Integrated Analysis Plan

Study Number:	MS201618_0034
Clinical Study Protocol Title:	Phase 2a Proof of Concept, Multicenter, Randomized, Open-label Study to Evaluate the Efficacy, Safety and Pharmacokinetics of a single dose of the combination M5717-Pyronaridine as Chemoprevention in Asymptomatic Adults and Adolescents with Plasmodium Falciparum Malaria Infection
Study Phase:	Phase 2a
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Approval Page

Integrated Analysis Plan: MS201618_0034

Phase IIa Proof of Concept, Multicenter, Randomized, Open-label Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of the Combination M5717 plus Pyronaridine Administered Once Daily for 1 or 2 Days to Adults and Adolescents with Acute Uncomplicated *Plasmodium falciparum* Malaria

Approval of the IAP by all Merck Data Analysis Responsible has to be documented within EDMS via eSignature. With the approval, the Merck responsible for each of the analysis also takes responsibility that all reviewers' comments are addressed adequately.

By using eSignature, the signature will appear at the end of the document.

1 Table of Contents

2 List of Abbreviations and Definition of Terms

ADaM	Analysis Data Model
AE	Adverse Event
AEIR	Adverse Event Incidence Rate
ATC	Anatomical Therapeutic Chemical classification
BLQ	Below the lower limit of quantification
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
(e)CRF	(electronic) Case Report Form
CSR	Clinical Study Report
CTP	Clinical Trial Protocol
ECG	Electrocardiogram
EDMS	Electronic Document Management System
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
GBS	Global Biostatistics
HR	Hazard Ratio
IAP	Integrated Analysis Plan
ICE	Intercurrent Event
ICH	International Conference on Harmonization
ITT	Intention To Treat
KM	Kaplan-Meier
LLN	Lower Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
PT	Preferred Term
CCI	[redacted]
PK	Pharmacokinetics
SAE	Serious Adverse Event

SAF	Safety Analysis Set
SCR	Screening analysis set
SD	Stable Disease or Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TLF	Tables, Listings, and Figures
ULN	Upper Limit of Normal
WHO-DD	World Health Organization Drug Dictionary

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	03-Sep-2024	PPD	Initial version
2.0	21-May-2025	PPD	- Inconsistencies in the definition of intercurrent events of some of the estimands were resolved - Analysis of gametocytemia and CCI [redacted] was removed since data will not be available.

4 Purpose of the Integrated Analysis Plan

The purpose of this IAP is to document technical and detailed specifications for the final analysis of data collected for protocol MS201618_0034.

The IAP is based on the study protocol and protocol amendments and is prepared in compliance with ICH E9. It describes analyses planned in the protocol Version 1.0 dated 01 March 2023.

The wording used in this IAP is chosen to best match the respective wording in the study protocol template, the Clinical Study Report (CSR) template, CDISC requirements and special requirements for table layouts. Therefore, the following approach is used:

Generally, the term 'participant' will be used instead of 'subject' or 'patient'. However, in tables and listings the term 'subject' will be used to match CDISC requirements, except for in-text tables where 'participant' will be used to match the CSR and protocol templates. Similarly, the term 'study intervention' will be used in this document instead of 'treatment' to match protocol and CSR templates, however, tables and listings will use 'treatment' for brevity reasons. Exceptions from this rule are commonly used terms like "on-treatment", "treatment-emergent", "treatment policy", "subject-years", "by-subject", or names of eCRF pages like "Treatment Termination" page.

5 Objectives and Estimands

Objectives	Estimands/Endpoints	Ref. #
Primary		
To evaluate the time of protection of different doses of M5717 in combination with pyronaridine in adults and adolescents with asymptomatic falciparum malaria compared with the natural incidence of infection as measured in Cohort 4	**Endpoint:** Time to parasitemia since negative blood smear after treatment **Population:** Asymptomatic adult and adolescent patients infected with *P. falciparum* **Treatment:** • Single dose 60 mg M5717 plus 720 mg pyronaridine (≥ 65 kg) or 540 mg pyronaridine (≥ 45 to < 65 kg) (Cohort 1) • Single dose 200 mg M5717 plus 720 mg pyronaridine (≥ 65 kg) or 540 mg pyronaridine (≥ 45 to < 65 kg) (Cohort 2)	1

Objectives	Estimands/Endpoints	Ref. #
	• Single dose 660 mg M5717 plus 720 mg pyronaridine (≥ 65 kg) or 540 mg pyronaridine (≥ 45 to < 65 kg) (Cohort 3) • 3 doses of Malarone (1,000 mg atovaquone plus 400 mg proguanil hydrochloride [proguanil]) to clear all parasites to measure the natural incidence of infection (Cohort 4) **Intercurrent Event Strategy:** • Intake of rescue medication: composite variable strategy, i.e. endpoint is considered as failure (=positive blood smear at the time of rescue medication intake) • Intake of antibiotics or other prohibited medication that impacts treatment effect (e.g. drug with antimalarial activity) at any timepoint: On-treatment strategy, i.e. time to parasitemia is censored at the time of antibiotics or prohibited medication intake • Experience of any event that affects absorption (e.g. vomiting within the first 24 hours after dosing): Treatment policy strategy, i.e. treatment effect is estimated regardless of ICE. • Death due to malaria: Composite variable strategy, i.e. parasitemia event is assumed at time of death. • Death due to other reasons: On-treatment strategy, i.e. time to parasitemia is censored at the time of death **Population-Level Summary** HRs estimated from Cox' Proportional Hazards Model for each dose of M5717 compared to Cohort 4	
Secondary		
To evaluate the time of protection of different doses of M5717 in combination with pyronaridine in adults and adolescents with asymptomatic falciparum malaria compared with the natural incidence of infection as measured in Cohort 4	**Endpoint:** Incidence of parasitemia (positive blood smear). **Population:** See primary endpoint **Treatment:** See primary endpoint **Intercurrent Event Strategy:** • Intake of rescue medication: composite variable strategy, i.e. endpoint is considered as failure (=positive blood smear at the time of rescue medication intake) • Intake of antibiotics or other prohibited medication that impacts treatment effect (e.g. drug with antimalarial activity) at any timepoint: On-treatment strategy, i.e. time to parasitemia is censored at the time of antibiotics or prohibited medication intake • Experience of any event that affects absorption (i.e. vomiting within the first 24 hours after dosing): Treatment policy strategy, i.e. treatment effect is estimated regardless of ICE • Death due to malaria: Composite variable strategy • Death due to other reasons: On-treatment strategy, i.e. time to parasitemia is censored at the time of death **Population-Level Summary:** Proportion of participants with parasitemia using Kaplan-Meier estimates for each dose of M5717 and for Cohort 4	2
	Endpoint: : Incidence of PCR-adjusted parasitemia (thick smear/microscopy, after adjustment for parasitemia due to new infections as determined by genotyping using PCR techniques). **Population:** See primary endpoint **Treatment:** See primary endpoint	3

