NOVARTIS

Clinical Development

COA566

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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

Statistical Analysis Plan (SAP)

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08-Oct-2021	Amendment 1	Update of notable ranges to be in line with protocol.		
28-Aug-2023	Amendment 2	Updated table values		Table 5-5 (Normal body temperature)
		Updated planned analyses		Section 2.5.4 (sensitivity analyses)
		Specified the sensitivity analysis		Section 2.7.2.1.2
		Adopted updated text and Figure from Protocol V01		Section 1.1, Figure 1-2

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List of abbreviations

ACPR	Adequate Clinical and Parasitological Response
AE	Adverse Event
ALT	Alanine aminotransferase
ART C_{max}	Artemether C_{max}
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
CDC	Centers for Diease Control and Prevention
CM	Concomitant medications
C_{max}	Maximum concentration
CSR	Clinical Study report
CV	Coefficient of variation
DAIDS	Division of AIDS
DBL	Database lock
DHA	Dihydroartemisinin
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
ETF	Early treatment failure
FAS	Full Analysis Set
FCT	Fever Clearance Time
FDA	Food and Drug Administration
GM	Geometric mean
IRT	Interactive Response Technology
LCF	Late clinical failure
LPF	Late parasitological failure
LUM	Lumefantrine
MedDRA	Medical Dictionary for Drug Regulatory Affairs
PCT	Parasite Clearance Time
PK	Pharmacokinetics
PPS	Per-Protocol Set
PT	Preferred Term
RBC	Red blood cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analysis which is planned in the protocol. This study is composed of two cohorts, Cohort 1 consisting of infants aged more than 28 days (<5kg) and Cohort 2 consisting of neonates aged 28 days or less (<5kg). After the core period of each Cohort an interim assessment will be performed by Novartis and results presented to an independent Data Monitoring Committee (DMC). Potential outputs for the DMC will be included in the CSR TFL shell document. No separate SAP or TFL shell document will be prepared for the interim assessments. This SAP will be used as a basis for the clinical study report, which will be prepared after the final database lock (DBL).

1.1 Study design

This is 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 infants/neonates 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 1-1), 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 (study protocol 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 1-2). 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 at all or if recruitment is not feasible in any of the 3 age subgroups, 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.

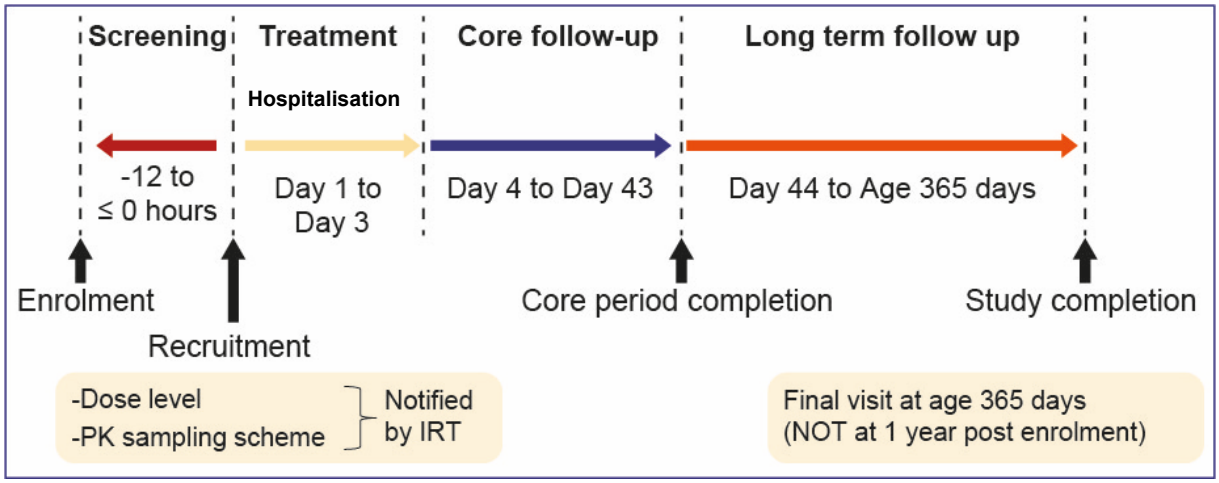
Patients will be admitted to the hospital on or before Day 1 (see Figure 1-1). After meeting all the inclusion and exclusion criteria in the study, they will receive study drug. The starting dose regimen in Cohort 1 will be two dispersible tablets twice daily for three consecutive days. The dose must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

