Integrated Analysis Plan

Clinical Study Protocol Identification No.	MS201618-0003
Title	A Phase Ib, Randomized, Double-Blind, Placebo Controlled, Sequential Study of Single Oral Doses of M5717 to Explore the Chemoprophylactic Activity of M5717 in a Controlled Plasmodium falciparum Sporozoite Challenge Model in Healthy Participants
Study Phase	Ib
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Approval Page

Integrated Analysis Plan: MS201618-0003

A Phase Ib, Randomized, Double-Blind, Placebo Controlled, Sequential Study of Single Oral Doses of M5717 to Explore the Chemoprophylactic Activity of M5717 in a Controlled Plasmodium falciparum Sporozoite Challenge Model in Healthy Participants

"Approval of this IAP by all Merck Data Analysis Responsible is documented within ELDORADO. With the approval within ELDORADO, the Merck responsible for each of the analysis also takes responsibility that all reviewers' comments are addressed adequately".

Merck responsible	Date	Signature
PPD , Biostatistics PPD		

1 Table of Contents

2 List of Abbreviations and Definition of Terms

ADaM	Analysis Data Model
AE	Adverse Event
AUC	Area Under the Plasma Concentration-Time Curve
CI	Confidence Interval
CM	Concomitant Medication
C_{max}	Maximum blood concentration observed
CRO	Contract Research Organization
CSR	Clinical Study Report
CV%	Percentage coefficient of variation
DMP	Data Management Plan
DVI	Direct Intravenous Inoculation
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FU	Follow-up
GM/GeoMean	Geometric Mean
IAP	Integrated Analysis Plan
ICH	International Council for Harmonization
ICH	International Conference on Harmonization
ITT	Intention-To-Treat Analysis Population
KM	Kaplan-Meier
LCI	Lower Limit of the Confidence Interval
LLOQ	Lower Level of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MH	Medical History
ND	Not Determined
PD	Pharmacodynamics
PfSPZ	Plasmodium falciparum Sporozoite
PK	Pharmacokinetics
PKP	Pharmacokinetic Analysis Population
PP	Per Protocol Analysis Population
PR	Pulse Rate

PT	Preferred Terms
Q1	First Quartile
Q3	Third Quartile
qPCR	Quantitative Polymerase Chain Reaction
SAE	Serious Adverse Event
SAF	Safety Analysis Population
SCR	Screening Analysis Population
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SMC	Safety Monitoring Committee
SoA	Schedule of Activities
SOC	System Organ Class
TEAEs	Treatment Emergent Adverse Events
TLF	Table, Listings and Figures
t_{max}	Time when C_{max} is Observed
UCI	Upper Limit of the Confidence Interval
WHO-DD	World Health Organization Drug Dictionary
WONCBP	Women of Non-Childbearing Potential

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	12 March 2021	PPD	Initial document

4 Purpose of the Integrated Analysis Plan

The purpose of this IAP is to document technical and detailed specifications for the primary, secondary as well as exploratory analysis of data collected for protocol MS2001618-0003. 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 upon section 9 (Statistical considerations) of the study protocol and protocol amendments and is prepared in compliance with ICH E9. All efficacy analyses will be performed on the Per-Protocol Analysis population.

5 Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)	IAP section
Primary		
To assess chemoprophylactic activity of single oral doses of M5717 administered after DVI of Plasmodium falciparum sporozoites (PfSPZ) challenge in healthy participants.	Response endpoints: ➢ Number of participants over time with positive parasitemia defined as first positive qPCR outcome equal or greater than 100 asexual parasites per mL of blood within 28 days of PfSPZ challenge ➢ Time to parasitemia, defined as time from PfSPZ DVI to the first qPCR outcome equal or greater than 100 asexual parasites per mL of blood (time frame: number of days from PfSPZ DVI challenge to positive parasitemia, or 28 days) ➢ Number of participants with documented blood stage parasite growth, defined as an increase of qPCR measured asexual parasites per mL compared to the first parasitemia measurement, within 28 days of PfSPZ DVI ➢ Clinical symptoms of malaria using the Malaria Clinical Score.	14.1.1
To explore the dose-exposure-response relationship of a single oral dose of M5717 administered after DVI of PfSPZ challenge in healthy participants.	Dose-exposure-response relationship: ➢ Selected pharmacokinetic (PK) endpoints/ concentrations (e.g. AUC_{0-24}, AUC_{0-168}, C_{24}, C_{168}) and pharmacodynamic (PD) endpoints (cured/not-cured) will be used for PK/PD modeling approaches.	16.2
Secondary		

