Integrated Analysis Plan

Study Number:	MS201618_0033
Clinical Study Protocol Title:	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
Study Phase:	IIa
Merck Compound:	M5717
Protocol Version:	02 November 2022/Version 3.0
Integrated Analysis Plan Author:	**Coordinating Author** PPD **Function** / **Author(s) / Data Analyst(s)** PPD / PPD
Integrated Analysis Plan Date and Version:	21 October 2024 / Version 2.0
Integrated Analysis Plan Reviewers:	**Function** / **Name** PPD

Approval Page

Integrated Analysis Plan: MS201618_0033

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

ACPR	Adequate Clinical and Parasitological Response
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse events of special interest
AT	Aminotransferase
ATC	Anatomical Therapeutic Chemical classification
AUC	Area under the curve
BLQ	Below the Lower Limit of Quantification
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CNS	Central nervous system
(e)CRF	(electronic) Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of variation
ECG	Electrocardiogram
EDMS	Electronic Document Management System
ETF	Early Treatment Failure
FAS	Full Analysis Set
FU	Follow-up
GeoCV	Geometric coefficient of variation
GeoMean	Geometic Mean
IAP	Integrated Analysis Plan
ICE	Intercurrent Event
ICH	International Conference on Harmonization
ITT	Intention To Treat
KM	Kaplan-Meier
LCF	Late Clinical Failure
LPF	Late Parasitological Failure

Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
NA	Not Applicable
NCA	Non-compartmental analysis
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
PK	Pharmacokinetics
PKAS	PK Analysis Set
PCR	polymerase Chain Reaction
PT	Preferred Term
QTcF	corrected QT interval by Fridericia' formula
Q1	25^{th} percentile
Q3	75^{th} percentile
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TB	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TLF	Tables, Listings, and Figures
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	25SEP2024	PPD	Original version
2.0	21OCT2024	PPD	Updates in Section 7 and 14.5 to include only participants who had a temperature >37.5°C at the pre-dose visit or during the 24 hours following dosing will be included. If the fever medication was taken prior to dosing, participants will still be included for analysis. Strategies for intercurrent events will not apply.

4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for the primary, secondary and CCI analyses of data collected for protocol MS201618_0033. Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this IAP may be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

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 3.0 with changes documented in section 7 below. The IAP may be updated as a result of protocol amendments, clarifications, or corrections. The IAP will not be updated with every protocol amendment unless protocol changes affect data analyses describe in this IAP. Any updates to the IAP prior to data review will be documented in the modification history above and will be reviewed and approved accordingly. Any changes to the described analysis occurring after data review will be labeled as such and documented in the CSR.

The wording used in this IAP is chosen to best match the respective wording in the study protocol template, the 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 Endpoints

Part A:

Objectives	Estimands/Endpoints	Ref. #
Primary		
To evaluate the safety and tolerability of the M5717-pyronaridine combination in adult participants with acute uncomplicated malaria due to *P. falciparum.*	**Endpoint:** Incidence, severity, and seriousness of study intervention-related treatment-emergent adverse events (TEAEs), as per Common Terminology Criteria for Adverse Events (CTCAE) v 5.0 Additional endpoints related to safety and tolerability up to Day 29 (± 2 days): laboratory assessments, ECGs, and vital signs.	1
Secondary		
To characterize the PK of M5717 and pyronaridine in adult participants with acute uncomplicated malaria due to *P. falciparum*	**Endpoint:** • PK profiles for M5717 and pyronaridine • PK parameters of M5717 and pyronaridine such as $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}24}$, C_{max}, $t_{½}$, t_{max}, CL/F, VZ/F, when data permits	2
To describe the clinical efficacy of the M5717-pyronaridine combination in adult participants with acute uncomplicated malaria due to *P. falciparum*	**Endpoint:** Early treatment failure (ETF) defined as meeting any of the following: • Danger signs or severe malaria 1, 2, or 3 days after treatment, in the presence of parasitemia • Parasitemia 2 days after treatment higher than on day of treatment, irrespective of axillary temperature • Parasitemia 3 days after treatment with temperature ≥ 37.5°C • Parasitemia 3 days after treatment ≥ 25% of count on day of treatment **Target Population:** Adult patients with acute uncomplicated malaria due to *P. falciparum* **Treatment:** Single dose M5717 330 mg plus pyronaridine 360 mg **Intercurrent Event Strategy:** • Intake of rescue medication before or at Day 4: Composite variable strategy, i.e., endpoint is considered as failure (= presence of ETF) • Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity) before or at Day 4: Treatment policy strategy, i.e., treatment effect is estimated regardless of intercurrent event (ICE) • Experience of any event that affects absorption (i.e., vomiting within the study intervention absorptive period of 2 × median t_{max}) or immune response (severe immunocompromised participants): Treatment policy strategy, i.e., treatment effect is estimated regardless of intercurrent event or Principal Stratum strategy • Premature study discontinuation before or at Day 4 due to lack of efficacy: Composite variable strategy • Death due to malaria before or at Day 4: Composite variable strategy **Population-level Summary:** ETF rate, i.e. proportion of participants with ETF.	3
	Endpoint: Late clinical failure (LCF) defined as:	4

