historical data especially those from children ≥5-<15kg BW in Study B2303.

12.4.3 Handling of missing values/censoring/discontinuations

Patients without sufficient PK concentrations for the derivation of ART C_{max} will not be included in the analysis.

12.4.4 Sensitivity and supportive analyses

Sensitivity analyses

Ninety percent (90%) confidence intervals for ART C_{max} will be calculated based on the log normal distribution by cohort and treatment group using the PPS. Patients with missing ART C_{max} will be excluded from the analysis.

Supportive analyses

If there are treatment groups that are used for multiple cohorts, ninety ercent (90%) confidence intervals for ART C_{max} will be calculated for these treatment groups based on the log normal distribution using the PK set by pooling data from all cohorts.

12.5 Analysis of secondary endpoints

Descriptive statistics for each secondary variable will be provided by cohort and treatment group. If there are treatment groups that are used for multiple cohorts, descriptive statistics will be calculated for these treatment groups by pooling data from all cohorts.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Secondary Efficacy variables are:

- PCR-corrected ACPR at Day 15, Day 29 and Day 43.
- Uncorrected ACPR at Day 8, Day 15, Day 29, and Day 43.
- Incidence rate of recrudescence and new infections at Days 15, 29 and 43
- Parasite and Fever clearance Times (PCT and FCT)

At each visit, the ACPR rate with 95% confidence intervals will be provided using the Pearson-Clopper method for each treatment group by cohort using PPS for PCR-corrected ACPR and FAS for uncorrected ACPR. Data will be handled as follows:

- Treatment failures after 7 days (i.e., Study Day 8) due to new infections based on PCR genotyping are not considered as failure for PCR-corrected analyses.

- For uncorrected ACPR, patients will be treated as failure on and after the visit when a reinfection with *P. falciparum* or other species is detected (which might be either recrudescence or a new infection).
- Patients who received rescue medication for the treatment of *P. falciparum* malaria (except for the treatment of a new infection) will be considered treatment failures. Patients who received other concomitant medication having an effect on malaria for reasons other than rescue therapy e.g., for the treatment of *P. vivax* (e.g., primaquine, certain antibiotics (sulfonamides, tetracycline, etc.) will be considered in the analysis as if they had not taken the drug.
- Patients will be counted as failure at a visit (e.g. Study Day 15, etc.) if (a) they did not have a parasite count, i.e., missing parasite count at that visit unless these patients could be classified as cured based on absence of parasitemia (parasite count = 0) at a later time (e.g., Study Day 29), or (b) they did not have valid PCR evaluations at baseline and the visit if parasitaemia was present at that time (e.g., Study Day 15).
- For intermediate missing data, (a) once a patient experienced a treatment failure at a timepoint (eg. Day 15), the patient is considered as treatment failure at all later timepoints (eg. Day 29), (b) is a patient is considered as cured at a timepoint (eg. Day 29), the patient is considered as cured at earlier timepoints (eg. Day 15).

In addition, PCR-corrected ACPR rate will be calculated and plotted using the Kaplan-Meier method (Stepniewska and White 2006; WHO 2015) for each treatment group by cohort in the FAS. Treatment failure is the event for analysis. For patients who do not experience treatment failure and do not have Study Day 43 data, treatment failure is considered as censored. The PCR-corrected ACPR rate at Study Day 29 is estimated by the survival function at Study Day 29. Patients who had a new infection with *P. falciparum* or other species without *P. falciparum* recrudescence on or after Study Day 8 will be censored at the time of the first PCR that indicate the infection; patients who took antimalarial medications for reinfection or reasons other than rescue medication given for *P. falciparum* related treatment failure will be censored at the first time of such antimalarial medications; other patients without treatment failure will be censored at the time of last parasitemia assessment.

Recrudescence and new infection

New infection is defined as appearance of asexual parasites after clearance of initial infection with a genotype different from those parasites present at baseline. New infection must be confirmed by PCR analysis.

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

Incidence rates of recrudescence and new infection at Days 15, 29 and 43 will be estimated by Kaplan-Meier method based on the subset of FAS patients who have clearance of initial infection by Day 7. Time to event (recrudescence or new infection) will be calculated from the time of first study medication to the date of first event if a patient experience the event and be censored at the time of last parasite assessment if a patient does not experience the event.

Parasite clearance time (PCT) and fever clearance time (FCT)

Descriptive statistics (mean, standard error, median, quartiles) will be presented for each treatment by cohort using the Kaplan-Meier method based on the FAS. Kaplan-Meier curves will be provided. PCT will be calculated based on uncorrected parasite counts. Patients without parasite clearance for whatever reason will be censored at the time of last parasite assessment. Patients who had no fever at pre-dose will not be included in the analysis of FCT. Patients without fever clearance for whatever reason will be censored at the time of last temperature assessment. In case that a patient receives rescue medication before (parasite or fever) clearance, the time to event will be censored at the first use of rescue medication.

