# Integrated Analysis Plan

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| **Clinical Study Protocol Identification No.** | MS201618-0013 |
| **Title** | A Phase I, First-in-Human, Randomized, Double Blind, Placebo-Controlled Trial of Single and Multiple Ascending Doses of M5717 to Assess the Safety, Tolerability and Pharmacokinetic Profile of Oral Doses, and to Assess the Antimalarial Activity of M5717 Against Plasmodium falciparum in Healthy Male and Female Adult Subjects |
| **Study Phase** | I |
| **Investigational Medicinal Product(s)** | M5717 |
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| **Integrated Analysis Plan Author** | **Coordinating Author**<br>PPD Merck PPD<br>**Function** / **Author(s) / Data Analyst(s)**<br>PPD PPD<br>PPD PPD<br>PPD PPD |
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# Signature Page

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| Merck responsible | Date | Signature |
|---|---|---|
| PPD PPD | Via ELDORADO approval process | |
| PPD PPD | Via ELDORADO approval process | |

# 1 Table of Contents

## 2 List of Abbreviations and Definition of Terms

| | |
|---|---|
| ADaM | Analysis Data Model |
| CCI [redacted] | |
| AE(s) | Adverse event(s) |
| AESI(s) | Adverse event(s) of special interest |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| AUC | Area under the curve |
| $AUC_{0-24h}$ | AUC from time zero (= dosing time) to 24 hours postdose |
| $AUC_{0-24h}$/Dose | Dose-normalized $AUC_{0-24h}$ |
| $AUC_{0-144h}$ | AUC from time zero (= dosing time) to 144 hours postdose |
| $AUC_{0-144h}$/Dose | Dose-normalized $AUC_{0-144h}$ |
| $AUC_{0-t}$ | AUC from time zero (= dosing time) to the last sampling time ($t_{last}$) at which the concentration is at or above the lower limit of quantification |
| $AUC_{0-t}$/Dose | Dose-normalized $AUC_{0-t}$ |
| $AUC_{0-\infty}$ | The AUC from time zero (dosing time) extrapolated to infinity |
| $AUC_{0-\infty}$/Dose | Dose-normalized $AUC_{0-\infty}$ |
| $AUC_{extra\%}$ | The AUC from time $t_{last}$ extrapolated to infinity given as percentage of $AUC_{0-\infty}$ |
| BMI | Body mass index |
| CCI [redacted] | |
| BP | Blood pressure |
| CI | Confidence interval |
| $CL_{/f}$ | Apparent total body clearance of drug following extravascular administration, taking into account the fraction of dose absorbed |
| $C_{max}$ | Maximum observed concentration |
| $C_{max}$/Dose | Dose-normalized $C_{max}$ |
| CRF | Case report form |
| CSR | Clinical Study Report |
| CV% | Coefficient of variation |
| DBS | Dried blood spot |

| | |
|---|---|
| DIPLD | Drug-induced phospholipidosis |
| $EC_{50}$ | Half maximal effective concentration |
| $EC_{90}$ | 90% of maximal effective concentration |
| ECD | Early Clinical Development |
| CCI | |
| GCP | Good Clinical Practice |
| GeoCV% | Geometric coefficient of variation |
| GeoMean | Geometric mean |
| IAP | Integrated Analysis Plan |
| CCI | |
| CCI | |
| ICH | International Council for Harmonisation |
| IMP | Investigational medicinal product |
| IV | Intravenous |
| $\lambda_z$ | Terminal first order (elimination) rate constant |
| LLOQ | Lower limit of quantification |
| LOQ | Limit of quantification |
| MAD | Multiple ascending dose(s) |
| Max | Maximum |
| Mean | Arithmetic mean |
| MedDRA | Medical Dictionary for Regulatory Activities |
| CCI | |
| Min | Minimum |
| MPC | Minimal parasiticidal concentration |
| mRNA | Messenger ribonucleic acid |
| N | Number of non-missing observation |
| ND | Nondetectable/not detected |
| NR | No result |
| PCR | Polymerase chain reaction |
| CCI | |
| CCI | |

| | |
|---|---|
| CCI [redacted] | |
| PK | Pharmacokinetic(s) |
| PLD | Phospholipidosis |
| CCI [redacted] | |
| PT | Preferred Term |
| Q1 | 25th percentile |
| Q3 | 75th percentile |
| qPCR | Quantitative PCR |
| QTc | QT interval corrected for heart rate |
| QTcB | QT interval corrected for heart rate according to Bazett's formula |
| QTcF | QT interval corrected for heart rate according to Fridericia's formula |
| Rsq | Goodness of fit statistic for calculation of $\lambda_z$ |
| SAD | Single ascending dose(s) |
| SAE(s) | Serious adverse event(s) |
| SAF | Safety Analysis Set |
| SAS | Statistical Analysis System |
| SD | Standard deviation |
| SDTM | Study Data Tabulation Model |
| SE | Standard error |
| SI | Système International |
| SMC | Safety Monitoring Committee |
| SOC | System Organ Class |
| $t_{>10\ ng/mL}$ | Time above or equal to the predicted M5717 mouse MPC of 10 ng/mL |
| $t_{>3\ ng/mL}$ | Time above or equal to the predicted M5717 mouse MIC of 3 ng/mL |
| $t_{½}$ | Apparent terminal half-life |
| TEAE(s) | Treatment-emergent adverse event(s) |
| $t_{last}$ | The last sampling time at which the concentration is at or above the lower limit of quantification |
| $t_{max}$ | Time to reach the maximum observed concentration |
| ULOQ | Upper limit of quantification |
| $Vz_{/f}$ | Apparent volume of distribution during the terminal phase following extravascular administration |

| | |
|---|---|
| WHO DDE | The Enhanced World Health Organization Drug dictionary |