Objectives	Estimands/Endpoints	Ref. #
	Intercurrent Event Strategy: See endpoint #2 **Population-Level Summary:** See endpoint #2	
	Endpoint: Incidence of PCR-adjusted parasitemia (thick smear/microscopy, after adjustment for parasitemia due to recrudescence as determined by genotyping using PCR techniques). **Population:** see primary endpoint **Treatment:** See primary endpoint **Intercurrent Event Strategy:** See endpoint #2 **Population-Level Summary:** See endpoint #2	4
To evaluate the parasite clearance time in adults and adolescents with asymptomatic *P. falciparum* malaria treated with different doses of M5717 in combination with pyronaridine	**Endpoint:** Parasite clearance time defined as time from dosing to the first negative (no parasites) blood film (microscopy) **Target Population:** See primary endpoint **Treatment:** See primary endpoint **Intercurrent Event Strategy:** • Intake of rescue medication after study treatment and before negative blood smear: treatment policy strategy, i.e. treatment effect is estimated regardless of ICE • Intake of antibiotics or other prohibited medication that impacts treatment effect (e.g. drug with antimalarial activity) at the time or after the time of study treatment, but before first negative blood smear: Treatment policy strategy • Experience of any event that affects absorption (i.e. vomiting within the first 24 hours after dosing): Treatment policy strategy, i.e. treatment effect is estimated regardless of ICE • Death before negative blood smear: On-treatment strategy, i.e. time to parasite clearance is censored at the time of death **Population-level Summary:** Median parasite clearance time as estimated by Kaplan-Meier method for each dose of M5717	5
To evaluate the safety and tolerability of different doses of M5717 in combination with pyronaridine in adults and adolescents with asymptomatic *P. falciparum* malaria	**Endpoint**: Incidence, severity, and seriousness of TEAEs, treatment-emergent study intervention related AEs, as per CTCAE v 5.0	6
To characterize the PK profile of the M5717plus pyronaridine combination	PK parameters of M5717 and pyronaridine using noncompartmental analysis, as appropriate.	7

Objectives	Estimands/Endpoints	Ref. #
CCI		

6 Overview of Planned Analyses

This IAP covers analyses of efficacy, pharmacokinetic (PK), pharmacodynamic (PD), and safety based on the data at the end of the study.

7 Changes to the Planned Analyses in the Clinical Study Protocol

- For estimand #5 (time to parasite clearance) the intercurrent event strategies were changed. Applying ICE handling strategies equivalent to estimand #2, as defined in the protocol, was not adequate.
- CCI

8 Analysis Sets and Subgroups

8.1 Definition of Analysis Sets

The following Analysis Sets will be used:

Analysis Set	Description
FAS	The FAS will include all randomized participants . Participant will be analyzed according to the treatment assigned at randomization as per the Intention-to-Treat (ITT) principle.
SAF	All participants who were administered any dose of any study intervention. Analyses will consider participants as treated.
PK Analysis Set	All participants , who receive 1 dose of study intervention, have no clinically important protocol deviations or important events affecting PK, and provide ≥ 1 measurable postdose concentration. Participants will be analyzed per the actual study intervention they received.

Note that important protocol deviations or important events that lead to exclusion of participants from the PK Analysis Set are identified during the data review process.

The following table summarizes the use of the analysis sets in the different analyses.

	Analysis Set		
Analyses	**FAS**	**SAF**	**PK Analysis Set**
Baseline Characteristics	✓	✓*	
Previous and Concomitant Therapies	✓	✓*	
Compliance and Exposure		✓	
Efficacy: Primary Endpoints/Estimands	✓		
Efficacy: Secondary Endpoints/Estimands	✓		
CCI			
Safety and Tolerability		✓	
PK analyses			✓

*only to be created if discordance between FAS and SAF is more than 5%

In addition to the above defined sets used for analysis, the Screened Analysis Set will be used only for the disposition table. The Screened Analysis Set contains all subjects who signed the informed consent.

8.2 Subgroup Definition and Parameterization

For subgroup analyses the following will be used:

- Age (years)
  - ≥12 to <18
  - ≥18
- Country

9 General Specifications for Data Analyses

9.1 Treatment Groups

Treatment groups are defined according to the different doses of M5717 as “M5717 60 mg”, “M5717 200 mg”, “M5717 660 mg”, “Natural Infection”, and “Pyramax External” (note that Cohort 5 consists of external data obtained from a clinical study sponsored by Shin Poong (please refer to the Clinical Trial Protocol (CTP) for details)).

CCI

The PS for participant *i* is defined by:

$$PS_i = P(Z_i = 1|X_i = x_i)$$

i.e. the conditional probability of being exposed to a treatment Z (with Z=1 if treated with M5717+pyronaridine, Z=0 if treated with Pyramax 1-day treatment).

In a first step, the PS for each participant is estimated by use of a logistic regression model

$$P(Z_i = 1|X_i = x_i) = \frac{\exp(z)}{1 + \exp(z)}$$

where $z = \alpha+\beta_1x_1+\ldots+\beta_nx_n$. Factors and covariates to be included in the model are sex, age at baseline, body weight at baseline, and parasite density at baseline.

In a second step participants of this trial are matched with participants of the external control arm by use of a nearest neighbor matching. The distance measure that will be used is propensity score difference, which is the difference between the PS of each treated and control unit. A matching with replacement is done (i.e. controls can be used as matches for more than one treated individual from different cohorts, but not within the same cohort). Hence, the matching order does not matter.

In case other matching algorithms (e.g. optimal matching) show better results in terms of data which can be used for the analysis, additional sensitivity analyses might be conducted.