12.5.2 Safety endpoints

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

Safety summaries (tables, figures) include only data from the core period (up to Day 43) 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 include only the core period events, with a start date during that period.

Adverse events

A treatment-emergent AE is defined as any AE that develops after initiation of the study treatments or any event already present that worsens following exposure to the study treatment.

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

The number (and percentage) of subjects with treatment emergent adverse events will be summarized in the following ways:

- by cohort, treatment group, primary system organ class and preferred term.
- by cohort, treatment group, primary system organ class, preferred term and maximum severity.
- by cohort, 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 adjustment if there are enough events.

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

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

Vital signs

All vital signs data will be listed by cohort, treatment group, subject, and visit/time and if ranges are available, clinically notable abnormalities will be flagged. Summary statistics will be provided by cohort, treatment group, and visit/time.

Weights and heights

All weight and height data will be listed by cohort, treatment group, subject, and visit/time. Summary statistics will be provided by cohort, treatment group, and visit/time.

Clinical laboratory evaluations

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

12.5.3 Pharmacokinetics

The PK set will be used for all PK analyses. Artemether, DHA and lumefantrine plasma concentration and AUC data (as applicable) will be listed by cohort, treatment group, subject, and visit/sampling time point. Descriptive summary statistics will be provided by cohort, treatment group, and visit/sampling time point, including the frequency (n, %) of concentrations below the lower limit of quantification (LLOQ) and reported as zero.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum. PK concentrations below the LLOQ will be treated as zero in summary statistics and for the calculation of pharmacokinetic parameters by non-compartmental analysis. A geometric mean will be calculated using half LLOQ value for concentrations below LLOQ.

For each PK parameter, the 90% confidence intervals will be calculated on the natural log scale and then anti-log transformed back to the original scale for the following comparisons:

- Artemether vs. historical data (Reference)
- DHA vs. historical data (Reference)
- Lumefantrine vs. historical data (Reference)

Artemether, DHA and lumefantrine PK is considered to be comparable with historical data if the 90% confidence interval contains the Historical values.

For review of the first 9 patients in each cohort (treated with the same dose) and the first 3 patients in each subgroup or optional PK checks in Cohort 2, the following data at all time points will be used to make a decision on a potential dose modification:

- ART C_{max} (higher concentration between the concentrations at 1 hour and 2 hours post first dose) (Primary)
- Day 8 (168 h) lumefantrine concentration
- C_{max} of DHA following the first dose from patients providing 1 h and 2 h data
- C_{max} of artemether and DHA following the last dose from patients providing 1 h and 2 h data
- C_{max} of lumefantrine from patients providing data after the last dose (due to potential accumulation for lumefantrine).

For the first 3 patients in each age subgroup in Cohort 2, the PK check is intended to make sure that the exposure for these patients is within the expected safety interval based on the historical data.

For the first 9 patients in each cohort or optional PK checks, the PK review is intended to check if the C_{max} is within approximately 2-fold of the C_{max} which has been found to be safe and efficacious in previous studies.

Non-compartmental PK will be used to calculate the pharmacokinetic parameters. Due to the limited number of samples collected in this study, a naive pool approach for data analysis may also be followed for reporting PK parameters such as ART C_{max} /other C_{max} and AUC, if feasible.

12.5.4 PK/PD relationships

A PK/PD analysis may be attempted based on available historical information. Due to the small sample size in this study, detailed PK/PD assessment based on this study alone may be of limited value.

12.5.5 Patient reported outcomes

Not applicable

[redacted]

[redacted]

12.7 Interim analyses

There will be informal PK checks (together with a review of efficacy and safety data as available) at various time points, and two planned interim data assessments, one between cohorts 1 and 2, and one again (of both Cohorts' data) after all patients in Cohort 2 have completed Day 43.

After the first 9 patients in Cohort 1 and the first 3 patients in the highest age subgroup of Cohort 2 have completed Day 15, artemether, DHA, and lumefantrine concentrations will be reviewed (together with a review of efficacy and safety data as available) for potential dose modifications (See Section 6.5.1.2). Another such review will be done after the first 9 patients of Cohort 2 have completed Day 15 (and optionally once 9 patients from the age group 15-28 days have completed Day 15). All available data including PK parameters, safety and efficacy will be reviewed by the DMC at these time points as described in Figure 3-2.