Objectives	Endpoints (Outcome Measures)	IAP section
To evaluate the safety and tolerability of single, oral doses of M5717 in healthy participants following infection with PfSPZ challenge	➢ Nature, incidence, frequency, severity of adverse events (AEs)/ serious adverse events (SAEs), and relationship to the study intervention ➢ Incidence of clinically significant changes and abnormalities in safety laboratory parameters (hematology, coagulation, biochemistry [specifically alanine aminotransferase (ALT) and aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin (total)], and urinalysis) ➢ Incidence of clinically significant changes and abnormalities in vital signs and 12 lead electrocardiogram (ECG).	15
To investigate the PK of M5717 after administration of single, oral doses in healthy participants following infection with PfSPZ	Exposure endpoints: ➢ Concentration-time curve for M5717 after single-dose administration ➢ Pharmacokinetic parameters of M5717 such as $AUC_{0-\infty}$, $AUC_{0-tlast}$, AUC_{0-24}, AUC_{0-168}, C_{max}, C_{24}, C_{168}, t_{max}, $t_{1/2}$, λ_z, CL/f and $V_{z/f}$.	16.1
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6 Overview of Planned Analyses

The SMC was established before enrollment of the first participant. The SMC will review the data after each cohort is completed, and decide on the dose, dose regimen, and number of participants for the next cohort as per protocol. Details of the procedure and analyses are provided in the SMC charter version 1.0, dated 31 October 2019 and SMC statistical analysis plan version 2.0, dated 05 Mar 2021.

All final, planned analyses identified in the Clinical Study Protocol and this Integrated Analysis Plan will be performed only after the last participant has completed the last visit, i.e., Follow Up/End of Study visit, with all study data inhouse, all data queries resolved, and the database locked.

Statistical analyses will be performed based on CDISC SDTM as well as ADaM data.

A data review meeting will be held prior to any database lock. In addition, no database can be locked, and no randomization code should be unblinded until this IAP has been approved, please refer to the latest version of unblinded plan for more details.

7 Changes to the Planned Analyses in the Clinical Study Protocol

The definition of cured/not cured participants has been updated as follows:

- Cured: Negative qPCR outcome throughout the study period are referred as cured. A participant with a solitary (single) positive qPCR that is not confirmable in subsequent qPCR tests and remains < 100 /mL and not used rescue medication within 28 days of PfSPZ challenge is also to be classified as cured.
- Not-cured: Participants with documented blood stage parasite growth defined as an increase of qPCR measured asexual parasites per mL compared to the first positive parasitemia measurement (equal or greater than 100 asexual parasites per mL of blood) within 28 days of PfSPZ challenge or if a participant receives rescue medication within 28 days of PfSPZ challenge are referred to as not-cured.

8 Analysis Populations and Subgroups

8.1 Definition of Analysis Populations

The final decision to exclude participants from any analysis population will be made during a blinded data review meeting prior to database lock and unblinding.

Screening Analysis Population (SCR)

All participants who provided informed consent, regardless of the participant's randomization and study intervention status in the study.

Intention-To-Treat Analysis Population (ITT)

All participants, who were randomized to study intervention (M5717 or Placebo). Analyses performed on the ITT population will consider participants' allocation to study intervention groups as randomized.

Safety Analysis Population (SAF)

All ITT participants, who have been inoculated using a DVI of PfSPZ and who were administered one dose of study intervention (M5717 or placebo).

All Safety analyses will be based on this analysis set. Analyses will consider participants as treated.

Per Protocol Analysis Population (PP)

All SAF participants who comply with the protocol and meet no criteria that could impact the proper evaluation of key objectives of the study (as mentioned in this Integrated Analysis Plan section 5 and approved at the Blind Data Review Meeting). Participants who meet one of the following criteria will be excluded from the PP population:

- Incorrect study intervention group allocation, different to assignment at randomization.

All Efficacy analyses will be based on this analysis set.