# 3 Modification History

| Unique Identifier for Version | Date of IAP Version | Author | Changes from the Previous Version |
|---|---|---|---|
| 1.0 | 16AUG2018 | PPD<br>PPD<br>PPD<br>PPD | Original document |
| 2.0 | 13MAY2019 | PPD<br>PPD<br>PPD | 1) Update based on the latest Protocol Version 5.0 including Amendment 4<br>2) Urine and feces pharmacokinetic analysis (Section 16.1.2.2) to be performed and reported separately<br>3) Pharmacodynamic parameter analysis (Section 16.2.1) to be performed and reported separately |

# 4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for the final analysis of data collected for Clinical Study Protocol MS201618-0013. 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 will 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 upon the Clinical Study Protocol Version 5.0 including Amendment 4 and is prepared in compliance with International Council for Harmonisation (ICH) E9. It focuses on the detailed description of the statistical analyses for safety, pharmacokinetics (PK), pharmacodynamics (PD), and other variables. Part B of the study (multiple ascending doses [MAD]) is designated as optional in the protocol and will not be conducted, so the analysis is not currently defined in this IAP.

# 5 Objectives and Endpoints

The objectives and endpoints below pertain to Part A and Part C only.

| | Objective | Endpoint | IAP Section |
|---|---|---|---|
| **PART A** | | | |
| **Primary Objective** | To investigate the safety and tolerability of single ascending oral doses of M5717 | Primary Endpoints<br>• Nature, incidence, and severity of AEs/ SAEs, including relationship to study treatment, AEs/SAEs leading to dose modification or discontinuation of study treatment<br>• Incidence of clinically significant changes and abnormalities in safety laboratory parameters (hematology, coagulation, biochemistry [specifically ALT and AST], and urinalysis)<br>• Incidence of clinically significant changes and abnormalities in vital signs (body temperature, BP, heart rate, and respiratory rate) and 12-lead ECG | 15 |
| **Secondary Objectives** | To investigate the PK of single ascending oral doses of M5717 | Secondary Endpoints<br>• PK parameters for M5717: $C_{max}$, $t_{max}$, $\lambda_z$, $t_{½}$, AUC ($AUC_{0-\infty}$, $AUC_{0-t}$, and $AUC_{0-144h}$), $AUC_{extra\%}$, $CL_{/f}$, $V_{z/f}$, and dose-normalized $AUC_{0-\infty}$, $AUC_{0-144h}$, $AUC_{0-t}$, and $C_{max}$, as well as $t_{>10\ ng/mL}$ and $t_{>3\ ng/mL}$ | 16.1.2 |
| [redacted] | | | |

| | Objective | Endpoint | IAP Section |
|---|---|---|---|
| **PART C** | | | |
| **Primary Objective** | To characterize the PK/PD relationship between M5717 PK and parasite clearance in healthy subjects following infection with P. falciparum blood stage parasites during the IBSM challenge by assessment of the PK-to-PRR relationship | Primary Endpoints<br>• PRR as observed through qPCR analysis<br>• All M5717 PK parameters as defined in Part A or Part B (depending on dosing regimen in Part C) | 16.2, 16.1.2 |
| **Secondary Objectives** | To characterize the PK/PD relationship between M5717 PK and parasite clearance in healthy subjects following infection with P. falciparum blood stage parasites during the IBSM challenge by assessment of the relationship of PK with the PD parameters: PCT, MIC, $PCt_{1/2}$, MPC, lag time, and frequency of recrudescence<br>To characterize the parasiticidal activity of M5717 on P. falciparum asexual blood stage parasites in the blood of healthy subjects in the IBSM challenge | Secondary Endpoints<br>• PCT, MIC, $PCt_{1/2}$, MPC, lag phase<br>• Number and percentage of subjects with recrudescence | 16.2 |
| | To evaluate the safety and tolerability of M5717 in healthy volunteers following infection with P. falciparum blood stage parasites during the IBSM challenge | • Malaria Clinical Score<br>• Nature, incidence, and severity of AEs/SAEs, including relationship to study treatment, AEs/SAEs leading to dose modification or discontinuation of study treatment<br>• Incidence of clinically significant changes and abnormalities in safety laboratory parameters (hematology, coagulation, biochemistry [specifically ALT and AST], and urinalysis)<br>• Incidence of clinically significant changes and abnormalities in vital signs (body temperature, BP, heart rate, and respiratory rate) and 12-lead ECG | 15 |
| [redacted] | | | |