After all patients in Cohort 1 have completed the core period (Day 43), artemether, DHA, and lumefantrine concentrations, PK parameters, key efficacy and safety endpoints will be analyzed by the study biostatistics team (interim assessment 1). These results will be reviewed by the DMC to reach a decision about progression to Cohort 2 and the starting dose level in that Cohort. A second interim assessment will be performed after all patients have completed the core period of the study (Day 43). For the second interim assessment, all data up to Day 43 will be cleaned and included.

Additional interim assessments may be conducted to support decision making based on early read-out of study data.

Additional ad-hoc safety reviews may be requested by the DMC or Novartis if needed (e.g. in case of SAEs).

12.8 Sample size calculation

The sample size is calculated and justified based on the precision of estimating artemether C_{max} (primary endpoint) and Day 8 (168 h) lumefantrine concentration (secondary endpoint) separately for Cohort 1 and Cohort 2.

12.8.1 Primary endpoint(s)

Artemether C_{max} (represents the higher concentration between the concentrations at 1 hour and 2 hours) after the first dose is the primary endpoint. The distribution of C_{max} is best described by log normal distribution. The half width of the 2-sided 90% confidence interval for log C_{max} is the target for sample size calculation. The relevant historical data for sample size calculation are the standard deviations of log C_{max}, which are usually invariant to the dosage (See Table 12-1).

Table 12-1 Standard deviation for log C_{max} in Coartem studies A2102 and B2306

Study and formulation of artemether-lumefantrine	Artemether C_{max}	Day 8 Lumefantrine concentration
A2102* (healthy volunteers) 80:480 mg tablet	0.58	-
A2102 (healthy volunteers) 4 tablets of 20:120 mg	0.52	-
B2306 (infants >28 days of age) 20:120 mg dispersible tablet	0.65	0.654

*Study CCOA566A2102; **Study CCOA566B2306

The table shows that the standard deviation for log C_{max} was about 12% to 25% higher for infants in Study B2306 than for healthy volunteers in Study A2102. The patient population in the current study (B2307) is similar to the patient population in Study B2306.

For log C_{max}, a standard deviation of 0.65 from Study B2306 will therefore be used. Based on the standard deviation of 0.65 in log scale, a sample size of 16 evaluable patients will provide 80% probability that the observed half width of 2-sided 90% CI for log C_{max} is ≤0.337 or 1.4 times (covering the targeted C_{max}) in terms of ratio (nQuery Advisor 8). This sample size is applied to each cohort.

PK sampling will be designed in order to get all patients evaluable for artemether C_{max} analysis. Taking into account about 10% of patients not evaluable for this PK analysis, about 18 patients should be enrolled in each cohort.

For each cohort the sample size will be increased slightly to allow for higher dropouts for the secondary endpoint, Day 8 (168 h) lumefantrine concentration (see Section 12.8.2).

12.8.2 Secondary endpoint(s)

Power consideration for Day 8 (168 h) lumefantrine concentration

The Day 8 (168 h) lumefantrine concentration is the key secondary endpoint. The distribution of Day 8 lumefantrine concentration is best described by log normal distribution. In Study B2306, the standard deviation for the log concentration from 16 infants was 0.65. Based on the standard deviation of 0.65 in log scale, a sample size of 16 evaluable patients will provide 80% probability that the observed half width of 2-sided 90% CI for the log concentration is ≤0.337 or 1.4 times in terms of ratio (nQuery Advisor 8). This sample size is applied to each cohort.

The percentage of patients who are not evaluable for Day 8 lumefantrine concentration may be higher than that for artemether C_{max} which is based on the concentrations on Day 1. Taking into account about 25% of patients not evaluable for this PK analysis, about 22 patients will be enrolled in each cohort in order to achieve the number of patients evaluable for this analysis as specified above.

Power consideration for PK checking in each cohort

After about 9 patients have been enrolled in each cohort, PK checking will be performed to see if the dose level should be adjusted. Considering that about 10% of patients would be non-evaluable for artemether C_{max} , this will lead to about 8 patients evaluable for artemether C_{max}.

The probability that the observed half width of 2-sided 90% CI in log scale is ≤0.693 or 2 in terms of ratio for artemether C_{max} is 96% if the standard deviation in log scale is same as the assumed 0.65 or 80% if the standard deviation in log scale is as high as 0.85 (nQuery Advisor 8).

Note:

The requirement for an evaluable number of patients is 16 for both the primary endpoint (artemether C_{max} (max concentration between concentrations at 1 hour and 2 hours)) and the secondary endpoint (Day 8 (168 h) lumefantrine concentration). An additional number of patients is included due to potential dropouts for each endpoint. In case that the number of dropouts is less than expected, the enrollment for a cohort may be stopped after at least 16 patients are deemed evaluable for PK analyses (C_{max} or Day 8 concentration).