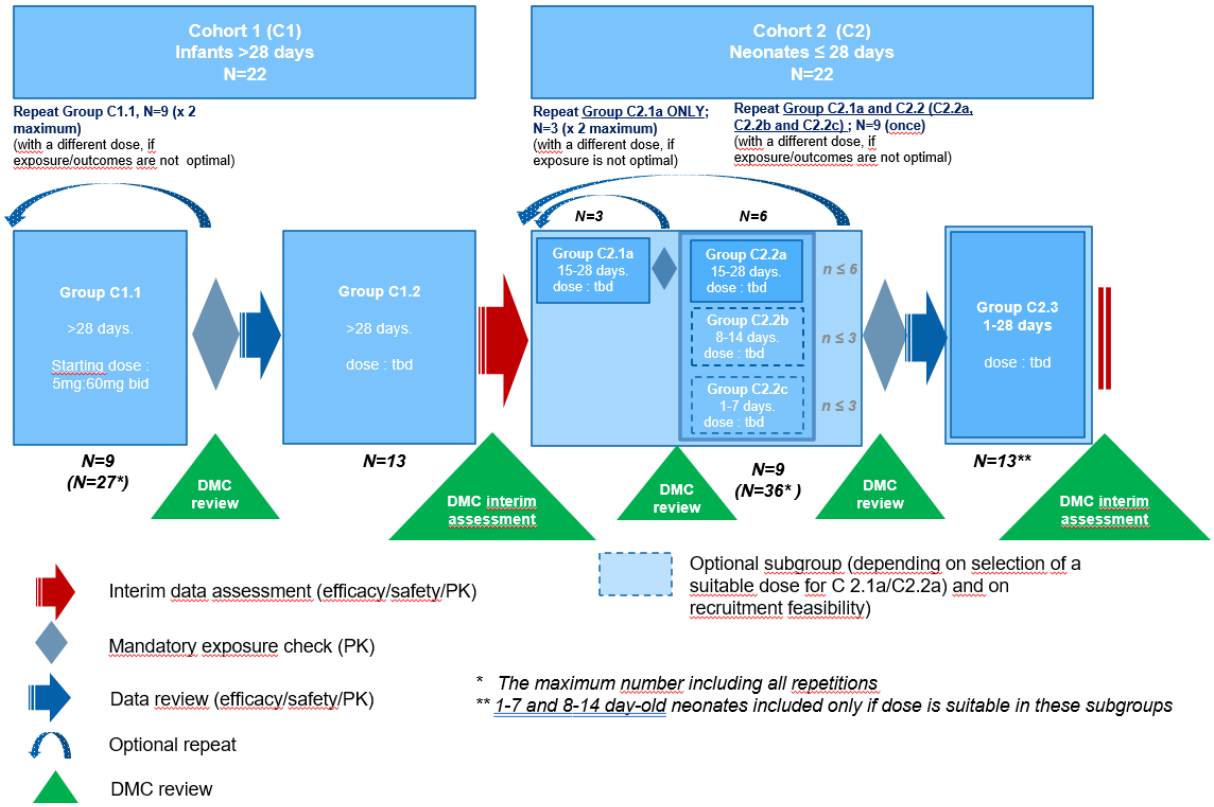
Patients will then attend a long term safety follow-up visit [redacted]

Figure 1-1 Patient participation overview



In this study, a stepwise and sequential approach will be adopted in order to minimize the risk for patients (Figure 1-2).