| | Objective | Endpoint | IAP Section |
|---|---|---|---|
| CCI | | | |

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUC = area under the curve; $AUC_{0-\infty}$ = AUC from time zero (dosing time) extrapolated to infinity; $AUC_{0-t}$ = AUC from time zero (dosing time) to the last quantifable sampling time; $AUC_{0-144h}$ = AUC from time zero (dosing time) to 144 hours postdose; $AUC_{extra\%}$ = AUC from time of the last quantifiable sample extrapolated to infinity given as percentage of $AUC_{0-\infty}$; CCI BP = blood pressure; $CL/f$ = apparent total body clearance of drug following extravascular administration; $C_{max}$ = maximum observed concentration; CCI ECG = electrocardiogram; IBSM = Induced Blood Stage Malaria; CCI $\lambda_z$ = terminal first order (elimination) rate constant; MIC = Minimal inhibitory concentration; MPC = Minimal parasiticidal concentration; PCT = parasite clearance time; $PCt_{1/2}$ = parasite clearance half-life; PK = pharmacokinetic(s); PD = pharmacodynamic(s); PLD = phospholipidosis; PRR = parasite reduction ratio; qPCR = quantitative polymerase chain reaction; QTcB = QT interval corrected for heart rate according to Bazett's formula; QTcF = QT interval corrected for heart rate according to Fridericia's formula; SAE = serious adverse event; $t_{½}$ = apparent terminal half-life; $t_{max}$ = Time to reach the maximum observed concentration; $V_{z/f}$ = Apparent volume of distribution during the terminal phase following extravascular administration; $t_{>10\ ng/mL}$ = time above or equal to the predicted M5717 mouse MPC of 10 ng/mL; $t_{>3\ ng/mL}$ = time above or equal to the predicted M5717 mouse MIC of 3 ng/mL.

The analyses of the endpoints will be described in the respective sections for efficacy, safety, PK, PD, or other endpoints, regardless of whether the endpoint is a primary endpoint or not.

# 6 Overview of Planned Analyses

## 6.1 Analyses for the Safety Monitoring Committee Meetings

For Parts A and C, the Safety Monitoring Committee (SMC) will regularly meet to evaluate safety and tolerability data (adverse events [AEs], safety laboratory data, electrocardiogram [ECG], and vital signs), PK data, and PD (parasitemia) data (Part C only). Details of the SMC meetings and related analysis methodology are covered in the SMC Charter.

## 6.2 Final Analysis

All final, planned analyses identified in the Clinical Study Protocol and in this IAP will be performed only after the last subject has completed the double-blind (as applicable) treatment phase of the study with all study data in-house, all data queries resolved, and the database locked. Details of the final PK, PD, and safety/tolerability analyses are further described in the PK (Section 16.1), PD (Section 16.2), and safety/tolerability sections (Section 15), respectively.

A data review meeting will be held prior to database lock. In addition, no database can be locked and no randomization code should be unblinded until this IAP has been approved for the final analyses.

# 7 Changes to the Planned Analyses in the Clinical Study Protocol

In the clinical trial protocol, the PK parameters, area under the curve from time zero (dosing time) to 24 hours postdose ($AUC_{0-24h}$) and dose-normalized $AUC_{0-24h}$ ($AUC_{0-24h}$/Dose), were specified for calculation for single doses (ie, Part A, and Part C if applicable) for the purpose of

combining/comparing PK exposures between single doses and multiple doses (ie, Part B). Since Part B is not being conducted, these parameters are not being calculated for Parts A and C.

A correlation analysis of M5717 concentrations from dried blood spot (DBS) assay and whole blood will be performed as described in Section 16.1.3.

# 8 Protocol Deviations and Analysis Sets

## 8.1 Definition of Protocol Deviations and Analysis Sets

Important protocol deviations or events are protocol deviations and events that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

A subset of these important protocol deviations or events that lead to the exclusion of a subject from an analysis set (see Section 8.2) are considered clinically important.

The following important deviations or events will be identified and confirmed prior to or at the Data Review Meeting:

- Subjects who are dosed on the study despite not satisfying the inclusion criteria
- Subjects who develop withdrawal criteria whilst on the study but are not withdrawn
- Subjects who receive the wrong treatment or an incorrect dose
- Subjects who receive an excluded concomitant medication
- Deviation from Good Clinical Practice (GCP)
- Other events/factors related to PK and/or PD, which include, but may not be limited to, events that could affect PK and/or PD, will be evaluated on a case-by-case basis:
  - Vomiting following oral dosing (these instances will be discussed on a case-by case basis)
  - Sample processing errors that may lead to inaccurate bioanalytical or PD results
  - Incomplete data (due to lost samples, insufficient sample volumes for assay, etc.)
  - Inaccurate dosing or dosing errors
  - Inadequate fasting prior to and following dosing
  - Concomitant medication violations (refer to Section 6.5.2 of Clinical Study Protocol), that could affect PK or PD.

In case of a deviation or event that may affect PK and/or PD data, collected PK and/or PD data which is likely to be affected may be excluded from the study results after consultation and agreement with Sponsor or sponsor representative. These deviations or events could be classified as clinically important and confirmed prior to or at the Data Review Meeting before database lock and unblinding of Part A. Other changes to the procedures or events which do not significantly impact the quality of the PK and/or PD data will not lead to exclusion from the PK and/or PD Analysis Sets. A common example of an event which usually does not lead to exclusion from the

PK Analysis Set is a missed PK blood sample or deviations from PK blood collection times, with the requirement that the actual time of collection is recorded.

In the case subjects or data are excluded from the PK and/or PD Analysis Sets, their PK and/or PD data will be listed in the CSR and flagged.

All protocol deviations will be documented in Study Data Tabulation Model (SDTM) datasets whether identified through site monitoring, medical review, or programming.