9.2 Investigational Medical Product (IMP)

The IMP is the combination of M5717 and pyronaridine (given at 2 different dose levels according to body weight (540 mg for participants between 45 and 65 kg and 720 mg for participants with a body weight above 65 kg)) and Malarone. It has to be noted, though, that no effect of Malarone is investigated with the trial; it is only used to initially clear all parasites from the participants in order to monitor the natural incidence of reinfections (since after parasite clearance participants are left untreated).

9.3 Presentation of Tables/Figures/Listings

Tables and figures will be presented by the different treatment groups as denoted within the previous paragraph. Individual participant data listings will be provided. All listings will be sorted by treatment group (starting with the lowest M5717 dose and ending with the natural infection cohort), subject ID and scheduled time point.

Repeated and unscheduled measurements included in the listings will not be used for statistical analyses or summaries, unless the repeated measurement was performed due to unreliable values/technical reasons, e.g., clotted samples. They will be flagged as such in the listings.

Presentation of continuous and qualitative variables

Unless otherwise specified, continuous variables will be summarized using descriptive statistics, i.e. the number of participants with non-missing values (n), the number of participants with missing values, (nmiss), mean, standard deviation, median, 25th percentile (Q1) and 75th percentile (Q3), minimum, and maximum.

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise stated the calculation of proportions will be based on the number of participants of the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

Descriptive statistics by nominal visit or time point, e.g., for laboratory measurements, will include only data from scheduled visits.

9.4 Analysis visit windows

For weekly visits (Visit 5 to Visit 12) and for the EOS visit (Visit 13) a visit window of ±1 and ±2 days are defined in the CTP. Visit windows for the visits on days 1 and 2 can be taken from Table 2 of the CTP in Section 1.3.

In case any visit occurred outside of the defined visit windows it will be allocated to "unscheduled". In case too many measurements are observed outside of the defined visit windows, it will be decided on an individual basis whether those can be allocated to scheduled visits in a reasonable manner during data review before database lock.

9.5 Software

All analyses will be performed using SAS® Software version 9.2 or higher or R (www.r-project.org), Version 3.2.5 or higher.

9.6 Data handling after Cut-off Date

In this study, data cut-offs can be necessary in the case of an ad-hoc DMC meeting. Details of planned analyses and modes of conduct will be defined within a separate DMC IAP based on the current version of the DMC Charter.

By its nature, data after cut-off may be incomplete and subject to further change and will not be used for summary statistics, statistical analyses, listings or imputations.

Stop dates are not affected by this rule, e.g. a stop date of AEs, which starts prior to the cut-off, but stops after date of cut-off, will not be changed.

9.7 Definition of Baseline and Change from Baseline

Baseline is defined as the last non-missing measurement (including those collected at an unscheduled visit) prior to the first dose of IMP. If an assessment that is planned to be performed before study intervention per protocol is performed on the same day as the start of study

intervention, respectively, but the assessment time is not available, it will be assumed that it was performed prior and will be considered as baseline.

Change from baseline **(**CFB) and percent CFB any post-baseline visit will be computed as follows:

- CFB = visit value – baseline value
- %CFB = 100*(visit value – baseline value) / baseline value

9.8 Study Day / Study Intervention Day

Day 1 is the day of randomization and start of study intervention, the day before is Day -1 (no Day 0 is defined). Study day is defined relative to Day 1. In case the start of study intervention is delayed and is not happening on the same day as randomization, Day 1 is defined as the day of start of study intervention.

9.9 Definition of Duration and 'Time Since' Variables

Duration will be calculated as the difference between start and stop dates plus 1 (e.g. the duration of an Adverse Event (AE) = AE end date – AE start date + 1). Durations will be calculated only when both dates are available, i.e. imputed dates will not be used to compute the duration unless otherwise specified.

The time since an event variables will be calculated according to the following rules:

- Date of event - Reference date + 1 if the date of the event is equal or greater than the reference date (e.g. days on study at onset of AE = AE start date – date of randomization + 1)
- Reference date – date of event otherwise

If Age at the Time of an Event is derived, the following algorithm will be used for the derivation:

- Year of Event minus Year of Birth

9.10 Conversion Factors

To convert days into weeks, months or years the following conversion factors will be used:

- 1 week = 7 days
- 1 month = 30.4375 days
- 1 year = 365.25 days

9.11 Date of Last Contact

The date of last contact will be derived for participants not known to have died at the analysis cut-off or database lock using the latest complete date prior to or at the data cut-off or database lock date among the following:

- Date of last AE start date
- Date of last blood sample
- Date of last ECG or vital sign assessment
- Date of last temperature or malaria signs and symptoms assessment

Only dates associated with actual examinations of the participant reported in the eCRF will be used in the derivation. Dates associated with a technical operation unrelated to participant status such as the date a blood sample was processed will not be used.

9.12 Definition of On-treatment Period

The on-treatment period is defined as the time from the date of first dose of study intervention to the date of premature study termination, cut-off or database lock date or death, whichever occurs first.

9.13 Imputation of Missing Data

No action will be taken to handle missing data. A participant who withdraws prior to the last planned observation in a study period will be included in the analyses up to the time of discontinuation.

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

In order to determine treatment-emergent AEs, incomplete AE-related start dates will be imputed as follows:

- In case the onset date is missing completely or missing partially but the onset month and year, or the onset year are equal to the start of study intervention then the onset date will be imputed by the minimum of start of study intervention and AE resolution date (if not missing). If AE resolution date is completely or partially missing, the study intervention date will be used.
- In all other cases, the missing onset day or missing onset month will be imputed by 1.

Incomplete or missing stop dates will not be imputed, since no durations of AEs are planned to be derived.

Missing or partially missing dates for Medical History will not be imputed.

In order to allocate medications to either previous or concomitant, the following imputation rules for (partially) missing start dates will be applied:

- If the day is missing, it will be imputed by the 1st day of the month.
- If both day and month are missing the date will be imputed by 1st January.
- If the date is completely missing, no imputation will be performed.

10 Study Participants

The subsections in this section include specifications for reporting participant disposition and study intervention/study discontinuations. Additionally, procedures for reporting protocol deviations are provided.