In order to support an early readout of the study based on observed PK, efficacy and safety,enrollment may be stopped. Thereafter, the criterion of 0.337 for the observed half width of 2-sided 90% CI for the log concentration will be increased to a threshold that is appropriate for the sample size.

Additional modeling and simulation may be performed to support the planned analyses.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

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

13.3 Publication of study protocol and results

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

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

13.4 Quality Control and Quality Assurance

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

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

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

14 Protocol adherence

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

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

14.1 Protocol amendments

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

Only amendments that are required for subject 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 subject 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.

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and reference ranges (vital signs, [redacted])

Table 16-1 Normal Vital Signs according to Age

Age	Heart Rate * (beats/min)	Blood Pressure (mm Hg)		Respiratory Rate (breaths/min)
		Systolic	Diastolic	
0-3 months	100-150*	65-85	45-55	35-55
3-6 months	90-120	70-90	50-65	30-45
6-12 months	80-120	80-100	55-65	25-40

Reference: Kliegman et al 2007.

* In sleep, infant heart rates may drop significantly lower, but if perfusion is maintained, no intervention is required

For information only, Premature : Heart rate (beats/min): 120-170*; Blood pressure (mm Hg): 55-75/35-45; Respiratory rate (breaths/min): 40-70

Reference ranges for magnesium are presented in Table 16-2 and for potassium in Table 16-3 (adapted from Hay et al 2018).

Table 16-2 Reference ranges for magnesium (mg/dL) by age range (male-female)

Age	***Male***	***Female***
0-7 days	1.2-1.6	1.2-1.6
>7-30 days	1.6-2.4	1.6-2.4
>1 mo-2 y	1.6-2.6	1.6-2.6
>2-6 y	1.5-2.4	1.5-2.4
>6-10 y	1.6-2.3	1.6-2.3
>10-14 y	1.6-2.2	1.6-2.2
>14 y	1.5-2.3	1.5-2.3

Table 16-3 Reference ranges for potassium (mmol/L) by age range (male-female)

Age	***Male***	***Female***
0-7 days	3.7-5.9	3.7-5.9
>7 d-3 mo	4.1-5.3	4.1-5.3
>3 mo-18 y	3.4-4.7	3.4-4.7
>18 y	3.5-5.0	3.5-5.0

Reference curves from WHO for head circumference are presented in Figure 16-1 and Figure 16-2 for males, and in Figure 16-3 and Figure 16-4. for females (https://www.who.int/childgrowth/standards/hc_for_age/en/).

Figure 16-1 Reference ranges for head circumference in males (0-13 weeks)