Pharmacokinetic Analysis Population (PK)

All participants, who receive one dose of M5717, have no clinically important protocol deviations or important events affecting PK, and provide at least one measurable postdose concentration. Participants will be analyzed per the actual study intervention they received. All PK analyses will be based on the PK analysis set.

Note: Important events which are affecting the PK will be identified on a case by case basis.

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

	Analysis Population				
Analyses	**Screening Analysis Population (SCR)**	**Intention-To-Treat Analysis Population (ITT)**	**Safety Analysis Population (SAF)**	**Per Protocol Analysis Population (PP)**	**Pharmacokinetic Analysis Population (PK)**
Disposition of Participants and Discontinuations	✓				
Important Protocol Deviations		✓			
Demographics and Other Baseline Characteristics		✓	✓		
Medical History			✓		
Previous or Concomitant Medications/Procedures			✓		
Study Treatment: Compliance and Exposure		✓			
Primary Efficacy Analysis (Positive Parasitemia, Time to Parasitemia, Documented blood stage parasite growth and Malaria Score)				✓	
Safety and Tolerability (Adverse Events, Clinical Laboratory Evaluation, Vital Signs, 12 Lead Electrocardiogram (ECG) and Physical Examination)			✓		
Pharmacokinetics (PK)					✓
PK/PD-exposure-relationship modelling			✓		

8.2 Subgroup Definition and Parameterization

Not Applicable.

9 General Specifications for Data Analyses

Unless otherwise indicated, all the analyses summary table will be presented by pooled placebo, M5717 dose groups and its total and overall total. Cohort 1-4 i.e. Early Liver Stage will be combinedly presented and analyzed. Cohort 5 i.e. Late Liver Stage will be presented and analyzed separately.

The Treatment will be labeled as mentioned below:

- Pooled Placebo
- M5717 200 mg

- M5717 100 mg
- M5717 60 mg
- M5717 30 mg
- M5717 xxx mg
- All M5717 Doses
- Overall= Pooled Placebo + All M5717

The listings will be presented by treatment and participants. All participants will be included in individual participant data listings. All derived data will also be listed.

No formal statistical hypothesis testing will be performed. Missing data will not be imputed. 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.

Study intervention groups are defined and labelled as M5717 xxx mg and Placebo.

9.1 Presentation of continuous and qualitative variables

Unless otherwise specified, the below mentioned continuous variables will be summarized using descriptive statistics, i.e.

- number of non-missing observations,
- mean, standard deviation,
- median, 25th percentile, 75th percentile (Q1, Q3),
- minimum and maximum.

Unless otherwise specified, the qualitative variables will be summarized by frequencies and percentages.

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

For reporting the descriptive statistics “Merck BOA-General Output Specification” guideline will be followed.

For the creating the mock-shells “Merck BOA TLFs Template” will be followed

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

The compiled final file will be presented which include overall analysis in PDF format with TOC for listing and table/figures. The single output files of Table, Listing and Figures will be provided for overall final analysis in RTF and PDF files using the SAS® Output Delivery System (ODS).

9.2 Presentation of Study Visits

The study analysis visits for early and late liver stage, i.e., cohort 1-5 will be presented as mentioned below:

- For analyses, for all participants: Study Day = Study Intervention Day = Day 1 for both scenarios Screening (Early Liver Stage: Study Day -28 to -2; Late Liver stage: Study Day -33 to -6
- Analysis visits will be presented in table/listings/figures for baseline visit as "Baseline" and for remaining visits as "Study Day X" format.
- End of the Study visit will be presented as "End of the Study

For the PK Data analysis, schedule and actual timepoints will be presented in table/listings/figures as mentioned below,

- Pre-dose
- x

Here, Pre-dose means 0-hour timepoint before administration of study intervention (M5717 or Placebo) and for remaining timepoints, X represents the time in hours. For example: 0.5.

9.3 Definition of Baseline and Change from Baseline

The last non-missing measurement prior to the study intervention (M5717 or Placebo). administration, including scheduled and unscheduled results (if necessary, Example, for laboratory data when the re-test is needed, etc.) will serve as the baseline measurement.

Change from baseline = visit value – baseline value

Note: If baseline observation is missing then respective participant's change from baseline will not be calculated.