10.1 Disposition of Participants and Discontinuations

The following will be presented in a summary table:

- Total number of participants screened (i.e., participants who gave informed consent)
- Number of screened participants who discontinued from the trial prior to randomization
    - Participant did not meet all eligibility criteria
    - Withdrew consent
    - Progressive disease
    - Lost to follow-up
    - Death
    - Other
- Number of randomized participants
- Number of randomized participants who did not receive treatment (as applicable)
- Number of treated participants
- Number and percentage of treated participants who completed study
- Number and percentage of treated participants who discontinued the study, with the primary reason of discontinuation by treatment and overall

A frequency table displaying the number of participants of the different Analysis Sets will be provided in addition.

10.2 Protocol Deviations / Exclusion from Analysis Sets

10.2.1 Important Protocol Deviations

Important protocol deviations will be identified for all participants by either site monitoring, medical review processes or programming and confirmed prior to or at the Data Review Meeting at the latest.

Any important protocol deviation is documented in SDTM datasets whether identified through site monitoring, medical review or programming. The management of protocol deviations is outside of this IAP document.

A frequency table as well as a listing of important protocol deviations, will be provided based on the FAS.

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

A frequency table organized according to reason for exclusion from the PK analysis set, as well as a listing, will be provided.

11 Demographics and Other Baseline Characteristics

11.1 Demographics

Descriptive statistics will be presented for age, adolescent status, sex, ethnicity, and race. Adolescent status is defined by age ≥12 to <18 years.

11.2 Medical History

The medical history will be summarized from the "Medical History" eCRF page, using MedDRA version 27.1, preferred term as event category and system organ class (SOC) body term as Body System category. Each participant will be counted only once within each PT or SOC.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order.

11.3 Other Baseline Characteristics

Summary and frequency tables, as applicable, will be provided for ECG results (number of participants with abnormal ECG findings and summary statistics of ECG results for participants with abnormal findings), height, weight, BMI, vital signs and laboratory results.

12 Previous or Concomitant Therapies/Procedures

Previous medications are defined as any medication discontinued prior to the administration of study intervention. If the date values do not allow a medication to be classified as previous

medication (e.g. due to missing dates which are not imputed; see Section 9.13), the medication will be considered as a concomitant medication.

Concomitant medications are defined as any medication taken during the course of the study, with a starting date greater than or equal to the administration of study intervention, or with a starting date prior to the administration of study intervention and ongoing at the time of the administration of study intervention.

The World Health Organization Drug dictionary (WHO-DD) version effective at the date of database lock will be used for coding of prior and concomitant medications and they will be described using Preferred Term (PT) as applicable.

Previous and concomitant medications will be listed. Concomitant procedures, if any, will also be listed.

A frequency table of previous and concomitant medications will be provided by ATC level 2 and PTs sorted by ATC and PTs in alphabetical order.

13 Study Intervention: Compliance and Exposure

M5717+pyronaridine will be administered once as single dose on Day 1, when the participants are hospitalized. Thus, compliance for the combination is not applicable.

Malarone is given at three consecutive days starting at Day 1 in hospital. The last dose on Day 3 has to be taken by the participants at home. Compliance, though, is not assessed.

A frequency table displaying intake of study treatment, reasons for not taking study treatment and number of participants with different dose combinations of M5717 and pyronaridine will be provided.

14 Efficacy Analyses

14.1 Primary Estimand

For the description of the attributes of the primary estimand please refer to the Clinical Study Protocol, Section 3.

14.1.1 Primary Objective: Derivation and Analysis of the Primary Estimand

The primary endpoint is defined as the time (in days) to first recorded parasitemia (parasite count >0) since the first negative blood smear (parasite count of 0) after treatment (followed at least by 1 subsequent visit with a negative blood film), i.e. the time without a positive blood smear. For the endpoint assessment it is irrelevant whether the recurrent parasite detected after treatment is genetically the same strain present at baseline or a new one. Participants who never had a negative blood smear after treatment are not considered for this analysis of time to repositivation.

In order to derive the population-level summary of the estimand related to time to parasitemia, different intercurrent events (ICE) have to be considered. ICE as defined by the study protocol will be identified and handled as described in the following:

- **Intake of rescue medication:** filtering concomitant medications programmatically for all artemisinin based combination therapies (artemether-lumefantrine, artesunate-amodiaquine, dihydroartemisinin-piperaquine, artesunate-sulphadoxine-pyremethamine), chloroquine, quinine, halofantrine, primaquine and by medical review. A composite variable strategy is applied, i.e. the primary endpoint is considered as failure (= positive blood smear at the time of rescue medication intake).

- **Intake of antibiotics or prohibited concomitant medication with an antimalarial effect:** filtering concomitant medications programmatically for sulphadoxine-trimethoprim, doxycycline, quinolone antibiotics including fluoroquinolones, azithromycin, erythromycin and all other macrolides and by medical review. An on-treatment strategy is applied, i.e. time to parasitemia is censored at the time of antibiotics or prohibited medication intake.

- **Experience of any event that affects absorption, e.g. vomiting within the first 24 hours after dosing:** filter AE data programmatically for preferred term (PT) "Vomiting" within the System Organ Class (SOC) "Gastrointestinal disorders" and by medical review. A treatment policy strategy is applied, i.e. treatment effect is estimated regardless of ICE.

- **Death due to malaria or other reasons:** filter SAEs programmatically for fatal events with outcome "death" and by medical/safety review. Death cases for which the primary reason is ticked as "progressive disease and/or disease-related condition" qualify as death due to malaria. A composite variable strategy is applied if the death was due to malaria (i.e. a parasitemia event is considered at the time of death) and an on-treatment strategy is defined if death was due to other reasons (i.e. time to parasitemia is censored at the time of death)

The population-level summary is defined as the Hazard Ratios (HRs) for each dose of M5717 relative to the untreated participants in Cohort 4. HRs are estimated from a Cox Proportional Hazards Model with time to parasitemia included as the dependent variable and dose cohorts, site and sex included as independent factors, and baseline age, body weight and parasite density included as independent covariates. Participants will be censored in case of occurrence of an ICE as described above, at the last available visit in case of premature study discontinuation or at the end of study in case no parasitemia event was observed.

For the multivariable (primary) model, a table showing HRs together with 95% Wald CIs will be provided which will contain in addition estimates of coefficients, SEs and p-values (based on Likelihood Ratio Test) in order to assess whether the factors and covariates included into the model have a significant influence on the time to parasitemia. As additional information a table providing information on censoring frequency and occurrence of ICEs will be provided.