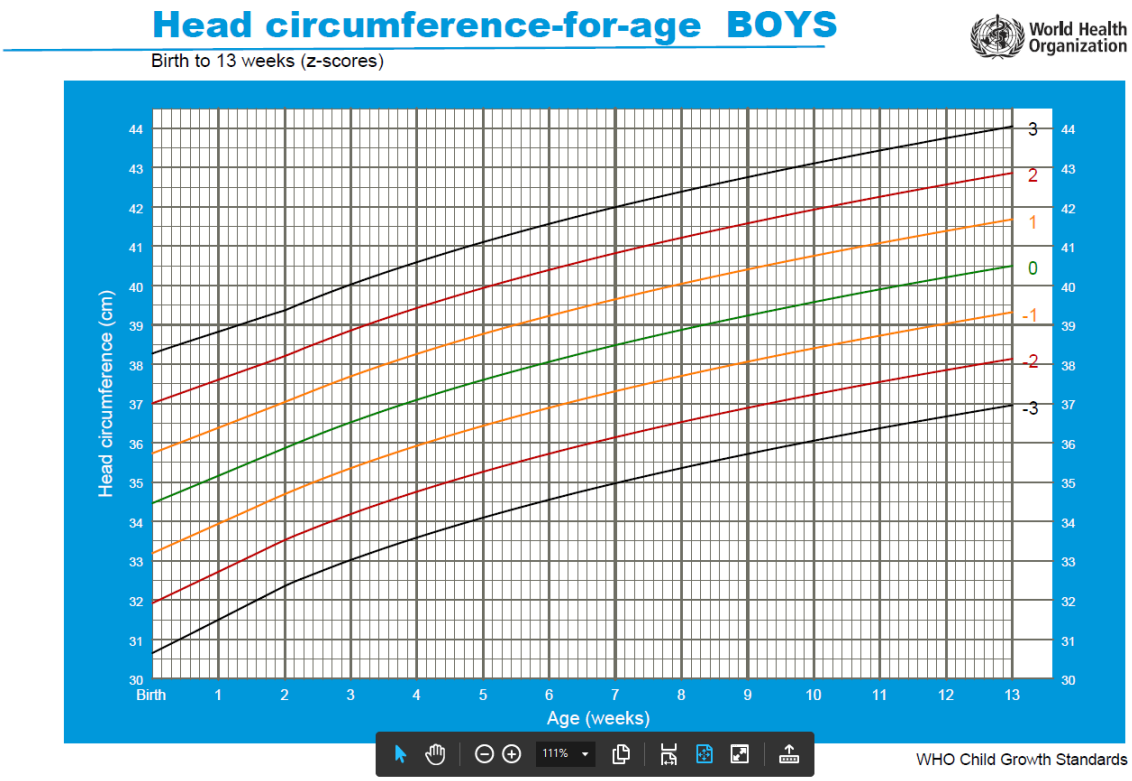


Figure 16-2 Reference ranges for head circumference in males (0-2 years)

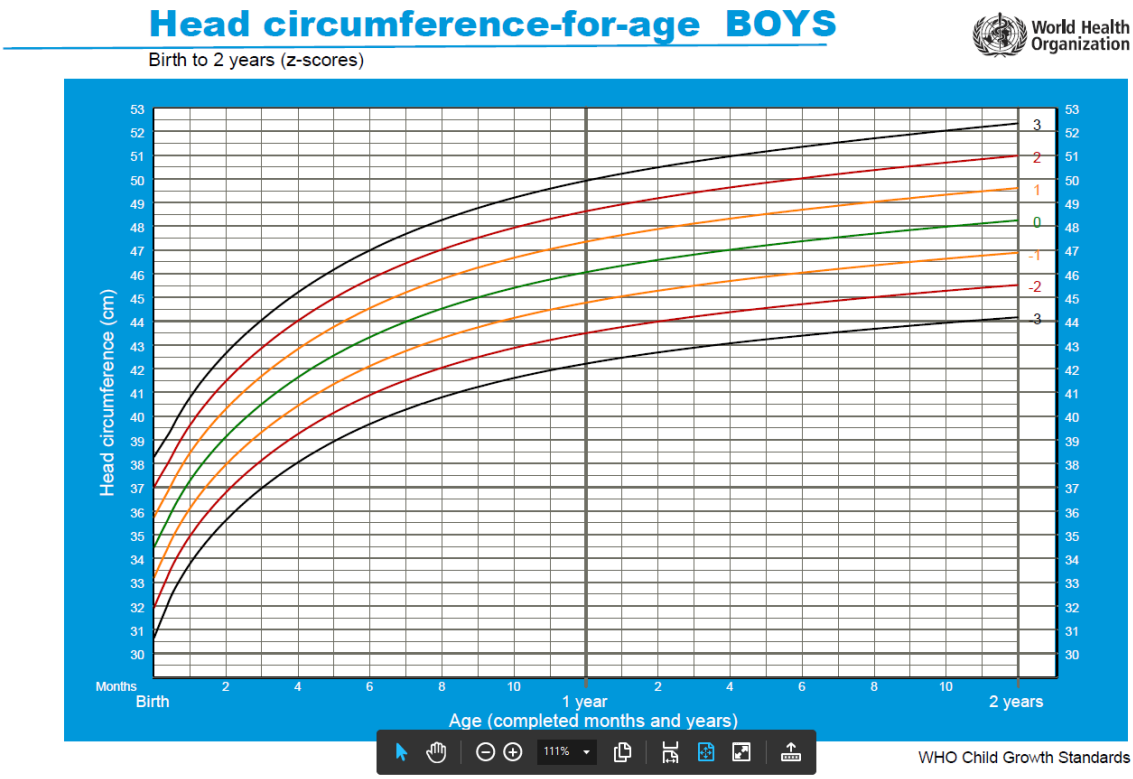


Figure 16-3 Reference ranges for head circumference in females (0-13 weeks)