9.4 Definition of Duration and 'time since' Variables

Durations in days will be calculated by the difference of start and stop date + 1 (e.g. time to parasitemia (days) = date of first qPCR outcome equal or greater than 100 asexual parasites per mL of blood – date of PfSPZ DVI + 1) if not otherwise specified.

The time since an event (e.g. time since first diagnosis) will be calculated as reference date minus date of event.

9.5 Definition of End of the Study

A participant has completed the study if he/she has completed all study parts, including the last study visit (End of Study visit).

The end of the study is defined as the date of the last visit of the last participant.

9.6 Imputation of Missing Data

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

In all participant data listings, imputed values will be presented, and imputed information will be flagged.

Missing statistics, e.g. when they cannot be calculated, should be presented as not determined. "nd". For example, if n=1, the measure of variability (SD) cannot be computed and should be presented as "nd" and if n=0 then all the summary statistics left blank.

If required for an analysis, incomplete start and stop date (as appropriate) fields will be imputed. The whole missing date will not be imputed for this study and only partial date imputation will be performed. Conventions pertaining to partial dates are presented below:

Adverse events	Partial AE start and stop dates will be imputed as follows: Imputation for AE start date: • If AE start day is missing and AE start month = Treatment start month and AE start year = treatment start year, then AE start day= minimum of (treatment start day and AE end day) Otherwise AE start day=01 • If AE start day and month is missing and AE start year = treatment start year, then AE start day and month = minimum of (treatment start day and month or AE stop day and month) Otherwise AE start day and month = "01 Jan" • For missing AE start day, month, and year no imputation will be performed. Imputation for AE stop date: • If AE stop day is missing and AE stop month = study conclusion month and AE stop year =study conclusion year, then AE stop day =study conclusion day Otherwise AE stop Day = last day of respective month • If AE stop day and month is missing and AE stop year =study conclusion year, then AE stop day and month= study conclusion day and month Otherwise AE stop day = last day of respective month and AE stop month = last month of the year • For missing stop day, month, and year no imputation will be performed.

9.7 Software(s)

- Non-compartmental computation of PK parameters will be performed using the computer program Phoenix® WinNonlin® version 6.4, or higher (Certara, L.P., 1699 S Hanley Road, St Louis, MO 63144, USA).

- The statistical software to be used is SAS® (Statistical Analysis System, SAS-Institute, Cary, NC, USA, windows version 9.1 or higher).
- PK/PD modeling will be performed using NONMEM 7. (version 7.3.0 or higher) and/or R 3.5.1 or higher.

10 Study Participants

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

10.1 Disposition of Participants and Discontinuations

- Total number of screened participants (i.e., participants who gave informed consent).
- Number of participants who discontinued from the study prior to randomization (as applicable), with reason of discontinuation (including COVID-19-related and COVID-19-non-related).
- Number of randomized participants (use as denominator for percentages calculation for the categories below)
- Number of participants who received DVI
- Number of randomized participants who did not receive dose (as applicable)
- Number of treated participants
- Number of treated participants who completed the study
- Number of treated participants who discontinued the study with the reason of discontinuation (including COVID-19-related and COVID-19-non-related)
- Number of participants in the SCR, ITT, SAF, PP and PK analysis population.

The number and percentage of participants in each of the above disposition categories will be presented in table and corresponding individual listings for the study termination status, study entry (including screening failure), randomization and discontinued participants with their reason for withdrawal will be presented.

10.2 Protocol Deviations / Exclusion from Analysis Populations

10.2.1 Important Protocol Deviations

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

Important protocol deviations included but not limited:

- Participants that are dosed on the study despite not satisfying the inclusion or meeting the exclusion criteria, i.e. any inclusion/exclusion criteria violations.
- Participants that develop withdrawal criteria whilst on the study but are not withdrawn
- Participants that receive an excluded concomitant medication
- Deviation from Good Clinical Practice (GCP)
- PK Samples and assessments obtained outside the allowed time window (see Table 5 in protocol) from dosing will be captured as a minor protocol deviation, if the exact time of the assessment/sample collection is noted on the source document and data collection tool (e.g., eCRF).

Important protocol deviations documented in the SDTM DV dataset whether identified through sites monitoring, medical review or programming.