## 8.2 Definition of Analysis Sets and Subgroups

For purposes of analysis, the following populations are defined:

| Population | Description |
|---|---|
| Enrolled | The Enrolled Analysis Set will include all subjects who provided signed informed consent, regardless of treatment status in the study. This set will be used for subject disposition. |
| Safety (SAF) | The Safety Analysis Set will include all subjects who receive investigational medicinal product (M5717 or placebo for Part A; M5717 for Part C). Subjects will be analyzed according to the actual treatment they receive. |
| Pharmacokinetics (PK) | The Pharmacokinetic Analysis Set will consist of all subjects who receive M5717, have no clinically important protocol deviations or important events affecting PK, and provide at least one (measurable) postdose concentration. Subjects will be analyzed according to the actual treatment they receive. All PK analyses will be based on this analysis set. Subjects who receive placebo will not be part of the Pharmacokinetic Analysis Set. |
| Pharmacodynamics (PD) | The Pharmacodynamic Analysis Set will be defined for Part C only. The Pharmacodynamic Analysis Set will include all subjects who receive M5717 in Part C without clinically important protocol deviations or important events affecting PD. Subjects in the Pharmacodynamic Analysis Set must have evaluable postdose PD data. All PD analyses will be based on this analysis set. |

With respect to the use of the analysis sets in the different analyses, it could be presented in a table such as the following:

| Analyses | Enrolled Analysis Set | Safety Analysis Set | PK Analysis Set | PD Analysis Set |
|---|---|---|---|---|
| Subject Disposition | ✓ | | | |
| Baseline Assessments | | ✓ | | |
| Past and Concomitant Therapies | | ✓ | | |
| Compliance and Exposure | | ✓ | | |
| PK Analysis | | | ✓ | |
| PD Analysis | | | | ✓ |
| Safety and Tolerability | | ✓ | | |

No subgroup analyses are planned.

# 9 General Specifications for Data Analyses

Data will generally be presented separately for each part (Part A or Part C) of the study, although some combination of data across parts may be done, where appropriate (see Section 16.1.3).

Details on PK and PD data presentation can be found in Section 16.

**Listings**

All listings will be sorted by treatment/dose, subject, and/or nominal time point, as appropriate. Data which are only measured before administration of the investigational medicinal product (IMP) will be sorted by subject and nominal time point (if appropriate).

Safety data will be reported and analyzed with the same precision as the source data provided, regardless of how many significant figures or decimal places the data carry.

**Tables and Descriptive Statistics**

All data will be summarized by study part, dose group, day, and/or nominal time point, as appropriate. Data for subjects who received placebo will be pooled across dosing cohorts belonging to the same trial part. 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, eg, clotted samples.

**Presentation of Continuous and Qualitative Variables for Demographics, Other Baseline Characteristics, and Safety**

Continuous variables will be summarized using descriptive statistics, ie:

- number of subjects, number of subjects with non-missing values
- mean, standard deviation (SD)
- median, 25th Percentile - 75th Percentile (Q1-Q3)
- minimum (Min) and maximum (Max).

Qualitative variables will be summarized by counts and percentages.

Unless otherwise stated, the calculation of proportions will be based on the number of subjects in the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

When the analysis refers only to certain visits, percentages will be based on the number of subjects still present in the study at that visit, unless otherwise specified.

Mean, Median, Q1, Q3, Min, and Max will have the same precision as collected for SDTM datasets for non-derived data. Standard deviation will be presented with one digit more than the mean. Statistics on derived data will be rounded to reasonable digits whereas maximal digits should be

available in Analysis Data Model (ADaM) datasets. Percentage and percent change from baseline will be reported using 1 decimal digit, if not otherwise specified.

**Definition of Baseline**

If not otherwise specified, "Baseline" refers to the last scheduled measurement before the IMP administration, as appropriate. However, if a subject is missing the baseline collection, the previous non-missing evaluation (as applicable) will become the baseline value. Baseline of laboratory parameters will correspond to Day 1 predose for Part A, and Day -1 for Part C. Baseline will correspond to Day 1 predose for all parts of the study for vital signs and safety ECGs. Baseline of biomarkers will correspond to Day -1 for Part A,

**Common Calculations**

For quantitative measurements:

Change from baseline will be calculated as: Test Value at Visit X – Baseline Value

Age [years]: ([date of informed consent - date of birth] +1)/365.25

**Definition of Duration**

Duration in days will be calculated by the difference of start and stop date + 1 if not otherwise specified.

**Handling of Missing Data**

Unless otherwise specified, missing data will not be replaced.

Handling of missing data for PK parameter calculations are discussed under Section 16.1.

**Software**

Pharmacokinetic parameters will be derived using the validated computer program Phoenix® WinNonlin® 6.4 or higher, and/or SAS® (Statistical Analysis System, SAS-Institute, Cary, North Carolina, USA) Windows Version 9.4 or higher. Pharmacodynamic parameters (excluding those calculated by PK/PD modeling; see Section 16.2.3) will be derived using SAS®. Pharmacokinetic and PD tables, figures, and listings for the final analysis will be developed using SAS®. All other statistical analyses will be performed using SAS®.

# 10 Study Subjects

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

## 10.1 Disposition of Subjects and Discontinuations

A summary table describing the number and percentage of subjects (as applicable) in each of the following disposition categories will be produced by dose and overall:

- Total number of enrolled subjects (ie, subjects who gave informed consent)
- Number of subjects who discontinued from the study prior to randomization (as applicable), with the reason of discontinuation
- Number of randomized subjects
- Number of randomized subjects who did not receive dose (as applicable)
- Number of treated subjects (used as denominator for percentage calculation for the categories below)
- Number of treated subjects who completed the study
- Number of treated subjects who discontinued the study, with the reason of discontinuation

Corresponding individual listings for study termination status, study entry (including screening failures), and randomization will be prepared. Discontinued subjects will be listed with their reason of withdrawal.