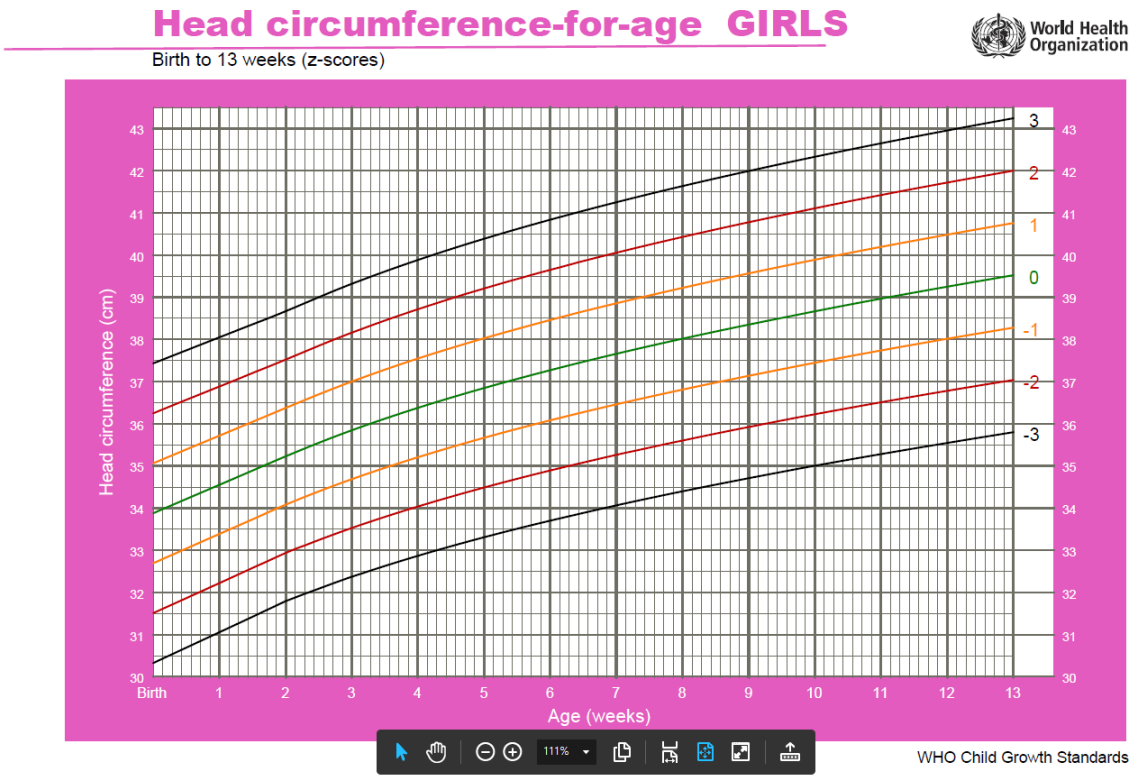
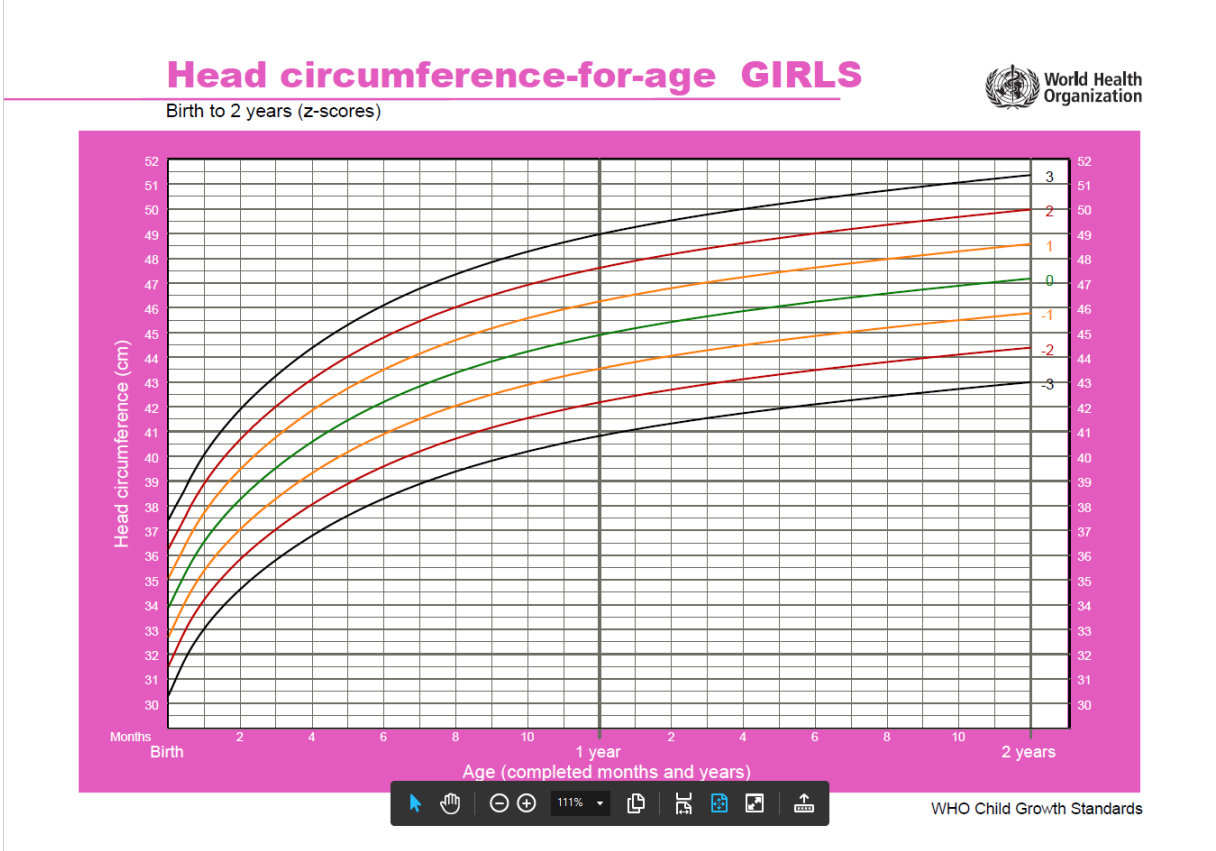