	• Danger signs or severe malaria in the presence of parasitemia on any day between 4 and 28 days after treatment (i.e., between Days 5 and 29) in participants who did not previously meet any of the criteria of ETF • Presence of parasitemia on any day between 4 and 28 days after treatment with temperature ≥ 37.5°C in participants who did not previously meet any of the criteria of ETF **Target Population:** See endpoint 3 **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** • Intake of rescue medication between 4 and 28 days after treatment: Composite variable strategy, i.e., endpoint is considered as failure (= presence of LCF) • Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity) between 4 and 28 days after treatment: Treatment policy strategy, i.e., treatment effect is estimated regardless of ICE • Experience of any event that affects absorption (i.e., vomiting within the study intervention absorptive period of 2 × median t_{max}) or immune response (severe immunocompromised participants): Treatment policy strategy, i.e., treatment effect is estimated regardless of intercurrent event or Principal Stratum strategy • Premature study discontinuation between 4 and 28 days after treatment due to lack of efficacy: Composite variable strategy • Death due to malaria between 4 and 28 days after treatment: Composite variable strategy **Population-level Summary:** LCF rate, i.e., proportion of participants with LCF	
	Endpoint: Late parasitological failure (LPF) defined as: Presence of parasitemia on any day between 7 and 28 days after treatment (i.e., between Days 8 and 29) with temperature < 37.5°C in participants who did not previously meet any of the criteria of ETF or LCF **Target Population:** See endpoint 3 **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** • Intake of rescue medication between 7 and 28 days after treatment: Composite variable strategy, i.e., endpoint is considered as failure (= presence of LPF) • Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity) between 7 and 28 days after treatment: Treatment policy strategy, i.e., treatment effect is estimated regardless of ICE • Experience of any event that affects absorption (i.e., vomiting within the study intervention absorptive period of 2 × median t_{max}) or immune response (severe immunocompromised participants): Treatment policy	5

	strategy, i.e., treatment effect is estimated regardless of intercurrent event • Premature study discontinuation between 7 and 28 days after treatment due to lack of efficacy: Composite variable strategy or Principal Stratum strategy • Death due to malaria between 7 and 28 days after treatment: Composite variable strategy **Population-level Summary:** LPF rate, i.e., proportion of participants with LPF	
	Endpoint: Crude (polymerase chain reaction [PCR]-uncorrected) Adequate Clinical and Parasitological Response (ACPR) 28 and 42 days after treatment defined as absence of parasitemia (thick smear/microscopy), irrespective of axillary temperature, in participants who did not previously meet any of the criteria of ETF, LCF, or LPF **Target Population:** See endpoint 3 **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** • Intake of rescue medication at any timepoint: Composite variable strategy, i.e., endpoint is considered as treatment failure • Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity) at any timepoint: Treatment policy strategy, i.e., treatment effect is estimated regardless of ICE • Experience of any event that affects absorption (i.e., vomiting within the study intervention absorptive period of 2 × median t_{max}) or immune response (severe immunocompromised participants): Treatment policy strategy, i.e., treatment effect is estimated regardless of intercurrent event or Principal Stratum strategy • Premature study discontinuation at any timepoint due to lack of efficacy: Composite variable strategy • Death due to malaria at any timepoint: Composite variable strategy **Population-level Summary:** Crude ACPR rate at each timepoint, i.e., proportion of participants with crude ACPR at each timepoint	6
	Endpoint: PCR-adjusted ACPR 28 and 42 days after treatment defined as absence of parasitemia (thick smear/microscopy, after adjustment for parasitemia due to new infections as determined by genotyping using PCR techniques), irrespective of axillary temperature, in participants who did not previously meet any of the criteria of ETF, LCF, or LPF. **Target Population:** see endpoint 3 **Treatment:** see endpoint 3 **Intercurrent Event Strategy:** see endpoint 6	7