Summary of the number and percentage (as applicable) of subjects included in each analysis set (as described in Section 8.2) will be presented.

## 10.2 Protocol Deviations

### 10.2.1 Important Protocol Deviations

A listing of important protocol deviations will be provided.

Any PK concentrations which are erroneous due to a protocol violation (as defined in the Clinical Study Protocol), documented handling error, or analytical error (as documented in the bioanalytical report) may be excluded from the PK analysis if agreed upon prior to performing any statistical analyses. In this case, the rationale for exclusion must be provided in the CSR. Any PK concentrations excluded from the PK analysis set will be listed and flagged. Any other PK concentrations that appear implausible to the Pharmacokineticist/PKPD Data Analyst must not be excluded from the analysis. Any implausible data will be documented in the CSR.

### 10.2.2 Reasons Leading to the Exclusion from an Analysis Set

If subjects are excluded from the PK Analysis Set and/or PD Analysis Set, the reasons for exclusion will be listed.

## 11 Demographics and Other Baseline Characteristics

Demographics and baseline characteristics will be presented for the Safety Analysis Set.

## 11.1 Demographics

Descriptive statistics will be presented for age, height, weight, and body mass index (BMI). Frequency counts and percentages will be presented for sex, race, ethnicity, and skin type. The summary will be performed by dose and overall.

## 11.2 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 20.1, and listed.

## 11.3 Other Baseline Characteristics

Other baseline measurements, such as virus screen, alcohol and drugs of abuse screen, pregnancy test and follicle-stimulating hormone assessment in women, nicotine and alcohol consumption, will be listed.

In addition, glucose-6-phosphate dehydrogenase status will be listed for Part C.

# 12 Previous or Concomitant Medications/Procedures

## 12.1 Previous or Concomitant Medications

Medications will be presented for the Safety Analysis Set.

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

The Enhanced World Health Organization Drug dictionary (WHO DDE), Version SEP2017, 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.

## 12.2 Rescue Medication

Subjects in Part C will be prescribed an approved regimen for curative therapy for malaria, to assure final parasite clearance, at recrudescence or at the end of the study.

Rescue medication data will be listed by subject, including day after inoculum administration.

## 12.3 Intravenous Malaria Inoculum

Intravenous (IV) inoculum will be administered at Day -8 in Part C. Data will be provided in a listing.

# 13 Treatment Compliance and Exposure

The IMP will be administered at the study site under supervision. The administration of IMP will be listed.

# 14 Efficacy Analyses

There are no efficacy endpoints defined for Part A.

For Part C, parasitical effect of M5717 will be analyzed as specified in Section 16.2. The malaria clinical score will be analyzed as described in Section 15.2.3.

# 15 Safety Analyses

The subsections in this section include specifications for summarizing safety endpoints that are common across clinical studies such as AEs, laboratory tests and vital signs.

All safety analyses will be performed for the Safety Analysis Set and will be presented by part and dose. An additional column for all active doses of M5717 may be presented when specified.

## 15.1 Adverse Events

All AEs recorded during the course of the study will be coded with the MedDRA, Version 20.1, and assigned to a System Organ Class (SOC) and a PT.

Treatment-emergent AEs (TEAEs) are those events with onset dates on or after the first IMP administration. Any AE occurring before the IMP administration on Day 1 and resolved before IMP administration or not worsening after IMP administration 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.

In case AE-related dates are partial, the available information will be used in a conservative approach to determine whether the AE is treatment-emergent.

All analyses described in this section will be based on TEAEs if not otherwise specified.

### 15.1.1 All Adverse Events

Treatment-emergent AEs will be summarized by dose and overall in tables with:

- The number and percentage of subjects with any TEAE, any IMP-related TEAE, any serious TEAE, any IMP-related serious TEAE, any Grade ≥3 TEAE, any IMP-related Grade ≥3 TEAE,

any AEs of special interest (AESI), any TEAE leading to death, any IMP-related TEAE leading to death, any TEAE leading to study discontinuation

- The number and percentage of subjects with at least one TEAE by SOC and PT
- The number and percentage of subjects with at least one TEAE by worst grade, SOC, and PT
- The number and percentage of subjects with at least one IMP-related TEAE by SOC and PT
- The number and percentage of subjects with at least one TEAE by PT only, sorted in decreasing incidence overall
- The number and percentage of subjects with non-serious TEAEs by SOC and PT
- The number and percentage of subjects with at least one AESI recorded by SOC and PT.

Unless otherwise stated, AEs will be displayed with SOC terms and PTs within each SOC term sorted alphabetically.

For determining incidence counts, within each level of TEAE term, if a subject experiences more than one occurrence, the subject will only be counted once for that TEAE.

If an AE is reported for a given subject more than once during treatment, the worst severity and the worst relationship to study treatment will be tabulated.

Adverse events related to IMP are those events with relationship missing, unknown or yes.

In case a subject had events with missing and non-missing severity, the maximum non-missing severity will be displayed.

### 15.1.2 Adverse Events Leading to Study Discontinuation

A listing of TEAEs leading to study discontinuation, if any, will be provided.