Figure 16-4 Reference ranges for head circumference in females (0-2 years)



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

Table 16-4 Follow up requirements for liver events and laboratory triggers

ALT	TBL	Liver symptoms	Action
ALT increase without bilirubin increase			
If normal at baseline: ALT > 3 x ULN	Normal	None	**No change to study treatment** • Measure ALT, AST, ALP*, GGT*, TBIL, INR*, albumin*, CK*, and GLDH* in 48-72 hours. • Follow-up for symptoms.
If elevated at baseline: ALT > 2 x baseline or > 200 U/L (whichever occurs first)	For patients with Gilbert's syndrome: No change in baseline TBL	None	**No change to study treatment** • Measure ALT, AST, ALP*, GGT*, TBIL, INR*, albumin*, CK*, and GLDH* in 48-72 hours. • Follow-up for symptoms.
If normal at baseline: ALT > 5 x ULN for more than two weeks	Normal	None	**Interrupt study drug** • Measure ALT, AST, ALP*, GGT*, TBIL, INR*, albumin*, CK*, and GLDH* in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
If elevated at baseline: ALT > 3 x baseline or > 300 U/L (whichever occurs first) for more than two weeks	For patients with Gilbert's syndrome: No change in baseline TBL.	None	**Interrupt study drug** • Measure ALT, AST, ALP*, GGT*, TBIL, INR*, albumin*, CK*, and GLDH* in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
If normal at baseline: ALT > 8 x ULN	Normal •	None	**Interrupt study drug** • Measure ALT, AST, ALP*, GGT*, TBIL, INR*, albumin*, CK*, and GLDH* in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
ALT increase with bilirubin increase:			

ALT	TBL	Liver symptoms	Action
If normal at baseline: ALT > 3 x ULN	TBL > 2 x ULN (or INR > 1.5)	None	I**Interrupt study drug** • Measure ALT, AST, ALP*, GGT*, TBIL, INR*, albumin*, CK*, and GLDH* in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
If elevated at baseline: ALT > 2 x baseline or > 200 U/L (whichever occurs first)	For patients with Gilbert's syndrome: Doubling of direct bilirubin	None	**Interrupt study drug** • Measure ALT, AST, ALP*, GGT*, TBIL, INR*, albumin*, CK*, and GLDH* in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
If normal at baseline: ALT > 3 x ULN	Normal elevated	Severe fatigue, nausea, vo miting, right upper quadrant pain	**Interrupt study drug** • Measure ALT, AST, ALP*, GGT*, TBIL, INR*, albumin*, CK*, and GLDH* in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
If elevated at baseline: ALT > 2 x baseline or > 200 U/L (whichever occurs first)	Normal elevated	evere fatigue, nausea, vo miting, right upper quadrant pain	**Interrupt study drug** • Measure ALT, AST, ALP*, GGT*, TBIL, INR*, albumin*, CK*, and GLDH* in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.

* If clinically indicated and within blood draw limitations

16.3 Appendix 3: Pharmacokinetic sampling

Table 16-5 PK Sampling scheme

Time (post first dose)*	1 h	2 h	62 h	66 h	68 h	84 h	168 h
Sample number	101	102	103	104	105	106	107
Scheme n°1	X	X	X	X			X
Scheme n°2	X	X			X	X	X

*Dosing times are 0, 8, 24, 36, 48 and 60 h

Perform the PK blood collection as outlined in the assessment schedule assigned to the patient (Table 16-4).