As part of descriptive analyses of the primary endpoint, which also covers the analysis of the second estimand (incidence of parasitemia), a table displaying number and percentages of

parasitemia events (estimated directly from the data) will be provided together with estimates of a Kaplan-Meier (KM) analysis. Median time of protection and 95% CI will be estimated using the KM method for each cohort. As a graphical illustration, a KM-figure will be provided showing time to parasitemia in days after parasite clearance.

14.1.2 Sensitivity Analyses of the Primary Estimand

As sensitivity analysis, an alternative strategy of handling the ICE "Experience of any event that affects absorption" is used. Instead of applying a treatment policy strategy, an on-treatment strategy is applied, i.e. the time to parasitemia is censored at the time the ICE occurred. If the ICE occurs prior to parasite clearance (the start time of survival analysis), the participants will be censored at the time of parasite clearance. All analyses as described within the previous section will be repeated unless the ICE did not occur. In case the sensitivity analyses will be conducted, the numbering of the outputs for the primary estimand will be split (i.e. 8.2.1.1 Analyses of Primary Estimand – Main Analysis; 8.2.1.2 Analyses of Primary Estimand – Sensitivity Analysis).

14.1.3 Subgroup Analyses of the Primary Estimand

In order to investigate treatment effects in predefined subgroups the Cox Proportional Hazards Model as described above is repeated by including age groups as defined in Section 8.2 and country as factors. Hazard Ratios and 95% confidence intervals for the subgroup levels will be obtained from the dose cohort and age group, and dose cohort and country main and interaction terms, respectively, which have to be included into the model. As a graphical presentation a forest plot of HRs by subgroups will be provided in addition.

14.2 Further Estimands

14.2.1 Parasitemia

To indirectly evaluate the additional time of protection of different doses of M5717 alone, the time to parasitemia as observed for Cohorts 1-3 will be compared to time to parasitemia from the Pyramax external control cohort. All analyses as described for the primary estimand will be repeated by comparing against the Pyramax external control cohort instead of the natural infection cohort. For this comparison only data of participants identified during the propensity score matching process (see Section 9.1) will be used.

If the number of identified matches is < 35, then the respective cohort will not be used for comparison to the synthetic control arm from the external study. If the number of matches is < 35 for all cohorts the use of the synthetic control arm will not be performed at all.

14.2.2 PCR-adjusted Parasitemia

For PCR-adjusted parasitemia (thick smear/microscopy, after adjustment for parasitemia due to new infections and due to recrudescence, respectively) the same analyses and outputs will be provided as for the primary estimand. For the derivation of the population-level summary the same ICEs and strategies are applied as for the primary estimand as described in Section 14.1.1.

14.2.3 Parasite Clearance Time

For estimating parasite clearance time (in hours), which is the time from dosing (first dose in the Malarone treatment cohort) to the first negative blood film (parasite count of 0 on microscopy), followed at least by 1 subsequent visit with a negative blood film. Patients should not be considered for analysis if they did not have parasites >0 at any timepoint. The same ICEs as defined in Section 5 will be considered. The median parasite clearance time will be estimated by use of Kaplan-Meier method for each cohort. Participants will be censored in case of occurrence of an ICE if the ICE occurred before the first negative blood film, at the last available visit in case of premature study discontinuation before the first negative blood film or at the end of study in case no parasite clearance event was observed.

15 Safety Analyses

This section includes specifications for summarizing safety endpoints that are common across clinical studies such as adverse events, laboratory tests and vital signs.

15.1 Adverse Events

Adverse Events will be coded according to MedDRA version 27.1. The severity of AEs will be graded using CTCAE v5.0.

Treatment-emergent AEs (TEAEs) are those events with onset or worsening dates on or after the first administration of study intervention. In case an AE starts on the day of study treatment administration and the AE start time is partially or completely missing, the AE is considered as treatment-emergent.

Any AE occurring before the administration of study intervention on Day 1 and resolved before administration of study intervention or not worsening after administration of study intervention will be included in the AE listings but will not be included in the summary tables (unless otherwise stated). These will be referred to as “pre-treatment” AEs.

Related AEs are those AEs with relationship to study treatment reported by the investigator as related or those of unknown relationship.

Serious AEs are those events reported on the AE eCRF form with the serious field ticked “Yes” or with unknown seriousness.

AEs leading to study discontinuation are those AEs that were referenced as reason for early study termination on the eCRF study termination page.

AEs of special interest are liver (AT increase, TB increase) and CNS signals which will be specifically followed-up through laboratory surveillance and a specific physical examination at specific visits during the study. AESIs are AEs which have been ticked to qualify as events of special interest per protocol on the AE eCRF form. In addition, a list of PTs will be appended to the table shells document with which AEs qualifying as AESIs will be identified.

Group/SOC terms will be sorted alphabetically. Preferred terms within each group/SOC will be sorted by descending frequency in the highest dose cohort, and alphabetically if multiple preferred terms have the same frequency.

If a participant experiences more than one occurrence of the same TEAE during the trial, the participant will only be counted once for that treatment (the worst severity and the worst relationship to trial treatment will be tabulated).

In case a participant had events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. AEs with missing classification concerning study intervention relationship will be considered related to the study intervention.

Incomplete AE-related dates will be handled as described in Section 9.13.

15.1.1 Overview of TEAEs

An overall summary of TEAEs will be provided including frequencies of participants experiencing at least any

- TEAE
- TEAE leading to study termination
- Related TEAE
- Serious TEAE
- Related serious TEAE
- TEAE by intensity (NCI-CTCAE grades 1-4)
- Related TEAE by intensity (NCI-CTCAE grades 1-4)
- AESI
- Related AESI
- TEAE leading to death
- Related TEAE leading to death

Frequency tables of TEAEs by SOC and PT will be provided for:

- All TEAEs
- TEAEs at a frequency threshold of 5%
- Serious TEAEs
- TEAEs leading to study termination
- TEAEs leading to death
- Related TEAEs
- Related serious TEAEs
- Related TEAEs leading to study termination
- Related TEAEs leading to death
- TEAEs of special interest

More specifically, tables displaying TEAEs by worst grade, SOC and PTs will be provided, separated by treatment cohorts. A graphical presentation of TEAEs occurring in >10% of participants will be provided separately for each treatment cohort as well.