	Population-level Summary: PCR-adjusted ACPR rate at each timepoint, i.e., proportion of participants with PCR-adjusted ACPR at each timepoint	
	Endpoint: Fever clearance time defined as the time from first dosing to the first measurement of temperature < 37.5°C for 2 consecutive temperature readings plus confirmed normal temperature 24 h after the first normal body temperature reading. **Target Population:** Adult patients with acute uncomplicated malaria due to *P. falciparum* with an increased temperature (≥ 37.5°C) **Treatment:** see endpoint 3 **Intercurrent Event Strategy:** • Intake of rescue medication within 3 days after treatment initiation: Composite variable strategy, i.e., time to fever clearance is censored at time of rescue medication intake. • Intake of concomitant medications as a continuous treatment that have an impact on fever within 3 days after treatment initiation: Composite variable strategy, i.e., time to fever clearance is censored at time of concomitant medication intake. • Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity) within 3 days after treatment initiation: Composite variable strategy, i.e., time to fever clearance is censored at time of prohibited medication intake. • Experience of any event that affects absorption (i.e., vomiting within the study intervention absorptive period of 2 × median t_{max}) or immune response (severe immunocompromised participants): Treatment policy strategy, i.e., treatment effect is estimated regardless of intercurrent event or Principal Stratum strategy • Premature study discontinuation due to lack of efficacy: On-treatment strategy, i.e., time to fever clearance is censored at the day of the last available body temperature assessment • Death due to malaria: On-treatment strategy, i.e., time to fever clearance is censored at the day of the last available body temperature assessment **Population-level Summary:** Median fever clearance time as estimated by Kaplan-Meier method	11
	Endpoint: Parasite clearance time defined as time from dosing to the first negative (no parasites) film (microscopy) **Target Population:** see endpoint 3 **Treatment:** see endpoint 3 **Intercurrent Event Strategy:** see previous endpoint with the exception of intake of concomitant medications, which is not an ICE for parasite clearance time.	12

	Censoring will be done at the day of the last available microscopy assessment. **Population-level Summary**: Median parasite clearance time as estimated by Kaplan-Meier method	

CCI

[redacted]

Cohort B0:

Objectives	**Estimands/Endpoints**	**Ref. #**
Primary		
To describe clinical efficacy of the M5717- pyronaridine combination in adult and adolescent participants with acute uncomplicated malaria due to *P. falciparum*	**Endpoint:** PCR-adjusted ACPR 28 days after first treatment (i.e., on Day 29) defined as absence of parasitemia (thick smear/microscopy, after adjustment for parasitemia due to new infections as determined by genotyping using PCR techniques), irrespective of axillary temperature, in participants who did not previously meet any of the criteria of ETF, LCF, or LPF **Target Population:** Adult and adolescent patients with acute uncomplicated malaria due to P. falciparum	19

	Treatment: Single dose M5717 660/500 mg (adolescents < 45 kg) plus pyronaridine 720 mg (≥ 65 kg), 540 mg (≥ 45 to < 65 kg), or 360 mg (≥ 24 to < 45 kg) **Intercurrent Event Strategy:** • Intake of rescue medication: Composite variable strategy, i.e., endpoint is considered as treatment failure (= presence of parasitemia) • Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity) at any timepoint: Treatment policy strategy, i.e., treatment effect is estimated regardless of the ICE • Experience of any event that affects absorption (i.e., vomiting within the study intervention absorptive period of 2 × median t_{max}) or immune response (severe immunocompromised participants): Treatment policy strategy, i.e., treatment effect is estimated regardless of intercurrent event or Principal Stratum strategy • Premature study discontinuation due to lack of efficacy: Composite variable strategy • Death due to malaria: Composite variable strategy **Population-level Summary:** PCR-adjusted ACPR rate, i.e., proportion of participants achieving PCR-adjusted ACPR at Day 29	
Secondary		
To describe the clinical and parasitological efficacy of the M5717-pyronaridine combination in adult and adolescent participants with acute uncomplicated malaria due to *P. falciparum*	**Endpoint:** ETF **Target Population:** See endpoint 19 **Treatment:** see endpoint 19 **Intercurrent Event Strategy:** See endpoint 3 **Population-level Summary:** See endpoint 3	20
	Endpoint: LCF **Target Population:** See endpoint 19 **Treatment:** see endpoint 19 **Intercurrent Event Strategy:** See endpoint 4 **Population-level Summary:** See endpoint 4	21
	Endpoint: LPF **Target Population:** See endpoint 19 **Treatment:** see endpoint 19 **Intercurrent Event Strategy:** See endpoint 5 **Population-level Summary:** See endpoint 5	22
	Endpoint: Crude (PCR-uncorrected) ACPR 28 and 42 days after treatment **Target Population:** See endpoint 19 **Treatment:** see endpoint 19 **Intercurrent Event Strategy:** See endpoint 6 **Population-level Summary:** See endpoint 6	23
	Endpoint: PCR-adjusted ACPR 42 days after treatment **Target Population:** See endpoint 19	24