## 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.

### 15.2.2 Serious Adverse Events

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

### 15.2.3 Other Significant Adverse Event

The following will be considered as AESIs in this study:

- Vomiting or diarrhea

- Liver enzyme elevations (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin)
- Cutaneous reactions (local tolerability measured by severity of redness, swelling, induration, bruising, and itching)
- Photosensitivity/light sensitivity
- Pregnancy in a female partner of a male subject.

These AESIs will be summarized by SOC and PT, as applicable, as specified in Section 15.1.1.

For Part C, the malaria clinical score for treatment initiation will be listed and summarized by dose.

## 15.3 Clinical Laboratory Evaluation

Listings and summary statistics at each assessment time will be presented using the Système International (SI) units. Normal ranges will be provided by the central laboratory, and out of range flags will be calculated based on the normal ranges. Laboratory data not transferred from the central laboratory in SI units will be converted to SI units before processing. Both original units and SI units will be provided in the SDTM domain.

Continuous clinical laboratory data (hematology, biochemistry, coagulation, and urinalysis) will be summarized by dose and time point using descriptive statistics for baseline (see definition in Section 9), each evaluation during the study, and change from baseline to each evaluation.

Box-and-whisker plots for the absolute change from baseline by dose, by time point will also be provided. Placebo data from all cohorts in part A will be pooled.

Listings of all clinical laboratory data for each subject will be provided, with values outside the normal ranges indicated. Listings of abnormal test results (low and high) will be provided.

## 15.4 Vital Signs

Vital signs data will be summarized by dose and time point using descriptive statistics for baseline (see definition in Section 9), each evaluation during the study, and change from baseline to each evaluation. Listing of vital signs data will be provided.

## 15.5 Other Safety or Tolerability Evaluations

### 15.5.1 12-lead Electrocardiogram

Safety ECG data will be summarized by dose and time point using descriptive statistics for baseline (see definition in Section 9), each evaluation during the study, and change from baseline to each evaluation. Listing of safety ECG data will be provided.

# 16 Analyses of Other Endpoints

## 16.1 Pharmacokinetics

### 16.1.1 Handling of Blood, Urine, and Fecal Concentrations

#### 16.1.1.1 Whole Blood

Concentrations of M5717 in whole blood will be measured in all cohorts in Parts A and C. Additionally, concentrations of M5717 metabolites may be measured in whole blood from male subjects receiving M5717 treatment in Part A (all cohorts).

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

Concentration values below the lower limit of quantification of the assay (LLOQ) will be taken as zero for summary statistics of PK concentration data.

In case of concentrations above the upper limit of quantification (ULOQ), the concentration will be set to missing.

Missing concentrations (eg, no sample, insufficient sample volume for analysis, no result or result not valid) will be reported and used generally as no result ("NR").

#### 16.1.1.2 Dried Blood Spot Assay

Concentrations of M5717 in DBS samples will be measured at selected time points in Part C cohorts.

Concentration values below the LLOQ of the assay will be taken as zero for summary statistics of DBS PK concentration data.

#### 16.1.1.3 Urine and Feces

Daily 24-hour urine and feces may be collected in male subjects only in one of the cohorts in Part A during the residential period (up to Day 7), and urine may be collected during the ambulant periods (24-hour collections around Day 15, Day 22, Day 33, and Day 44). Urine and fecal concentrations for M5717 and/or metabolites, if available, will be reported in a separate report.

### 16.1.2 Derivation of Individual Whole Blood, Urine, and Fecal Pharmacokinetic Parameters

#### 16.1.2.1 Whole Blood

Pharmacokinetic parameters will be calculated b PPD using standard non-compartmental methods and the actual administered dose. PK parameters will be calculated using the actual

elapsed time since dosing, given with a precision of 14 significant digits. In cases where the actual sampling time is missing, calculations will be performed using the nominal time. Otherwise, there will be no further imputation of missing data.

The following parameters will be calculated from M5717 whole blood concentrations in Part A and Part C. If M5717 whole blood metabolite concentrations are available in Part A, parameters may also be calculated for these metabolites (if applicable, and if sufficient data are available).

| Symbol | Definition |
|---|---|
| $AUC_{0-t}$ | The AUC from time zero (= dosing time) to the last sampling time ($t_{last}$) at which the concentration is at or above the lower limit of quantification. Calculated using the mixed log linear trapezoidal rule (linear up, log down). |
| $AUC_{0-t}$ /Dose | The dose-normalized $AUC_{0-t}$. Normalized using the actual dose, using the formula $AUC_{0-t}$ /Dose. |
| $AUC_{0-144h}$ | The AUC from time zero (= dosing time) to 144 hours postdose. Calculated using the mixed log linear trapezoidal rule (linear up, log down). |
| $AUC_{0-144h}$ /Dose | The dose-normalized $AUC_{0-144h}$. Normalized using the actual dose, using the formula $AUC_{0-144h}$ /Dose. |
| $AUC_{0-\infty}$ | The AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at $t_{last}$, and estimated using the linear regression from the determination of the terminal first order (elimination) rate constant ($\lambda_z$). $AUC_{0-\infty} = AUC_{0-t}+C_{last\ pred}/\lambda_z$. |
| $AUC_{0-\infty}$ /Dose | The dose-normalized $AUC_{0-\infty}$. Normalized using actual dose, using the formula $AUC_{0-\infty}$ /Dose. |
| $AUC_{extra\%}$ | The AUC from time $t_{last}$ extrapolated to infinity given as percentage of $AUC_{0-\infty}$. $AUC_{extra\%}$ = (extrapolated area/$AUC_{0-\infty}$)*100. |
| $CL_{/f}$ | The apparent total body clearance of drug following extravascular administration, taking into account the fraction of dose absorbed. CL/f = Dose /$AUC_{0-\infty}$. Calculated for M5717 only. |
| $C_{max}$ | Maximum observed concentration. |