The listing of important protocol deviations by treatment, participant and date of deviation, will be provided based on the ITT analysis population.

Specific to PK:
Clinically important protocol deviations or important events that might have an effect on PK include, but may not be limited to and will be identified on case-by case basis, the following:

- Adverse events, diarrhea etc. (these instances will be discussed on a case-by case basis)
- Vomiting after administration following oral dosing (these instances will be discussed in alignment with applicable regulatory guidelines on a case-by case basis)
- Sample processing errors that may lead to inaccurate bioanalytical results
- Inaccurate dosing or dosing errors (e.g. dose administration delayed, dose change or missed doses)
- Pre-dose sample collected after the actual start of dosing
- Concomitant medication violations

Should one or more of these events be available at the Data Review Meeting, its implication for PK evaluation will be discussed and agreed amongst relevant study team members (e.g. Sponsor Clinical Pharmacology/Biostatistics/Clinical Pharmacokinetics & Pharmacodynamics team representative).

10.2.2 Reasons Leading to the Exclusion from an Analysis Population

For participants excluded from the PP, PK analysis population, the reasons for exclusion will be listed by the SAF analysis population:

- Listing of reasons of exclusion from analysis population and which contain the participants included in respective analysis population (yes/no) and respective analysis population exclusion reason.

11 Demographics and Other Baseline Characteristics

11.1 Demographics

The below mentioned demographic characteristics will be summarized and listed as appropriate from the Screening/Baseline Visit eCRF pages.

- Sex: male, female, undifferentiated
- Race: white, black or African American, Asian, American Indian or Alaska Native, native hawaiian or pacific islander, not collected at site, other

  Note: "Multiple" Category will also be added for race variable in the table.
- Ethnicity: hispanic or latino, not hispanic or latino
- Year of birth
- Age (in years) at screening
- Weight (kg) at screening
- Height (cm) at screening
- BMI (kg/m2) at screening
- Serum Pregnancy test

The demographic characteristics table will be presented, and listings will be presented for ITT and SAF analysis population.

11.2 Medical History

The medical history will be captured from the "Medical History" eCRF page, using the MedDRA, version as mentioned in the Data Management Plan (DMP).

The listings will be presented by treatment, participant, start date of medical history and alphabetically for primary System organ class and preferred term within each primary system organ class for SAF analysis population.

12 Previous or Concomitant Medications/Procedures

Previous medications defined as, any medication discontinued prior to the IMP administration (i.e. start and end date less than the IMP administration date.

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

All the previous and concomitant medication will be listed by treatment, participants and alphabetically Anatomical Therapeutic Chemical (ATC) term 2nd level and preferred term using SAF analysis population.

Concomitant Procedures:

All Concomitant Procedures, which were undertaken any time on trial (if any), will be listed according to the eCRF page "Concomitant Procedure" using SAF analysis population.

- Concomitant procedures will be listed by treatment, participants, and alphabetically verbatim term

13 Study Treatment: Compliance and Exposure

The IMP will be administered at the study site under supervision. The administration of IMP will be listed by treatment, participants and date of IMP administration using ITT analysis populations.

14 Efficacy Analyses

14.1 Primary Analysis

Analysis (Analysis Population)	Derivation	Statistical Analysis Methods	Missing data handling
Primary endpoint: Number of participants over time with positive parasitemia defined as first positive qPCR outcome equal or greater than 100 asexual parasites per mL of blood within 28 days of PfSPZ challenge			
Primary Analysis Population: PP	Positive Parasitemia is defined as first positive qPCR result (aPf/mL) outcome ≥ 100 asexual parasites per mL of blood. The qPCR results (aPf/mL) will be taken from the eCRF "Parasitemia by qPCR" page.	No hypothesis testing will be performed. The response is binary: (Response= 1): if the first positive qPCR outcome equal or greater than 100 asexual parasites per mL of blood within 28 days of PfSPZ challenge. Otherwise, Response = 0. The number and proportion (%) of participants with positive parasitemia and the exact 95 % confidence interval of the proportion (%) of participants based on Clopper Pearson Method will be presented by each M5717 doses and Pooled Placebo. The PROC FREQ procedure in SAS will be used with the appropriate BINOMIAL and EXACT statements for the proportion and corresponding 95% CIs.	No imputation will be done
Primary endpoint: Time to parasitemia, defined as time from PfSPZ DVI to the first qPCR outcome equal or greater than 100 asexual parasites per mL of blood (time frame: number of days from PfSPZ DVI challenge to positive parasitemia, or 28 days)			
Analysis Population: PP	Time to Parasitemia is defined as the time (i.e. number of days) from the PfSPZ DVI (i.e. Date of DVI PfSPZ) to the first qPCR outcome ≥ than 100 asexual parasites per mL of blood.	The summary statistics will be presented for the number of days (i.e. time) to first positive parasitemia.	No imputation will be done