	Treatment: see endpoint 19 **Intercurrent Event Strategy:** See endpoint 7 **Population-level Summary:** See endpoint 7	
	Endpoint: Fever clearance time **Target Population:** Adult and adolescent patients with acute uncomplicated malaria due to P. falciparum with an increased temperature (≥ 37.5°C) **Treatment:** see endpoint 19 **Intercurrent Event Strategy:** See endpoint 11 **Population-level Summary:** See endpoint 11	28
	Endpoint: Parasite clearance time **Target Population:** See endpoint 19 **Treatment:** see endpoint 19 **Intercurrent Event Strategy:** See endpoint 12 **Population-level Summary:** See endpoint 12	29
To evaluate the safety and tolerability of the M5717-pyronaridine combination in adult and adolescent participants with acute uncomplicated malaria due to *P. falciparum*	**Endpoint:** Incidence, severity, and seriousness of study intervention-related TEAEs, as per CTCAE v 5.0 Additional endpoints related to safety and tolerability up to Day 29 (± 2 days): laboratory assessments, ECGs, and vital signs.	33
To characterize the PK of M5717 and pyronaridine in adult and adolescent participants with acute uncomplicated malaria due to *P. falciparum* in Cohort B0.	**Endpoint:** • PK profiles for M5717 and pyronaridine in Cohort B0. • PK parameters of M5717 and pyronaridine such as $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}24}$, C_{max}, $t_{½}$, t_{max}, CL/F, VZ/F, when data permits	34

CCI [redacted]

CCI

[redacted]

6 Overview of Planned Analyses

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

7 Changes to the Planned Analyses in the Clinical Study Protocol

- Due to the study's early termination decision by the Sponsor's Medical Safety and Ethics Board based on compelling efficacy and safety in Cohorts A and Cohort B0, Cohorts B1, B2, and B3 were not enrolled. Therefore, mention of Pyramax and Cohorts B1, B2, and B3 have been removed from the study objectives and estimands (see Section 5). Additionally, no comparison of treatment groups as described in the protocol section 9 will be conducted. The following analyses as described in the protocol will not be done: a log-rank test to investigate differences between treatment arms in median fever clearance time, parasite clearance time, time to recrudescence, time to re-infection, and time to re-emergence. Additionally, no logistic regression models will be used to investigate factors of ACPR, ETF, LCF, or LPF.

- For Estimands #6, 7, 23, and 24, the endpoints were changed to exclude ACPR 14 days after treatment. This will not be calculated as it is not meaningful.

- For Estimands #6, 7, 19, 23, 24, the ICE strategy for intake of prohibited medication that impacts treatment effect was changed. A treatment policy strategy will be applied and the treatment effect will be estimated regardless of the ICE.

- For Estimands #7 and 24, the ICE was changed. In the protocol section 3, the ICE strategy is defined as the same as for Endpoint #3 (ETF), which limits ICEs to events occurring before or after Day 4. However, Estimands #7 and 24 are defined as endpoints occurring >4 days after treatment. Thus, the ICE strategy was changed for these endpoints to those defined for Endpoint #6 (Crude ACPR 28 and 42 days after treatment) which defines ICE at any timepoint.

- For Estimands #11, 12, 28, and 29, the ICE was changed. Time to fever clearance and time to parasite clearance will be censored at the time of intake of rescue/fever/prohibited medications that are taken within 3 days after treatment initiation.

- For Estimands #11 and 28 (analysis of fever clearance), only participants who had a temperature >37.5°C at the pre-dose visit or during the 24 hours following dosing will be included. If the fever medication was taken prior to dosing, participants will still be included for analysis. Strategies for intercurrent events will not apply.

- Analysis of Estimands #8, 9, 25, and 26, crude and PCR-adjusted efficacy 8 days after treatment, will not be conducted as no new information would be added.

- CCI [redacted]

- Analysis of Estimands #13, 14, 15, 30, 31, and 32, time to recrudescence, re-infection, and re-emergence, will not be conducted as no new information would be added.

- For any analysis using axillary temperature, the temperature measured at other locations will be used instead without adjustment if the axillary temperature is not collected. The number of participants or visits with temperature measured at different body locations will be described in the footnote of the output.