Methodology for whole blood sampling:

Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein.

Handling of blood samples for plasma collection:

Artemether is rapidly degraded in whole blood and by products of haemolysis in plasma. It is essential that the samples are handled as follows:

- Collect 500 µL blood in K2EDTA.
- Immediately after each tube is drawn (within 5 minutes after collection), the sample should be inverted gently several times to ensure mixing and centrifuged at 4°C at 4000 rpm (2200 g) for 10min.
- Remove plasma (about 200 µL should be obtained) quickly and transfer into polypropylene, screw cap tubes (NUNC barcoded 1D plus 2D tubes from Thermofischer).
- Freeze aliquots immediately at ≤-70°C until analysis. No interim freezing at lower temperature should be done. If necessary, storage on dry ice for no more than one hour is acceptable.

The actual sample collection date and time will be entered on the PK blood collection page of the (e)CRF. Sampling problems will be commented on in the (e)CRFs.

16.4 Appendix 4: Signs and symptoms indicative of severe P. falciparum malaria (WHO 2015)

In a patient with *P. falciparum* asexual parasitaemia and no other obvious cause of symptoms, the presence of one or more of the following clinical or laboratory features classifies the patient as suffering from severe malaria. These severe manifestations can occur singly or, more commonly, in combination in the same patient. The full clinical picture should be considered rather than just one isolated parameter.

Clinical Features:

- Impaired consciousness A Glasgow coma score < 11 in adults or a Blantyre coma score < 3 in children.

- Prostration, i.e. generalized weakness so that the patient is unable walk or sit up without assistance.
- Multiple convulsions – more than two episodes in 24 h
- Deep breathing, respiratory distress (acidotic breathing)
- Shock: compensated shock is defined as capillary refill ≥ 3s or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure < 70 mm Hg in children or < 80 mm Hg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill).
- Clinical jaundice plus evidence of other vital organ dysfunction: plasma or serum bilirubin > 50 µmol/L (3 mg/dL) with a parasite count > 100 000/µL.
- Abnormal spontaneous bleeding: including recurrent or prolonged bleeding from the nose, gums or venepuncture sites; haematemesis or melaena.
- Pulmonary oedema: radiologically confirmed or oxygen saturation < 92% on room air with a respiratory rate > 30/min, often with chest indrawing and crepitations on auscultation.

Laboratory findings

- Hypoglycemia (blood or plasma glucose < 2.2 mmol/L or < 40 mg/dL)
- Severe malaria anaemia: haemoglobin concentration ≤ 5g/dL or a haematocrit of ≤ 15% in children < 12 years of age (< 7g/dL and < 20%, respectively, in adults) with a parasite count > 10 000/µL.
- 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.
- Hyperparasitaemia: P.Falciparum parasitaemia > 10%
- Renal impairment: plasma or serum creatinine > 265 µmol/L (3 mg/dL) or blood urea > 20 mmol/L.

16.5 Appendix 5: IMCI guidelines

Infants aged >2 months– check for danger signs

1. Not able to drink or breast feed

- Too weak to drink and is not able to suck or swallow when offered a drink or breast-fed
- If not sure ask mother to offer child a drink of clean water or breast milk
- A child may have difficulty sucking when his nose is blocked. If the nose is blocked, clean

2. Vomiting everything

- A child is not able to hold anything down at all
- If in doubt offer the child water

3. Convulsions (during this illness)

- Arms and legs stiffen because muscles are contracting
- The child may lose consciousness or not be able to respond to spoken directions or handling, even if eyes are open

- "Fits" or "spasms" or "jerky movements"

  Note: shiver is not a convulsion. There is no loss of consciousness.

4. Abnormally sleepy or difficult to awaken

- Drowsy and does not show interest in what is happening around him
- Stare blankly and appear not to notice what is going on around him
- Does not respond when touched, shaken or spoken to

Note: If the child is asleep and has cough or difficult breathing, count the number of breaths before you try to wake the child.

Infants aged 0- 2 months- check for signs of bacterial infection (except for fever: 37.5°C* or above)

Possible serious bacterial infection

- Convulsions
- Fast breathing (60 breaths per minute or more)
- Severe chest indrawing
- Nasal flaring
- Grunting
- Bulging fontanelle
- Pus draining from ear
- Umbilical redness extending to the skin
- Low body temperature (less than 35.5 °C* or feels cold)
- Many or severe skin pustules
- Lethargic or unconscious
- Less than normal movement

*These thresholds are based on axillary temperature. The thresholds for rectal temperature readings are approximately 0.5 °C higher

Possible local bacterial infection

- Red umbilicus
- Draining pus
- Skin pustules