15.1.2 The 3-Tier Approach

The 3-tier approach for summarizing and analyzing AEs in clinical studies will be followed. AEs in different tiers are analyzed using different types of statistical analysis.

The AEs identified for Tier 1 reporting are listed in below table together with the description how Tier 1 AEs will be analyzed:

Tier 1 AE	Within group summary	Between group comparison (Each dose cohort – natural infection cohort) 95% CI
Nervous system disorders (SOC 10029205)	n (%)	Δ [xx%, xx%]
ALT increased (PT 10001551)		
ALT abnormal (PT 10001547)		
AST increased (PT 10003481)		
AST abnormal (PT 10003477)		
AST/ALT ratio abnormal (PT 10082832)*		

* either documented AE or AST/ALT=abnormal in laboratory data. An AST/ALT ratio between 0.7 and 1.4 is thereby interpreted as "normal". Values outside of this range are "abnormal".

All Tier 1 events will be summarized in a table. Incidence rates and differences in incidence rates between each dose cohort and the natural infection cohort will be provided together with 95% CIs for the differences in incidence rates. For Tier 1 events which were observed for less than 3 participants the CIs will not be displayed in the Tier 1 table. 95% CIs for the differences in incidence rates will be estimated using Miettinen & Nurminen method. For graphical illustration a forest plot will be provided separately for the different treatment cohorts.

All TEAEs for which any PT or SOC is observed in 4 or more participants in any cohort are defined to be Tier 2 AEs. Tier 2 AEs are thus used for signal detection among common events. A frequency table by SOC and PT will be provided together with differences in incidence and 95% CI comparing different dose groups to the natural infection cohort. While analyses will be done for all Tier 2 TEAEs, only TEAEs with incidence proportion ≥5% in at least one cohort will be presented in the body of CSR. No multiplicity adjustment will be applied.

Remaining TEAEs are defined as TIER 3 AEs and frequencies of participants with at least one Tier 3 TEAE will be provided by SOC and PT.

15.1.3 Adverse Events Leading to Discontinuation of Study Intervention

Since the study intervention is administered as single dose treatment on Day 1, discontinuation of study intervention due to AEs or any other reason cannot happen.

15.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

15.2.1 Deaths

Death date and reason for death are collected on the "DEATH" CRF form. A participant data listing including date and reason of death, PT of AEs with fatal outcome together with selected dosing information (date of administration) will be provided

15.2.2 Serious Adverse Events

The following frequency tables will be prepared for serious TEAEs:

- Incidence of serious TEAEs by SOC and PT
- Incidence of related serious TEAEs by SOC and PT

A listing of SAEs will also be provided with the relevant information.

15.2.3 Other Significant Adverse Events

AEs of special interest (AESIs) include the following events as defined by the CTP:

- Liver events, monitored through LFTs that will include ATS, ALT, and AST, as well as TB and ALP
- Neurological events, monitored through specific neurological clinical examinations

AESIs will be identified by the corresponding flag on the AE page of the eCRF and by specifically search for them with an appropriate list of PTs. A frequency table of AESIs by SOC and PT will be provided.

15.2.4 Disease Related Events

Disease related events are captured separately in the same manner as Adverse Events. They will be separated by the time of their occurrence, i.e. events with onset or worsening dates on or after the first administration of study intervention and events with onset or worsening dates before the first administration of study intervention. Frequency tables displaying incidences of disease related events will be provided by SOC and PT separately for events occurring before and after study intervention as defined above.

15.2.5 Clinical Laboratory Evaluation

The following laboratory parameters will be measured during the trial and reported as part of the safety evaluation (for a detailed list of parameters refer to Appendix 10 of the CTP):

- Hematology
- Biochemistry

Summary tables over time displaying absolute values and changes from Baseline will be provided. For a graphical presentation line plots of lab parameters standardized to times ULN over time will be provided for each participant. Thereby, plots should be grouped by participants of different cohorts and by lab parameters in the following way:

- Biochemistry:

- Alanine Aminotransferase, Alkaline Phosphatase, Aspartate Aminotransferase, Bilirubin
- Calcium, Creatinine, Glucose, Chloride
- Potassium, Protein, Sodium

- Hematology:
  - Basophils, Eosinophils
  - Hematocrit, Hemoglobin
  - Leukocytes, Lymphocytes, Monocytes, Neutrophils, Platelets, Reticulocytes

In addition, shift tables from Baseline based on normal ranges will be given.

In order to investigate possible events of Hy's Law, an eDISH Plot will be provided

Outputs will be presented using the Merck Standard Unit Catalogue (see Appendix 2). Normal ranges will be provided by the local laboratories, and out of range flags will be calculated based on the normal ranges. Laboratory data not transferred in standard units will be converted to before processing. Both original units and standard units will be provided in the SDTM domain.

Subject Data Listings will only be provided for subjects with abnormal test results (lower than LLN and higher than ULN, abnormal CS and abnormal NCS).

15.3 Vital Signs

Frequency tables for the maximum changes from Baseline will be provided for the following vital sign parameters:

- Body temperature (°C)
- Systolic and diastolic blood pressure (mmHg)
- Respiration rate (bpm)
- Pulse rate (beats/min)
- Weight (kg)

The maximum changes of vital sign measurements from Baseline will be grouped as follows:

	Baseline Value	**Change from Baseline**
Body temperature increase	< 37 °C; 37 – < 38 °C; 38 – < 39 °C; 39 – < 40 °C; ≥ 40 °C	< 1 °C, 1 – < 2 °C, 2 – < 3 °C, ≥ 3 °C
Pulse rate increase from baseline	< 100 bpm; ≥ 100 bpm	≤ 20 bpm, > 20 – 40 bpm, > 40 bpm

Pulse rate decrease from baseline	< 100 bpm; ≥ 100 bpm	≤ 20 bpm, > 20 – 40 bpm, > 40 bpm
SBP increase from baseline	< 140 mmHg; ≥ 140 mmHg	≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg
SBP decrease from baseline	< 140 mmHg; ≥ 140 mmHg,	≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg
DBP increase from baseline	< 90 mmHg; ≥ 90 mmHg	≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg
DBP decrease from baseline	< 90 mmHg; ≥ 90 mmHg,	≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg
Respiration rate increase from baseline	< 20 bpm; ≥ 20 bpm	≤ 5 bpm, > 5 – 10 bpm, > 10 bpm
Respiration rate decrease from baseline	< 20 bpm; ≥ 20 bpm	≤ 5 bpm, > 5 – 10 bpm, > 10 bpm

SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure.
Lowest category does not include 0 since this indicates no change.