8 Analysis Sets

8.1 Definition of Analysis Sets

The following Analysis Sets will be used:

Full Analysis Set (FAS)

The FAS will include all enrolled participants. Participants will be analyzed according to the treatment assigned at enrollment as per the Intention-to-Treat principle.

Safety Analysis Set (SAF)

All participants, who were administered any dose of any study intervention. Analyses will consider participants as treated.

PK Analysis Set (PKAS)

All participants, who receive ≥ 1 dose of study intervention, have no clinically important protocol deviations or important events affecting PK, and provide ≥ 1 measurable post-dose concentration. Participants will be analyzed per the actual study intervention they received. All PK analyses will be based on this analysis set for the final analysis.

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	✓	✓*	
Efficacy: Primary Endpoint/Estimand	✓		
Efficacy: Secondary Endpoint/Estimand	✓		
Efficacy: CCI Endpoints/Estimands	✓		
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.

9 General Specifications for Data Analyses

9.1 Treatment Cohorts

For Part A and Part B Cohort B0, participants are not randomized but different doses of M5717 and Pyronaridine are used. Unless otherwise indicated, all analyses will be presented separately for Part A and Part B Cohort B0. The two dose levels in Cohort B0 will be combined in the reports.

9.2 Investigational Medical Product (IMP)

The IMP is the combination of M5717 and pyronaridine. For Part A, participants are administered 330 mg of M5717 and 260 mg of pyronaridine. For Part B Cohort B0, participants are administered different dose levels according to body weight: 500 mg of M5717 and 360 mg of pyronaridine for participants ≥24 to <45 kg, 660 mg of M5717 and 540 mg of pyronaridine for participants ≥45 to < 65 kg, and 660 mg of M5717 and 720 mg of Pyronaridine for participants ≥65 kg.

9.3 Presentation of Tables/Listings/Figures

Tables and Figures will be presented by Part, unless otherwise specified. A “Total” column will be included in non-efficacy tables. In the individual participant data listing all individual data will be listed as measured. Unless otherwise specified, all listings will be sorted by Part, M5717 dose, 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

Each participant will be followed up till Day 43 (± 2 days) or the day of premature discontinuation, including 4 continuous days (72 hours post first dose) in the hospital after admission, followed by 5 out-patient visits on Days 8, 15, 22, 29, and 43 (or day of premature discontinuation).

The time window is ± 30 minutes for each scheduled timepoint on Day 1 through Day 4. The visit window is ± 1 day for Day 8 and ± 2 days for Days 15, 22, 29 and 43.

In case any assessment occurs outside of the defined timepoint/visit window, it will be allocated to "unscheduled". These visits will not be included in descriptive statistics by nominal visit or time point and will be flagged in subject data listings. 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 the analyses will be performed in SAS® software version 9.4 or higher.

9.6 Data Handling After Cut-off Date

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

In general, the last non-missing scheduled measurement prior to the first study intervention administration will be used as the baseline measurement.

If an assessment is planned to be performed before study intervention per protocol but the assessment time is not available, it will be assumed that it was performed prior and considered as baseline.

If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be analyzed similarly to an unscheduled post-dose measurement.

Absolute and percent changes from baseline are defined as

absolute change = visit value – baseline value

percent change = 100 * (visit value – baseline value) / baseline value

9.8 Study Day / Study Intervention Day

If endpoints refer to specific timepoints, the timepoints given refer to days after treatment. Thereby, time of treatment start is defined to be on Day 1. Study day is defined relative to Day 1. If an endpoint defines the measurement to be taken, e.g., 7 days after treatment, this means that the measurement is taken on Day 8.

9.9 Definition of Duration, 'Time to' and 'Time Since' Variables

Duration will be calculated as the difference between start and end 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 to an event will be calculated as date of event – reference date + 1 (e.g., ADT – STARTDT + 1). If time to an event is calculated in hours, then it is calculated as the difference between event and reference SAS datetimes divided by 3600 (e.g., (ADTM – STARTDTM) / 3600).

The time since an event will be calculated as:

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

9.10 Conversion Factors

The following conversion factors will be used to convert days into months or years:

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 cutoff or database lock using the latest complete date prior to or at the data cutoff 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, end of study visit date 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.

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, then 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 AE 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 enrollment
    - Participant did not meet all eligibility criteria
    - Withdrew consent
    - Progressive disease
    - Lost to follow-up
    - Death
    - Other
- Number of enrolled participants
- Number of enrolled 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.

10.2 Protocol Deviations

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

A summary table of demographic characteristics will be provided including age, sex, race, and ethnicity.

11.2 Medical History

The medical history will be summarized from the "Medical History" eCRF page, using the most recent MedDRA version at time of database lock, 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. A listing displaying Medical History by participant will be provided.