Figure 1-2 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 (15-28 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 1-2).

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

Randomization

Due to single arm, treatment randomization will not be performed in this study. But patient will be randomly allocated to PK scheme 1 or 2.

Interim analyses

There will be two planned interim assessments performed at :

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). Efficacy and safety parameters and PK exposure data from both cohorts will be assessed.

Optional interim assessment

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

1.2 Study objectives and endpoints

Table 1-1 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]	

2 Statistical methods

2.1 Data analysis general information

Data will be analyzed by [redacted] on behalf of Novartis after the final DBL using SAS version 9.4 according to the data analysis presented in Section 12 of the study protocol which will also be available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details will be provided, as applicable, in Appendix 16.1.9 of the CSR.

There will be two planned interim assessments, one after Cohort 1, the second one after Cohort 2. More details can be found in Section 2.12.

Data analyses required for the interim assessments will also be analyzed by [redacted] and corresponding outputs will be provided to the DMC. Outputs for the DMC will be part of the CSR shell document. No separate SAP or TFL shell document will be prepared.
After the first 9 patients in Cohort 1 and the first 3 and 9 patients in the higher age subgroup of Cohort 2 (1-28 days) and after the first 3 patients in the 2 younger subgroups of Cohort 2 (if they are recruited) have been treated with the same dose and followed up for at least 2 weeks (and optionally once 9 patients from the age group 15-28 days have completed Day 15), the database will be cleaned reasonably, data management reports using the raw data will be used for the regular review meetings and PK summaries will be generated by Novartis PK scientist.

Statistical analyses will be performed 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 for the primary and key secondary endpoints.

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

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

There is no stratification done in this study.

2.1.1 General definitions

Study treatment: COA566 (artemether: lumefantrine 2.5 mg:30 mg dispersible tablet) is the investigation treatment. As this is a single-arm study there is no control treatment. COA566 is referred to as study treatment in the document.

Treatment group: Treatment group in this study means study drug dose level. Note that although there is only one study treatment, there are 4 possible dose levels (1 to 4 tablets per dose). The 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.

Date of first administration of study treatment: The date of first intake of study treatment within the study.

Date of last administration of study treatment: The date of last intake of study treatment within the study.

Baseline: The last available measurement prior to first administration of study treatment.

Study day: The day of first administration of study treatment is defined as Day 1 (opposed to WHO terminology where this would be Day 0). Day -1 will be the day before Day 1. Day 0 does not exist.

Core period: Core period of the study starting with (and including) Day 1 until (and including) Day 43.

Parasitaemia: *P. falciparum* asexual parasite count greater than zero.

2.1.1.1 Clearance and treatment failure definitions

Fever Clearance time (FCT), defined as time from the first dose until the first time the axillary body temperature decreased below and remained below 37.5°C axillary or 38.0°C oral/tympanic/rectal for at least a further 24 hours. Note: 38.0°C is the temperature threshold for fever using oral/tympanic/rectal, which will be also used in the treatment failure definition.

Parasite clearance time (PCT), defined as time from the first dose until the first total and continued disappearance of asexual parasite forms which remained at least a further 48 hours.

Early Treatment Failure (ETF)

- Development of danger signs or severe malaria on Day 2, Day 3, Day 4 in the presence of parasitaemia.

- Parasitaemia on Day 3 higher than Day 1 count irrespective of axillary temperature.
- Parasitaemia on Day 4 with axillary temperature ≥37.5°.
- Parasitaemia 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 parasitaemia without previously meeting any of the criteria of Early Treatment Failure.
- Presence of parasitaemia 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 parasitaemia 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.

2.2 Analysis sets

The Full Analysis Set (FAS) comprises all subjects that received any study drug and had Plasmodium falciparum present at Screening visit. Subjects will be analyzed according to the treatment(s) received as per protocol.

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 as per protocol. 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.