| Symbol | Definition |
|---|---|
| $C_{max}$ /Dose | The dose-normalized $C_{max}$. Normalized using the actual dose, and the formula $C_{max}$ /Dose. |
| $\lambda_z$ | 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. |
| $t_{1/2}$ | Apparent terminal half-life. $t_{1/2} = \ln(2)/\lambda_z$. |
| $t_{max}$ | The time to reach the maximum observed concentration collected during a dosing interval (in case of multiple/identical $C_{max}$ values, the first occurrence will be used). |
| $V_{Z/f}$ | The apparent volume of distribution during the terminal phase following extravascular administration, based on the fraction of dose absorbed. $V_{z/f}$ = Dose/($AUC_{0-\infty}$*$\lambda_z$) following single dose. Calculated for M5717 only. |
| $t_{>3\ ng/mL}$ | Time above or equal to the predicted M5717 mouse minimum inhibitory concentration (MIC) of 3 ng/mL. |
| $t_{>10\ ng/mL}$ | Time above or equal to the predicted M5717 mouse minimal parasiticidal concentration (MPC) of 10 ng/mL. |

For $CL_{/f}$ and $V_{Z/f}$ and all dose-normalized parameters, the actual M5717 dose after adjustment for molecular weight differences between salt and free base form will be used for calculation of these parameters (ie, Adjusted dose = Dose * 462.56/580.65), where 462.56 and 580.65 are the molecular weights of the M5717 free base and succinate salt, respectively.

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

- The time interval (h) of the log-linear regression ($\lambda_{z\ low}$, $\lambda_{z\ upp}$) to determine $\lambda_z$.
- Number of data points ($N_\lambda$) included in the log-linear regression analysis to determine $\lambda_z$.
- Goodness of fit statistic (Rsq) for calculation of $\lambda_z$.

The regression analysis for $\lambda_z$ 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. However, in some cases, further adjustment may be made by the pharmacokineticist, if warranted, after agreement from the Sponsor. The last quantifiable concentration should always be included in the regression analysis, while the concentration at $t_{max}$ and any concentrations below the LLOQ which occur after the last quantifiable data point should not be used.

The Rsq should be ≥0.800 and the observation period over which the regression line is estimated should be at least two-fold the resulting $t_{1/2}$ itself. If these criteria are not met, then the rate constants and all derived parameters will be included in the parameter outputs and descriptive statistics but will be flagged and discussed appropriately. The $AUC_{extra\%}$ should be less than 20.0%. If this criterion is not met, $AUC_{0-\infty}$ and all derived parameters will be included in the parameter outputs and descriptive statistics but will be flagged and discussed appropriately. Any flags should be included in the study specific SDTM.

Partial areas should be calculated using the nominal dosing interval, as defined in the clinical trial protocol. The actual dosing interval calculated from case report form (CRF) time data should not be used.

Concentrations below the LLOQ at any point in the profile will be taken as zero for calculating the AUC. 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 drug administration.

The Phoenix WinNonlin NCA Core Output will be provided in a separate listing.

#### 16.1.2.2 Urine and Feces

Urine and fecal parameters for M5717 and/or metabolites, if calculated, will be reported in a separate report.

### 16.1.3 Statistical Summary and Analysis

For Parts A and C, whole blood PK parameters (as described in Section 16.1.2.1) will be calculated, if estimable, using actual elapsed times and noncompartmental methods, PPD
PPD

All statistical analyses and descriptive summaries of PK concentrations and PK parameters will be performed on the PK Analysis Set. Any PK concentrations or PK parameters excluded from the PK Analysis Set will be listed and flagged.

Pharmacokinetic concentrations will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory or clinical laboratory. Actual elapsed sample collection times will be analyzed unrounded (maximum of 14 significant digits), but will be rounded to two decimal places with units of hours for reporting purposes in by-subject listings.

Pharmacokinetic parameters will be analyzed unrounded, but will be rounded to 3 significant digits for reporting, except for parameters directly obtained from the source data (such as $C_{max}$) which will be reported with the same precision as the source data, and $t_{max}$ which will be reported to 2 decimal places. In export datasets, as well as in the SDTM PP/XD domain, PK/PD parameters will be provided with full precision, and will not be rounded.

**Presentation of PK Blood Concentrations**

M5717 PK whole blood concentration data including dried blood spot assay concentrations will be descriptively summarized using: number of non-missing observations (N), arithmetic mean (Mean), SD, coefficient of variation (CV%), Min, Median, and Max.

Descriptive statistics of whole blood concentration data including dried blood spot assay concentrations will be calculated using values with the same precision as the source data, and rounded for reporting purposes only. The following PK conventions will be applied when reporting descriptive statistics:

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

**Presentation of PK Parameters**

Calculated PK parameters will be descriptively summarized using: N, Mean, SD, CV%, Min, Median, Max, geometric mean (GeoMean), the geometric coefficient of variation (GeoCV%) and the lower and upper bounds of the 95% confidence interval (CI) for the GeoMean (LCI 95% GM, UCI 95% GM). GeoMean, GeoCV, LCI 95% GM, and UCI 95% GM will not be presented for $t_{max}$.

Descriptive statistics of PK parameter data will be calculated using full precision values, and rounded for reporting purposes only.