11.3 Other Baseline Characteristics

Summary and frequency tables, as applicable, will be provided for baseline 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

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) current version at the date of data cut-off will be used for coding of prior and concomitant medications and they will be described using Preferred Term (PT) as applicable.

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.

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

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.

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 Crude and PCR-adjusted ACPR at Various Timepoints

Crude ACPR 28 and 42 days after first dose is defined as absence of parasitemia (parasite count = 0) from thick smear/microscopy, irrespective of axillary temperature, in participants who did not previously meet any of the criteria of ETF, LCF, or LPF.

PCR-adjusted ACPR 28 and 42 days after first dose is defined as absence of parasitemia (parasite count = 0) from thick smear/microscopy after adjustment for parasitemia due to new infections as determined by genotyping using PCR techniques, irrespective of axillary temperature, in participants who did not previously meet any of the criteria of ETF, LCF, or LPF. By PCR-adjustment all participants with parasitemia due to a new infection are considered responders. Note that PCR-adjusted ACPR 28 days after first dose is the endpoint of the primary estimand for Part B Cohort B0.

In order to derive the population-level summary of the estimands, different intercurrent events (ICEs) will be considered. ICE as defined by the study protocol will be identified and handled as described in the following if the ICE takes place before 28 or 42 days post treatment:

- **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 (= presence of parasitemia and no ACPR).

- **Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity) at any timepoint**: A treatment policy strategy is applied, i.e., treatment effect is estimated regardless of the ICE.

- **Experience of any event that affects absorption (i.e., vomiting within the study intervention absorptive period of 2 × median tmax) or immune response (severe immunocompromised participants)**: 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.

- **Premature study discontinuation due to lack of efficacy:** Participants who have primary reason for early termination set as "Lack of efficacy" on Study Termination eCRF. A composite variable strategy is applied, i.e., endpoint is considered as failure.

- **Death due to malaria:** 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, i.e., endpoint is considered as failure.

Participants who did not previously meet any criteria of ETF, LCF, or LPF, have no ICE, and are missing parasitemia data at the specified timepoint after first dose will be included in the denominator of the proportion and will be counted as 'N/A' in the summary table.

The population-level summaries are the proportion of participants achieving PCR-adjusted/Crude ACPR 28/48 days after first treatment (ACPR rates). ACPR rates will be estimated with 95% confidence intervals. Confidence intervals will be derived by use of Wilson's score method.

14.2 Early Treatment Failure (ETF)

ETF is defined as meeting any of the following:

a) Danger signs or severe malaria 1, 2, or 3 days after treatment (i.e., between Days 2 and 4), in the presence of parasitemia (parasite count > 0).
b) Parasitemia 2 days after treatment higher than on day of treatment (defined as count at baseline), irrespective of axillary temperature.
c) Parasitemia 3 days after treatment with temperature ≥ 37.5°C.
d) Parasitemia 3 days after treatment ≥ 25% of parasite count on day of treatment (defined as the count at baseline).

The same ICEs and strategies as defined for ACPR (see Section 14.1) will be applied for ETF, however, limited to events that occur before or at Day 4 (i.e., 3 days after treatment). Failure is considered presence of ETF.

The population-level summary is proportion of participants with ETF (ETF rate). ETF rate will be estimated with 95% confidence intervals. Confidence intervals will be derived by use of Wilson's score method.

14.3 Late Clinical Failure (LCF)

LCF is defined as meeting any of the following:

a) Danger signs or severe malaria in the presence of parasitemia on any day between 4 and 28 days after treatment (i.e., between Days 5 and 29) in participants who did not previously meet any of the criteria of ETF.
b) Presence of parasitemia on any day between 4 and 28 days after treatment with temperature ≥ 37.5°C in participants who did not previously meet any of the criteria of ETF.

The same ICEs and strategies as defined for ACPR (see Section 14.1) will be applied for LCF, however, limited to events that occur between 4 and 28 days after treatment (i.e., between Days 5 and 29). Failure is considered presence of LCF.

The same analyses and population-level summaries as described for ETF will be applied for LCF.

14.4 Late Parasitological Failure (LPF)

LPF is defined as presence of parasitemia on any day between 7 and 28 days after treatment (i.e., between Days 8 and 29) with temperature < 37.5°C in participants who did not previously meet any of the criteria of ETF or LCF.

The same ICE and strategies as defined for ACPR (see Section 14.1) will be applied for LPF, however, limited to events that occur between 7 and 28 days after treatment (i.e., between Days 8 and 29). Failure is considered presence of LPF.