2.2.1 Subgroup of interest

Not applicable.

2.3 Patient disposition, 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 25th and 75th percentiles will also be presented.

Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Relevant medical histories and current medical conditions at baseline will be summarized for FAS by cohort, treatment group system organ class and preferred term.

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 will be summarized under Concomitant medications/Significant non-drug therapies prior to start of study drug.

2.3.1 Patient disposition

The number and percentage of patients screened will be presented.

The number and percentage of patients who completed and who discontinued prematurely will be presented for each epoch (treatment and follow-up) by cohort for each treatment group.

For each protocol deviation, the number and percentage of patients for whom the deviation applies will be tabulated.

Data will be presented using FAS.

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

2.4.1 Study treatment / compliance

Number and percentage of tablets taken will be presented by cohort and treatment group. The percentage will be calculated based on the planned number of tablets per treatment group. Both number and percentage mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

Planned number of tablets in a treatment group = planned number of days of dosing x number of tablets to be administered per day in that treatment group.

For example, planned number of tablets for starting dose level 2 is 3 (planned number of days of dosing) x 2 (number of tablets) x 2 (twice a day) = 12 tablets.

Percentage of tablets taken will be calculated as Number of tablets consumed/Number of tablets planned x 100.

Compliance will be categorized by < 80 % and >=80 % of tablets taken and summarized by cohort and treatment group.

Number and percentage of patients with study drug vomiting and dose replacement will be presented by cohort and treatment group.

Safety set will be used.

2.4.2 Prior, concomitant and post therapies

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 latest version of WHO Drug Reference List dictionary which employs the Anatomical Therapeutic Chemical (ATC) classification system. The summaries will be presented by cohort, treatment group, ATC class and preferred term (PT). Data will be summarized as frequencies and percentages. Safety set will be used.

2.5 Analysis of the primary objective

A pharmacokinetic parameter for artemether after the first dose, artemether C_{max} (ART C_{max}) will be assessed as the primary endpoint.

2.5.1 Primary endpoint

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

The PK analysis set will be used.

2.5.2 Statistical hypothesis, model, and method of analysis

Ninety percent (90%) 2-sided confidence intervals for ART Cmax for the geometric mean will be presented by cohort and treatment group. Calculation will be based on the log normal distribution. The study objective will be considered to be met if 90% CIs for ART Cmax contain the desired values based on historical data especially those from children ≥5-<15kg BW in Study B2303. The desired values are displayed in the Appendix in Table 5-7.

2.5.3 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.

2.5.4 Supportive analyses

Sensitivity analyses

Ninety percent (90%) 2-sided confidence intervals for the geometric mean of 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 percent (90%) two –sided confidence intervals for the geometric mean of 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.

2.6 Analysis of the key secondary objective

2.6.1 Key secondary endpoint

The Day 8 (168 h) lumefantrine concentration (LUM C_{168h}) is a key secondary endpoint.

2.6.2 Statistical hypothesis, model, and method of analysis

Ninety percent (90%) 2-sided confidence intervals for the geometric mean will be calculated for Day 8 (168 h) lumefantrine concentration based on the log normal distribution by cohort and treatment group using the PK analysis set.

LUM C_{168h} is considered to be comparable with historical data if the upper limit of 90% confidence interval is not less than the Historical values. The desired historical values are displayed in the Appendix in Table 5-7.

2.6.3 Handling of missing values/censoring/discontinuations

Patients without evaluable Day 8 lumefantrine concentrations will be excluded from the analysis.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

Secondary Efficacy endpoints 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)

2.7.2 Statistical hypothesis, model, and method of analysis

There are no pre-specified hypotheses for secondary endpoints. Model and method of analysis are presented in the following sub-sections by topic.

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.

2.7.2.1 PCR-corrected ACPR and uncorrected ACPR

At each visit, the ACPR rate with 95% 2-sided confidence intervals will be provided using the Clopper-Pearson 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 parasitaemia (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).