Analysis (Analysis Population)	Derivation	Statistical Analysis Methods	Missing data handling
	The qPCR results (aPf/mL) will be taken from the eCRF "Parasitemia by qPCR" page.	PROC LIFETEST (SAS® Version 9.4 or above) will be used to analyze the response rates (cured vs. not cured). With the CENSOR variable, 1 is for censored observations (i.e. negative parasitemia); and 0 indicates the event occurred (positive parasitemia). For censored observations (CENSOR=1), the time variable value is the number of days from PfSPZ DVI to censoring, i.e., the minimum of the latest negative parasite measurement date and Day 28; for observations with CENSOR=0, the time variable value is the number of days from PfSPZ DVI to first positive parasitemia within Day 28. Kaplan-Meier curves and median estimates calculated using log-rank test (with 95% CI) of the time from DVI PfSPZ to positive parasitemia will be presented and compared by each M5717 doses versus Pooled Placebo. Spaghetti plots will be created based on qPCR data for each M5717 dose versus Pooled Placebo.	
Primary endpoint: Number of participants with documented blood stage parasite growth, defined as an increase of qPCR measured asexual parasites per mL compared to the first parasitemia measurement, within 28 days of PfSPZ DVI			
Analysis Population: PP	Documented blood stage parasite growth is defined as increase of qPCR measured asexual parasites per mL compared to the first parasitemia measurement (i.e. Date of DVI PfSPZ). The qPCR results (aPf/mL) will be taken from the eCRF "Parasitemia by qPCR" page.	No hypothesis testing will be performed. The response is binary: Response= 1: if Increase of qPCR measured asexual parasites per mL compared to the first parasitemia measurement within 28 days of PfSPZ DVI. Othewise, Response = 0 The number and proportion (%) of participants with documented blood stage parasite growth and the exact 95 % confidence interval of the proportion (%) based on Clopper Pearson Method will be presented by each M5717 doses and Pooled Placebo. The PROC FREQ procedure in SAS will be used with the appropriate BINOMIAL and EXACT statements for the proportion and corresponding 95% CIs.	No imputation will be done

Analysis (Analysis Population)	Derivation	Statistical Analysis Methods	Missing data handling
Primary endpoint: Overall Cured/Not Cured Status:			
Analysis Population: PP	The qPCR results (aPf/mL) will be taken from the eCRF "Parasitemia by qPCR" page.	The response is binary: Cured= 1: Negative qPCR outcome throughout the study period are referred as cured. A participant with a solitary (single) positive qPCR that is not confirmable in subsequent qPCR tests and remains < 100 /mL and not used rescue medication within 28 days of PfSPZ challenge is also to be classified as cured. Not Cured = 0: Participants with documented blood stage parasite growth defined as an increase of qPCR measured asexual parasites per mL compared to the first positive parasitemia measurement (equal or greater than 100 asexual parasites per mL of blood) within 28 days of PfSPZ challenge or if a participant receives rescue medication within 28 days of PfSPZ challenge are referred to as not-cured. The number (%) of participants with cured/ not cured status and the exact 95 % confidence interval of the proportion (%) of cured participants based on Clopper Pearson Method will be presented by each M5717 doses and Pooled Placebo. The PROC FREQ procedure in SAS will be used with the appropriate BINOMIAL and EXACT statements for the proportion and corresponding 95% CIs.	No imputation will be done