The same analyses and population-level summaries as described for ETF will be applied for LPF.

14.5 Fever clearance time

Fever clearance time is defined as the time (in hours) from first dosing to the first measurement of temperature < 37.5°C for 2 consecutive temperature readings, plus confirmed normal temperature (< 37.5°C) 24 hours after the first normal body temperature reading. Participants who are initially included on documented history of fever and who do not subsequently have a documented temperature reading of > 37.5°C at the pre-dose visit or during the 24 hours following initial dosing will not be considered for the population-level summary.

For fever clearance time, the ICEs as defined by the study protocol will be identified and handled as described in the following:

- **Intake of rescue medication:** See Section 14.1 for description of rescue medication. A composite variable strategy is applied, i.e., time to fever clearance is censored at the time of rescue medication intake. In order to qualify as ICE, the intake of rescue medication has to take place within the first 3 days after treatment initiation.

- **Intake of concomitant medications as a continuous treatment that have an impact on fever:** Filtering concomitant medications programmatically for paracetamol, acetaminophen, NSAIDs (ibuprofen, naproxen), salicylic acid, and by medical review. A composite variable strategy is applied, i.e., time to fever clearance is censored at the time of first concomitant medication intake. In order to qualify as ICE, the start date of intake of concomitant medication has to take place within the first 3 days after treatment initiation. If the fever medication was taken prior to dosing, participants will still be included for analysis. Strategies for intercurrent events will not apply.

- **Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity):** Filtering concomitant medications programmatically for sulphadoxine-trimethoprim, doxycycline, quinolone antibiotics including fluoroquinolones, azithromycin, erythromycin and all other macrolides and by medical review. A composite variable strategy is applied, i.e., time to fever clearance is censored at the time of prohibited medication intake. In order to qualify as ICE, the intake of prohibited medication has to take place within the first 3 days after treatment initiation.

- **Experience of any event that affects absorption (i.e., vomiting within the study intervention absorptive period of 2 × median t_{max}) or immune response (severe immunocompromised participants):** See Section 14.1 for description of events affecting absorption or immune response. A treatment policy strategy is applied, i.e., treatment effect is estimated regardless of intercurrent event.

- **Premature study discontinuation due to lack of efficacy:** See Section 14.1 for description of ICE. An on-treatment strategy is applied, i.e., time to fever clearance is censored at the day of the last available body temperature assessment. Note: If premature study discontinuation occurs after fever clearance has already been observed, then the strategy will not be applied.

- **Death due to malaria:** See Section 14.1 for description of death due to malaria. An on-treatment strategy is applied, i.e., time to fever clearance is censored at the day of the last available body temperature assessment. Note: If death occurs after fever clearance has already been observed, then the strategy will not be applied.

Median fever clearance time and 95% CIs will be estimated by use of the Kaplan-Meier method. Confidence intervals will be calculated using log-log transformation. Participants with no fever clearance or ICEs will be censored at the day of the last temperature assessment. Kaplan-Meier plots including a table with number of participants at risk and number of events will be provided. To explore whether there is an impact of dose group (Part A vs. Part B Cohort B0), age (continuous), sex, and parasite density at baseline on time to fever clearance, a Cox Proportional Hazards model will be applied.

14.6 Parasite clearance time

Parasite clearance time is the duration (in days) between first dosing and the first blood draw with parasite clearance (parasite count = 0). The subsequent readings up till at least 6 hours from the first zero reading must remain zero for the presence of parasites.

The same ICEs and strategies as defined for time to fever clearance (see Section 14.5) will be applied to parasite clearance time, with the exception of intake of concomitant medications with impact on fever, which is not an ICE for parasite clearance time. Since parasite clearance time is measured in days, censoring will be done at the day of the last available microscopy assessment.

The same analysis approaches as described for fever clearance time are applicable also to parasite clearance time (note that for the target population for parasite clearance time the prerequisite of showing an increased temperature does not hold). Participants with no parasite clearance or ICEs will be censored at the day of the last microscopy assessment.

CCI

CCI

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 the latest MedDRA version available at the time of database lock and assigned to a SOC and a PT. The severity of AEs will be graded using CTCAE v5.0.

Treatment-emergent AEs (TEAEs) are those events with onset dates on or after the first administration of study intervention.

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 (AESIs) are liver (Aminotransferase (AT) increase, Total Bilirubin (TB) increase) and central nervous system (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.

Group/SOC terms and PTs within each group/SOC will be sorted alphabetically.

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.

AE listings will include all AEs (whether treatment-emergent or not).