2.7.2.1.1 Analysis of PCR-corrected ACPR using Kaplan-Meier method

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 for Study Day 29 and 43. The PCR-corrected ACPR rate at Study Day 29 (43) is estimated by the survival function at Study Day 29 (43).

Event is defined as treatment failure. The censoring rules are as follows:

- For patients who do not experience treatment failure and do not have Study Day 43 data, time to treatment failure is considered as censored at the time of last parasitaemia assessment.
- 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.
- Time to treatment failure (event or censored) will be truncated at Day 43 to avoid sudden drop in number of patients at risk after Day 43.

2.7.2.1.2 Sensitivity Analysis

For the CSR, not for IA01, there will be a sensitivity analysis of ACPR wherein patients are excluded from the PPS if they have a new infection prior to Day 29.

2.7.2.2 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 experiences the event and be censored at the time of last parasite assessment if a patient does not experience the event.

Patients with new infection will be censored at the time of first new infection when analyzing time to recrudescence. Patients with recrudescence will be censored at the time of first recrudescence when analyzing time to new infection. Undetermined treatment failures due to missing PCR data will be considered as censored at the time of treatment failure.

Time (event or censored) will be truncated at Day 43 to avoid sudden drop in number of patients at risk after Day 43.

2.7.2.3 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.

Parasite clearance time

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.

Fever clearance time

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.

Handling of missing values/censoring/discontinuations

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.

2.8 Safety analyses

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.

2.8.1 Adverse events (AEs)

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.

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

For summaries by maximum severity the following applies: if a patient reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a patient reported more than one adverse event within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level.

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

All information obtained on adverse events will be listed 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.

Additionally the number and percentage of patients will be presented for the following summaries:

- AEs related to study medication.
- Deaths.
- Serious adverse events.
- AEs leading to discontinuation of study treatment.
- AEs leading to dose adjustment.

These summaries will be presented by cohort, treatment group, primary system organ class and preferred term.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 5% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by primary system organ class and preferred term on the safety set.

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

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

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

2.8.1.1 Adverse events of special interest / grouping of AEs

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

Risk names will be sorted alphabetically, and, within each risk name, the PTs will be sorted in descending order of frequency. If a patient reported more than one adverse event with the same PT, the AE will be counted only once. If a patient reported more than one AE within the same risk, the patient will be counted only once at that risk.

The adverse events of special interest are defined in the Case retrieval Sheet (CRS) which is updated for each MedDRA dictionary.

2.8.2 Laboratory data

All laboratory data will be listed by cohort, treatment group, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Notable values will be flagged as well.

Descriptive statistics will be generated for all clinical laboratory tests performed (actual values and changes from baseline) for two groups of laboratory tests (hematology and blood chemistry) by laboratory test, cohort, treatment group and visit/time. Change from baseline will only be summarized for patients with both baseline and post baseline values and will be calculated as:

change from baseline = post baseline value – baseline value.

The following laboratory parameters will be analyzed for hematology test group: hemoglobin, platelets, white blood cell count, Reticulocytes, hematocrit, red blood cell (RBC) count, lymphocytes, lymphocytes (%), monocytes, monocytes (%), eosinophils, eosinophils (%), neutrophils, neutrophils (%) , basophils, basophils (%), bands, bands (%), differential other and differential other (%).

The following laboratory parameters will be analyzed for blood chemistry test group: sodium, potassium, magnesium, glucose, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin.

Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst value within the core period. The direction of interest for worst value within core period for each laboratory parameter is given in Table 5-3.

2.8.3 Other safety data

2.8.3.1 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.

The following quantitative variables will be summarized: Temperature (°C), Pulse (beats/min), Systolic blood pressure (mmHg) and Diastolic blood pressure (mmHg).

Analysis in vital sign measurements using descriptive summary statistics for the actual value and change from baseline will be performed by vital sign, cohort, treatment group and visit/time. Change from baseline will only be summarized for patients with both baseline and post-baseline values and will be calculated as:

Change from baseline = post-baseline value – baseline value.