The following conventions will be applied when reporting descriptive statistics of PK parameter data, except for $t_{max}$ which will use the same level of decimal precision (instead of significant digits) as specified below:

| | |
|---|---|
| Means, Min, Median, Max, GeoMean, 95% CI: | 3 significant digits |
| SD: | 4 significant digits |
| CV%, GeoCV%: | 1 decimal place |

**Statistical Analysis**

All PK whole blood concentrations including dried blood spot assay concentrations, and whole blood PK parameters will be descriptively summarized by trial part, analyte, and dose group as described above. A listing of PK blood sample collection times as well as derived sampling time deviations will also be provided.

PK urine and fecal sample collection start and stop times, and urine volumes and fecal weights will be listed.

Individual whole blood concentration-time profiles by trial part, analyte, and dose group will be created using the actual time points and the numeric concentration data. These figures will include plots of all subjects in the same dose group on the same plot (spaghetti plots), as well as separate plots for individual subjects (by-subject plots). Arithmetic mean whole blood concentration-time profiles by trial part, analyte, and dose group will be provided using nominal time points and the numeric concentration data. All concentration-time plots for PK data will be presented both on a linear and on a semi-logarithmic scale. Mean plots will include SD error bars when plotted on a linear scale.

Linear scatter plots of individual and geometric mean values of non-normalized and dose-normalized parameters [$AUC_{0-\infty}$, $AUC_{0-t}$, $AUC_{0-144h}$, and $C_{max}$] versus M5717 dose (on continuous scale) will be prepared, as appropriate. Box plots of the dose-normalized parameters versus M5717 dose (on continuous scale) will be prepared. When applicable, parameters from Part A and Part C will be combined on the same plot (for scatter plots, different symbols will be used for data from the different study parts). Otherwise, plots will be prepared separately by trial part, as applicable.

The analysis of dose proportionality of single-dose PK parameters of M5717 will be quantified as part of an exploratory analysis using the power model on the original parameters ($\ln[\text{PK parameter}] = \alpha + \beta \times \ln[\text{dose}]$). This analysis will be based on $AUC_{0-\infty}$, $AUC_{0-t}$, $AUC_{0-144h}$, and $C_{max}$ in Part A and Part C. The intercept $\alpha$ and the slope $\beta$ together with 90% CIs will be estimated and presented. A p-value testing whether $\beta = 1$ will also be presented. For a given parameter, a minimum of 3 values must be available for a dose level, for that dose level to be included in the dose proportionality analysis.

A listing of the PK blood sample collection times for the DBS assay (for samples collected from subjects in Cohorts 1 and 2 of Part C) as well as derived sampling time deviations will be provided. A correlation analysis of DBS concentrations versus corresponding whole blood concentrations measured at the same nominal time will be performed. The concentration data will be log-transformed for the analysis. The estimate for correlation coefficient (r) and p-value testing whether $r = 0$ will be presented.

### 16.1.4 Population Pharmacokinetic Analysis

The PK and covariate data from this study will be analyzed jointly with data from other studies by nonlinear mixed effect approach in order to describe the PK concentration time profile, to identify covariates explaining (part of) the between subject PK variability, and to estimate the residual PK variability.

The population PK analysis plan will be prepared separately and the results will be reported separately from the CSR.

## 16.2 Pharmacodynamics (Part C)

Pharmacodynamic data will be collected in Part C only. All statistical analyses and descriptive summaries of PD data will be performed on the PD Analysis Set.

### 16.2.1 Statistical Analysis of Pharmacodynamic Parameters

The rational, methodology, analysis, and results about PD parameters measuring and estimating parasite clearance activities, concentrations, and times needed to meet various treatment targets will be described, performed, updated (as appropriate), and reported separately.

The PD parameters of interest, as defined in the Clinical Study Protocol, are as follows:

CCI

The parameters MIC and MPC may be derived in the PK/PD modeling (Section 16.2.3).

### 16.2.2 Statistical Summary of Pharmacodynamic Measurements

The parasitemia data will be descriptively summarized by dose group and measurement time.

Individual parasitemia-time profiles by dose group will be created using the actual measurement time points and the numeric parasitemia data (ie, geometric mean of the subject's replicates, at each time point). Arithmetic mean parasitemia-time profiles by dose group will also be provided using nominal time points. All parasitemia-time plots will be presented on a semi-logarithmic scale.

Overlay plots of individual parasitemia-time profiles (on semi-logarithmic scale) and whole blood concentration-time profiles (on linear scale) will be provided. Overlay plots of arithmetic mean parasitemia-time profiles (on semi-logarithmic scale) and arithmetic mean whole blood concentration-time profiles (on linear scale) will also be provided by dose group.

Any parasitemia data excluded from the PD Analysis Set will be listed and flagged. Additional statistical summaries and presentations of the PD concentration data would be described and reported separately.

### 16.2.3 PK/PD Modeling

The methodology for PK/PD modeling will be defined in a separate analysis plan and will be reported in a PK/PD modeling report separated from the CSR.

CCI [redacted]

CCI [redacted]

# 17 References

There are no references.

## ELECTRONIC SIGNATURES

## Document: ctp-ms201618-0013-iap-v2-0

| Signed By | Event Name | Meaning of Signature | Server Date (dd-MMM-yyyy HH:mm 'GMT'Z) |
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| PPD | Task Completed (Approval eSign): Approved | Business Approval | 14-May-2019 07:46 |
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