15.1.1 Treatment-Emergent Adverse Events

An overview summary of TEAEs will be provided including number of participants who experience at least any

- TEAE
- 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 study termination
- Related TEAE leading to study termination
- 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 frequency threshold of 5%
- Related TEAEs (if any)
- Serious TEAEs (if any)
- Related serious TEAEs (if any)
- TEAEs of special interest (if any)
- TEAEs leading to study termination (if any)
- Related TEAEs leading to study termination (if any)
- TEAEs leading to death (if any)
- Related TEAEs leading to death (if any)

Additionally, a summary table displaying the number of participants with TEAEs by Primary SOC and PT will be provided by worst severity grade. A graphical presentation of TEAEs occurring in >10% of participants will be provided as well.

A listing of all AEs will be provided. The listings will include seriousness, severity grade, relationship with study treatment, if time-emergent, and outcome.

15.1.2 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

A listing of deaths, if any, will be provided including date and cause of death.

15.2.2 Serious Adverse Events

A listing of serious AEs (SAEs), if any, will be provided.

15.2.3 Other Significant Adverse Events

A listing of AESIs, if any, will be provided.

15.3 Disease Related Events

Disease related events (DREs) are captured separately in the same manner as Adverse Events. A listing of DREs, if any, will be provided.

15.4 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 protocol):

- Hematology
- Biochemistry
- Coagulation

Summary tables over time displaying absolute values and changes from baseline will be provided for continuous data. For a graphical presentation line plots of lab parameters standardized to times ULN over time will be provided for each participant. Plots will be grouped by participants of different M5717 doses and by lab parameters in the following way:

- Biochemistry:
  - Alanine Aminotransferase, Alkaline Phosphatase, Aspartate Aminotransferase, Bilirubin
  - Calcium, Creatinine, Glucose, Lactate
  - Potassium, Protein, Sodium, Urea Nitrogen
- Hematology:
  - Basophils, Eosinophils, Ery. Mean Corpuscular Hemoglobin, Ery. Mean Corpuscular HBG Concentration, Ery. Mean Corpuscular Volume
  - Erythrocytes, Hematocrit, Hemoglobin
  - Leukocytes, Lymphocytes, Monocytes, Neutrophils, Platelets, Reticulocytes

- All coagulation parameters

In addition, shift tables from baseline based on normal ranges will be provided.

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

Outputs will be presented using the Merck standard lab units (see *Guidance Document Merck Standard Lab Units and Normal Ranges* Version 2.2 for reference) unless otherwise agreed. 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 from the central laboratory in Merck standard units will be converted to Merck standard units before processing. Both original units and SI 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).

15.5 Vital Signs

Summary tables over time displaying absolute values and 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)

A listing of all vital signs data will be provided.

15.6 Other Safety or Tolerability Evaluations

15.6.1 ECG Evaluations

The following analyses will be performed for each 12-lead ECG parameter (RR, PR, QRS, QT, ventricular rate -denoted as HR in what follows-, and QTcF):

- 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.

15.6.2 Malaria Signs and Symptoms

A frequency table per solicited symptom over time will be provided. Total score at each timepoint will also be summarized.

16 Analyses of Other Endpoints/Estimands

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 concentrations 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, SD:	3 significant digits
CV%:	1 decimal place

16.1.1 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

16.1.2 General Specifications for PK Concentration and PK Parameter Data

PK concentration samples taken before the first drug administration (predose samples) 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 the allowed time 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 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.

16.1.3 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.

16.1.3.1 Estimation of Pharmacokinetic Parameters in Whole Blood

PK parameters will be calculated using the nominal 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).

$AUC_{0\text{-}tlast}$/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.
$AUC_{0\text{-}\infty}$/Dose	The dose normalized AUC from time zero extrapolated to infinity. Normalized using dose, using the formula $AUC_{0\text{-}\infty}$ /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 $AUC_{0\text{-}\infty}$.

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 estimated/$t_{1/2}$
- AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0\text{-}\infty}$. ($AUC_{extra\%}$).

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 and included in the parameter outputs.

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

16.1.4 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. These outputs from Phoenix® WinNonlin are not expected to be provided to the DMC, though. The following PK tables, listings, and figures will be produced in SAS and provided to the DMC.

16.1.4.1 Listings and Tables

- Individual concentrations and descriptive statistics of concentrations by analyte, and group
- Individual PK parameters and descriptive statistics of PK parameters by analyte, and group
- Individual dose normalized PK parameters and descriptive statistics of dose normalized PK parameters by analyte, and group
- Individual diagnostic PK parameters by analyte, matrix, day and group

16.1.4.2 Graphical Summaries and Individual plots

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

17 References

Not applicable.