15.4 Other Safety or Tolerability Evaluations

15.4.1 ECG Evaluations

The following analyses will be performed for each applicable ECG parameter (RR, PR, QRS, QT, ventricular rate -denoted as HR in what follows-, and QTcF) by cohort and study intervention group:

- Descriptive statistics at Baseline, at each post-baseline time point and changes from baseline at each post-baseline time point
- Frequency (number and percentage) of participants with notable ECG values according to the following categories by analysis visit.
    - QT/QTcF >450 ms, >480 ms, >500 ms
- ECG interpretation (normal, abnormal/not clinically significant, abnormal/clinically significant) will be summarized at Baseline and during the on-treatment period.
- A graphical display, boxplots of change from baseline for ECG parameters will be provided in addition.

Complete ECG profiles will be provided for participants with at least one notable ECG value (related to ECG interpretation) as defined above (i.e. abnormal clinically significant, abnormal not clinically significant). For these participants, all ECG parameter values collected during the study will be provided.

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16.1 Pharmacokinetics

PK evaluation will be performed by Quantitative Pharmacology, Merck Healthcare KGaA, Darmstadt, Germany, or by a CRO selected by the Sponsor.

16.1.1 Descriptive Statistics of PK Concentration Data

PK measurements will be descriptively summarized per nominal time point using: number of non-missing observations (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median) and maximum (Max).

Descriptive statistics will only be calculated for n>2 in which a measurement of BLQ represents a valid measurement and will be taken as zero for summary statistics of PK concentration data.

Descriptive statistics of PK concentration data will be calculated using values with the same precision as the source data and rounded for reporting purposes only. In export datasets, as well as in the SDTM PC domain, PK concentrations will be provided with full precision and will not be rounded.

The following conventions will be applied when reporting descriptive statistics of PK concentration data:

n	0 decimal place
Mean, Min, Median, Max:	3 significant digits
SD:	4 significant digits
CV%:	1 decimal place

16.1.2 Descriptive Statistics of PK Parameter Data

PK parameter data will be descriptively summarized using number of non-missing observations (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median), maximum (Max), geometric mean (GeoMean), the geometric coefficient of variation (GeoCV), 95% CI for GeoMean.

PK parameters read directly from the measurements (i.e. C_{max}) will be reported with the same precision as the source data. All other PK parameters will be reported to 3 significant figures.

The following conventions will be applied when reporting descriptive statistics of PK parameter data:

n	0 decimal place

Mean, Min, Median, Max, GeoMean, SD, 95% CI for GeoMean:	3 significant digits
CV%, GeoCV%:	1 decimal place

16.1.3 General Specifications for PK Concentration and PK Parameter Data

Predose samples that occur before the first drug administration will be assigned a time of 0 hours, as if the sample had been taken simultaneously with the study intervention administration.

In case pre-dose samples have been taken after the subsequent dosing , the resulting concentrations will be included in concentration listings but excluded from descriptive statistics of concentrations and from PK parameter estimation. For post-dose samples collected outside of visit window, the resulting concentrations will be included in descriptive statistics of concentrations and in PK parameter estimation.

Values below the lower limit of quantification (BLQ) will be taken as zero for summary statistics of PK concentration data, PK parameter estimation (e.g. AUC) and for graphical presentations.

In case profiles have a measurable pre-dose concentration less than or equal to 5% of its C_{max} value, the participant's data will be included in the PK and statistical analyses without any adjustments. If the pre-dose value is greater than 5% of the C_{max}, the participant's data for this period will be included in the PK evaluation but excluded from descriptive summaries and further statistical evaluation after agreement with the sponsor.

Missing concentrations (e.g. no sample, insufficient sample volume for analysis, no result or result not valid) will be reported and used generally as "N.R.". A participant who withdraws prior to the last planned observation will be included in the analyses up to the time of discontinuation.

PK concentrations which are erroneous due to a sampling processing or analytical error (as documented in the bioanalytical report) may be excluded from the PK analysis if agreed by the Sponsor.

PK concentrations and PK parameters excluded from summary statistics will not be included in mean figures.

If less than 3 post-dose concentrations are available within a PK profile, derived PK parameters will be flagged and might be excluded from statistical evaluation after consultation with the Sponsor.

16.1.4 Estimation of Pharmacokinetic Parameters

The computer program Phoenix® WinNonlin® version 6.4, or higher (Certara, L.P., Princeton, New Jersey, USA) will be used to derive PK parameters applying non-compartmental analysis (NCA).

The statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary NC, USA, windows version 9.4 or higher) may be used to generate additional PK parameters, produce tables, listings and figures.

16.1.4.1 Estimation of Pharmacokinetic Parameters in Whole Blood

PK parameters will be calculated using the actual elapsed time since dosing and QC'd bioanalytical data sets.

The following M5717 and pyronaridine whole blood PK parameters will be calculated where appropriate:

Symbol	Definition
$AUC_{0-\infty}$	The area under the concentration-time curve (AUC) from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at tlast, as estimated using the linear regression from λz determination. $AUC_{0-\infty}$= $AUC_{0-tlast}$ +Clast pred/λz
AUC_{0-24}	The AUC from time zero (dosing time) to 24 hours post dose. Calculated using the mixed log linear trapezoidal rule (linear up, log down) using the nominal dosing interval.
CL/F	The apparent total body clearance of study intervention following extravascular administration. CL/ F= Dose p.o. /$AUC_{0-\infty}$.
C_{max}	Maximum observed concentration
$t_{½}$	Apparent terminal half-life. $t_{½}$ = ln (2)/λz
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, take the 1st occurrence in case of multiple/identical Cmax values)
VZ/F	The apparent volume of distribution during the terminal phase following extravascular administration. Vz/F = Dose/($AUC_{0-\infty}$*λz) following single dose.
λz	Terminal first order (elimination) rate constant. Determined from the terminal slope of the log-transformed concentration curve using linear regression on terminal data points of the curve.