2.8.3.2 Weights and heights

Weight (g) and Height (cm) will be summarized using descriptive summary statistics for the actual value and the change from baseline by cohort, treatment group and visit/time. For presentation of change from baseline the same rules as stated for vital signs do apply.

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

2.9 Pharmacokinetic endpoints

The PK set will be used for all PK analyses.

Artemether, DHA and lumefantrine plasma concentration, C_{max} 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). 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. CV for arithmetic mean will be computed as mean/SD x 100. CV for geometric mean will be computed as $\sqrt{e^{var(\log transformed\ data)} - 1}\ x\ 100$.

For DHA C_{max} and Lumefantrine C_{max} (LUM C_{max}) the 90% 2-sided confidence intervals for the geometric mean will be calculated on the natural log scale and then anti-log tranformed back to the original scale for the following comparisons:

- DHA C_{max} vs. historical data (Table 5-7)
- Lumefantrine C_{max} vs. historical data (Table 5-7)

DHA C_{max} and lumefantrine C_{max} are considered to be comparable with historical data if the 90% confidence interval contains the Historical values.
The analysis of ART C_{max} is described in Section 2.5, the analysis of LUM C_{168h} in Section 2.6.

Non-compartmental PK will be used to calculate the pharmacokinetic parameters wherever possible. 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.

2.10 PD and PK/PD analyses

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.

This analysis will be reported outside of the CSR.

2.12 Interim analysis

Interim assessment 1

Interim assessment 1 will be done 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. These results will be reviewed by Novartis Clinical team and the DMC to reach a decision about progression to Cohort 2 and the starting dose level in that Cohort.

Interim assessment 2

Interim assessment 2 will be done after all patients in Cohort 2 have completed the core period (Day 43). For this interim assessment all data up to Day 43 will be cleaned and included. Efficacy and safety parameters and PK exposure data from both cohorts will be assessed.

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).

3 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.

3.1.1 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 3-1).

Table 3-1 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 $\leq$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 3.1.2).

3.1.2 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). Additional optional PK checks can also be implemented.

Note:
The requirement for an evaluable number of patients is 16 for both the primary endpoint (artemether Cmax (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 (Cmax 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.

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Not applicable.

5.1.2 AE date imputation

Imputation of partial AE start dates will follow the general Novartis rules for imputation of AE start dates. Missing or partial AE end dates will not be imputed.

5.1.3 Concomitant medication date imputation

Concomitant medication date imputation will follow the general Novartis rules for imputation of CM start and end dates.

5.2 Visit windows

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

- The following rules are used to determine the window for other visits post baseline:
  - "Lower limit" = "upper limit of prior applicable visit" + 1
  - "Upper limit" = "target day of current visit" + integer part of ("target day of next applicable visit" – "target day of current visit")/2 with the exception of Day 43
  - Upper limit for analysis visit Day 43 is day 50

Based on the different assessments Table 5-1 describes the analysis visit window mapping. Repeat and/or unscheduled visits (which will be numbered in the database according to new NCDS standards) will be mapped for analysis purposes in the same way. If there are multiple measurements within an analysis window, the conventions defined in Table 5-2 will be used to determine the appropriate measurement to be selected for analysis.

The mapped visits will be used in the by visit analyses. However, the listings will show the collected data regardless of used in the by visit analyses.