AUC_{0-24}/Dose	The dose normalized AUC from time zero to 24 hours post dose. Normalized using the dose, using the formula AUC_{0-24}/Dose.
$AUC_{0-tlast}$	The AUC from time zero (= dosing time) to the time of the last quantifiable concentration (tlast), calculated using the mixed log-linear trapezoidal rule (linear up, log down).
$AUC_{0-tlast}$/Dose	The dose normalized AUC from time zero to the last sampling time (tlast) at which the concentration is at or above the lower limit of quantification. Normalized using the dose, using the formula AUC0-tlast /Dose.
$AUC_{0-\infty}$/Dose	The dose normalized AUC from time zero extrapolated to infinity. Normalized using dose, using the formula $AUC_{0-\infty}$ /Dose.
C_{max}/Dose	The dose normalized maximum concentration. Normalized using the dose, and the formula C_{max} /Dose

Additional PK parameters may be calculated where appropriate.

Units for PK parameter output will be based on concentration and dose units used in the study, unless otherwise specified. In case concentration data units change within the study, PK parameters will be reported using consistent units throughout study outputs.

The parameters C_{max}, and t_{max} will be obtained directly from the concentration-time profiles. If C_{max} occurs at more than one timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

In cases BLQ concentrations occur at the end of the collection interval, these concentrations might be set to missing for calculations of partial AUCs after agreement with the Sponsor. This is an exemption to the general BLQ handling rule and should be applied in case its application would result in estimation of implausible partial AUC values. Implausibility is considered in cases partial AUCs were greater than $AUC_{0-\infty}$.

The following PK parameters will be calculated for diagnostic purposes and listed, but will not be summarized:

- First (λz low) and last (λz up) time point of the time interval of the log-linear regression to determine λz.
- Number of data points (Nλ) included in the log-linear regression analysis to determine λz.
- Goodness of fit statistic (adjusted Rsq) for calculation of λz.
- Span ratio of interval over which $t_{1/2}$ was estimates/$t_{1/2}$
- AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$. ($AUC_{extra\%}$).

The regression analysis should contain data from at least 3 different time points in the terminal phase consistent with the assessment of a straight line on the log-transformed scale. Phoenix WinNonlin "best fit" methodology will be used as standard. If warranted, further adjustment may be made by the pharmacokineticist, after agreement with the Sponsor. The last quantifiable concentration >LLOQ should always be included in the regression analysis, while the concentration at t_{max} and any concentrations BLQ which occur after the last quantifiable data point >LLOQ should not be used.

If $AUC_{extra\%}$ is >20%, the coefficient of correlation (Rsq adj) of λ_z is <0.8, or the observation period over which the regression line is estimated (span ratio) is less than 2-fold the resulting $t_{1/2}$, the rate constants and all derived parameters (e.g. $t_{1/2}$, $AUC_{0-\infty}$, CL etc.) will be listed with appropriate flags and will still be included in the parameter summaries.

For calculation of dose-related parameters, no dose adjustment is required since dose administered is expressed as the free base dose.

16.1.5 Presentation of PK Concentration and PK Parameter Data

Appropriate figures or tables for PK sanity checks and/or data exploration will be performed during the NCA process in Phoenix® WinNonlin.

16.1.5.1 Listings and Tables

The following outputs will be produced for the PK Analysis Set in SAS:

- Listing and summary table including descriptive statistics of M5717 and Pyronaridine concentrations
- Listing and summary table including descriptive statistics of M5717 and Pyronaridine PK parameters

Only outputs programmed in SAS will be used for the final analysis.

16.1.5.2 Graphical Summaries and Individual plots (PK Analysis Set)

- Arithmetic mean of M5717 and Pyronaridine concentration time plots; linear (±SD for arithmetic mean) and semi-log; using scheduled (nominal) time points by analyte
- Individual M5717 and Pyronaridine concentration-time course on linear and semi-logarithmic scales
- Overlaid individual concentration versus time plots; linear and semi-log by analyte
- Boxplots of M5717 and Pyronaridine PK parameters

16.2 Pharmacodynamics

Details on PK/PD analyses will be documented in a separate Analysis Plan and will be referenced in the Appendix of this IAP.

16.2.1 Software

The population PK/PD analyses will be performed using the non-linear mixed effects modeling approach.

The Monolix software (version 2021R2) will be used in the analysis, installed on Merck AWS cloud with AWS EC2 autoscaling functionality and with LINUX (SUSE Linux Enterprise server 12(64-bit) SP5) operating system, with CPU allocation controlled by job scheduler SLURM (version 20.11) through an application portal EnginFrame (Version 2021.0-r1592) for user-friendly HPC job submission, control, and monitoring. R software will be used for model-based simulations and any other analyses not performed with Monolix. All preceding software are installed in a validated GxP environment.

16.2.2 Data handling procedures and data assembly methods

Input files will be created by the data scientists at Merck according to the specifications provided by the M&S analysis responsible, and files will be delivered to the M&S responsible of Merck on time. The analysis datasets will include sampling time, concentrations for both M5717 and pyronaridine, and parasitemia data, as well as body weight of the patients and the efficacy outcome. A detailed description of the required structure of these input files for PK and PD data will be defined in collaboration with internal data scientists.

16.2.3 PK and PK/PD data

Blood samples for measurement of M5717 and pyronaridine concentrations in whole blood, and blood films for parasite count will be collected at the assigned time points as per protocol. Actual date and time of the samplings, as well as data/time of drug administration, will be recorded in the eCRF. In the situation that actual sampling time or drug administration is not available for interim analyses, nominal information can be used.

Missing observations will not be included in the dataset for population analyses. Data below the lower limit of quantification (BLQ) will be imputed to the LLOQ of the assays and flagged. They will be excluded from the PK analysis. BLQ parasitemia data will be imputed to the LLOQ of the assay, flagged and handled using the M3 method for potential model update. Observations without corresponding dosing or sampling times will not be used in the analysis.

Missing covariate data (*i.e.* body weight) will be imputed to the median value in the study population.

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17 References

Crowe B. et al. “Recommendations for safety planning, data collection, evaluation and reporting during drug, biologic and vaccine development: a report of the safety planning, evaluation, and reporting team” Clinical Trials 2009; 6


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Approver Signatures

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Signature of Merck Healthcare Statistician

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Signature of Lead Biostatistician, CCI