Table 5-1 Analysis visit windows based on study day and time

Analysis Visit	Analysis timepoint	Vital signs	Weight/Height	Blood chemistry/ Hematolgy	Malaria blood film
Baseline	<0 h	up to 0 h	up to 0 h	up to 0 h	up to 0 h
Day 1	8 h	>0 to 16 h	-	-	>0 to 16 h

Day 2	24 h	>16 to 30 h	> 0 to 36 h	> 0 hrs to 42 h	>16 to 30 h
	36 h	>30 to 42 h	-	-	>30 to 42 h
Day 3	48 h	>42 to 54 h	> 36 to 60 h	-	>42 to 54 h
	60 h	>54 to 66 h	-	> 42 to 114 h	>54 to 66 h
Day 4	72 h	>66 to 84 h	>60 to 84 h	-	>66 to 84 h
Day 5	96 h	> 84 to 132 h	> 84 to 132 h	-	> 84 to 132 h
Day 8	168 h	> 132 h to Day 11	> 132 h to Day 11	> 114 h to Day 11	> 132 h to Day 11
Day 15	NA	Day 12 – 22	Day 12 – 22	Day 12 – 29	Day 12 – 22
Day 29	NA	Day 23 – 36	Day 23 – 36	-	Day 23 – 36
Day 43	NA	Day 37 - 50	Day 37 – 50	Day 30 – 50	Day 37 - 50
Age 365 days	NA	-	Aged between 335 – 395 days	-	-

Table 5-2 Rules for flagging variables

Timing of measurement	Type of data	Rule
Baseline	All data	The last measurement made prior to and including administration of the first dose of study treatment – note this may include measurements taken on the day of randomization. If a patient did not receive any dose of study treatment then the IRT date for the first study drug will be used.
Post-baseline efficacy	All data	The measurement closest to the target day/time will be used. In the event that two measurements are taken equally apart (e.g. 1 day before target date and 1 day after) the first one will be used.
Post-baseline safety	Summary visit information (e.g. lab, vital signs, etc.)	The measurement closest to the target day/time will be used. In the event that two measurements are taken equally apart, the first one will be used.
Post-baseline safety	Notable abnormalities (e.g. lab)	The most extreme measurement in the window will be used. Note this means a patient can have a notably high and notably low measurement within a window

5.3 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

5.4 Laboratory parameters derivations

The following table shows the direction of interest when analyzing worst case values within core period for laboratory shift tables. If the direction of interest is given as "High" the maximum value will be calculated and used as worst value, if the direction is given as "Low" the minimum value will be taken, and if it is given as "Low and high", both the minimum value and the maximum value will be calculated and presented in shift tables.

Table 5-3 Directions of interest for worst case value for laboratory parameters

Laboratory test group	Parameter	Directions of interest for worst case value
Hematology	Hemoglobin	low
Hematology	Hematocrit	low
Hematology	Reticulocytes	high
Hematology	RBC	low
Hematology	WBC	low and high
Hematology	Basophils	high
Hematology	Eosinophils	high
Hematology	Lymphocytes	low and high
Hematology	Monocytes	high
Hematology	Neutrophils	low and high
Hematology	Platelets	low
Hematology	Bands	Not applicable
Hematology	Differential other	Not applicable
Blood chemistry	Sodium	low and high
Blood chemistry	Potassium	low and high
Blood chemistry	Magnesium	low and high
Blood chemistry	Glucose	low and high
Blood chemistry	Creatinine	high
Blood chemistry	AST	high
Blood chemistry	ALT	high
Blood chemistry	Total bilirubin	high

5.5 Vital signs and Laboratory – definition of clinically notable values

The following two tables show the clinical notable criteria for vital signs. Clinically notable ranges for laboratory parameters will be defined as values graded or worse 3 (see Table 5-6) using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Corrected version 2.1, July 2017).

Table 5-4 Normal Vital Signs according to Age

Values below the lower limit or above the upper limit of normal will be listed as Abnormal.

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

Table 5-5 Normal body temperature

Vital sign parameter	Normal range
Oral/Tympanic/rectal body temperature (°C)	>= 37.0 and <= 37.9
Axillary body temperature (°C)	>= 36.5 and <= 37.4

5.6 Historical exposure values from previous studies

Table 5-6 Reference values for PK analyses

Study	Body weight in kg (and age in days for B2306)	ART Dose (mg)	First dose Artemether C_{max} (ng/mL) n, geo-mean	DHA C_{max} (ng/mL) n, geo-mean	LUM C_{max} (µg/mL) n, geo-mean	LUM C_{168h} (ng/mL) n, geo-mean
B2306	<5 kg >28 days	20	-	18, 70.2	19, 5.2	16, 666
B2303	≥5 kg - <15 kg	20	52, 101	52, 31.7	102, 3.9	27, 212
B2303	≥15 kg - <25 kg	40	30, 105	30, 45.0	48, 6.6	4, 388
B2303	≥25 kg - <35 kg	60	9, 112	9, 57.5	9, 8.3	-

ART: artemether; LUM: lumefantrine

5.7 Statistical models

5.7.1 Primary analysis

The primary analysis is detailed in Section 2.5.

The primary endpoint ART C_{max} will be displayed by cohort and treatment group using the geometric mean. The geometric mean will be calculated by deriving the mean of the log-transformed values followed by an exponential transformation, i.e. $Geometric\ Mean\ (GM) = e^{mean(\log(x))}$ with x = ART C_{max} of a participant.

Corresponding 2-sided 90% confidence intervals for the GM will be calculated assuming a log normal distribution of the primary endpoint. The lower and upper limits will be calculated as follows:

$$\exp\left(\bar{x} \pm t_{\left(1-\frac{\alpha}{2};n-1\right)} \times \frac{s}{\sqrt{n}}\right)$$

with $\bar{x}$ = the arithmetic mean of the log-transformed endpoint, $t_{\left(1-\frac{\alpha}{2};n-1\right)}$ = the $(1-\frac{\alpha}{2})$ critical value of the Student's t statistic with $n-1$ degrees of freedom, s = the standard deviation of the log-transformed endpoint, and n = the number of patients with available endpoint in the corresponding cohort and treatment group.

The logarithm to the natural base is used.

The calculation will be implemented in SAS using PROC MEANS on log data followed by an exponential transformation.

5.7.2 Key secondary analysis

The key secondary analysis is detailed in Section 2.6.

The calculation of the geometric mean and the corresponding 2-sided 90% confidence intervals will be done similarly as for the primary endpoint, see Section 5.4.1.

5.8 Rule of exclusion criteria of analysis sets

Table 5-7 Protocol deviations and non-PD criteria leading to exclusion from analysis sets ce values for PK analyses

Analysis Set	PD (description and ID) that causes subjects to be excluded	Non-PD criteria that cause subjects to be excluded
FAS	Informed Consent for study participation not obtained (INCL05) Plasmodium falciparum not present as parasite species at Screening visit (INCL04)	No study drug taken
SAF	Informed Consent for study participation not obtained (INCL05)	No study drug taken
PPS	Baseline Plasmodium falciparum parasite count is not >=500 and <100,000/µL at screening visit for patients in Cohort 1 (INCL04A) Baseline Plasmodium falciparum parasite count is not >=100 and <100,000/µL at	Not in FAS Did take less than 80% of planned study medication (see Section 2.4.1) PCR corrected cure status at Day 29 can not be defined Not classified as non-responder before Day 8, no positive blood smear parasite on Day 8

Analysis Set	PD (description and ID) that causes subjects to be excluded	Non-PD criteria that cause subjects to be excluded
	screening visit for patients in Cohort 2 (INCL04B)	onwards, and blood smear parasite result is missing at Day 29.
	Prohibited concomitant anti-malarial medication administered without experiencing ETF, LCF, LPF (PROH02)	Not classified as non-responder before Day 8, have at least one positive blood smear parasite result between Day 8 and Day 29 which cannot be determined as recrudescent or new infection based on PCR genotyping.
	Prohibited concomitant non-malaria medications with potential impact on efficacy/antimalarial activity (PROH01A)	
	Presence of another critical condition (EXCL06)	
PK		Not in FAS
		No evaluable PK parameter data available

6 References

Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet. 2011;377(9770):1011-1018. doi:10.1016/S0140-6736(10)62226-X.

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