Analysis (Analysis Population)	Derivation	Statistical Analysis Methods	Missing data handling
Primary endpoint: Clinical symptoms of malaria using the Malaria Clinical Score.			
Analysis Population: PP	The list of malaria symptoms for calculating the malaria clinical score is provided (Refer to the protocol Appendix 6). Each observed clinical symptom of malaria will have below four categories: • Absent (0) • Mild (1) • Moderate (2) • Severe (3) The malaria clinical score will be calculated using the sum of all observed symptoms clinical categories and the maximum malaria clinical score is 42. The Malaria Clinical score will be taken from the "Malaria Clinical Score Assessment" eCRF page.	The below mentioned summary will be presented for the malaria clinical score: • By symptoms (i.e., for each symptoms): number and percentage of participants within each category (absent, mild, moderate, severe) by visit. • Total Score: Descriptive statistics by visit. The listing will be presented.	No imputation will be done
Primary endpoint: Dose-exposure-response relationship of a single oral dose of M5717 administered after DVI of PfSPZ challenge, selected pharmacokinetic (PK) endpoints/ concentrations (e.g. AUC0-24, AUC0-168, C24, C168) and pharmacodynamic (PD) endpoints (cured/not-cured) will be used for PK/PD modeling approaches.			
Analysis Population: SAF	Refer to the section 16.2	Refer to the section 16.2	No imputation will be done

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15 Safety and Tolerability Analyses

The safety assessment is as follows,

- Adverse events (AEs)
- Safety laboratory parameters
- Vital signs
- 12-lead safety ECGs
- Physical Examination

Safety analyses will be done on the SAF analysis population.

15.1 Adverse Events

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, Version (refer the DMP for dictionary version). Details on AEs will be recorded on eCRF page "Adverse Events".

The AEs and SAEs reporting period for safety surveillance begins when the participant is initially included in the study (date of first signature of informed consent/date of first signature of first informed consent) and continues until the End of Study Visit.

Treatment-emergent adverse events (TEAE) are those events with onset date and time occurring on or after the treatment administration date or events that worsen after treatment administration date and time. Any AE occurring before the IMP administration 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.

Adverse events related to study treatment are those events with relationship to the investigations medicinal product is related based on the adverse event eCRF page.

The pre-treatment AEs, TEAEs and Serious TEAEs will be provided in the listing separately and sorted by treatment, participant, start date of adverse event and alphabetically for primary system organ class and preferred term within each primary system organ class.

Each participant will be counted only once within each SOC or PT. If a participant experiences more than one AE within a SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

For the analysis if required the incomplete date or date/time fields for the adverse events will be imputed as mentioned in the section 9.6 in this IAP.

15.1.1 All Adverse Events

The below overall summary of TEAEs table will include the number and percentage of participants with each of the following:

- TEAEs
- TEAEs, [by severity (Mild (Grade 1), Moderate (Grade 2) and Severe (Grade 3)]
- TEAEs related to study intervention (M5717 or Placebo)
- TEAEs related to study intervention (M5717 or Placebo), [by severity (Mild (Grade 1), Moderate (Grade 2) and Severe (Grade 3)]
- Serious TEAEs
- Non-Serious TEAEs
- Serious TEAEs related to study intervention (M5717 or Placebo)
- TEAEs leading to death
- TEAEs related to study intervention (M5717 or Placebo) leading to death
- TEAEs leading to study discontinuation

The below overall summary of AEs related to DVI table will include the number and percentage of participants with each of the following:

- AEs related to DVI
- AEs related to DVI, [by severity (Mild (Grade 1), Moderate (Grade 2) and Severe (Grade 3)]
- Serious AEs related to DVI

Note: For AEs related to DVI tables, all AEs related to DVI occurring before/after study intervention administration (M5717 or Placebo) will be considered.

The following summary tables will be provided for TEAEs and sorted by alphabetically for primary system organ class and preferred term within each primary system organ class along with statistics: number of participants, percentage, and number of events:

- TEAEs
- TEAEs related to study intervention (M5717 or Placebo)
- TEAEs by severity
- TEAEs related to study intervention (M5717 or Placebo) by severity
- TEAEs leading to subject withdrawal
- TEAEs leading to death
- TEAEs related to study intervention (M5717 or Placebo) leading to death

The following summary tables will be provided for AEs related to DVI and sorted by alphabetically for primary system organ class and preferred term within each primary system organ class along with statistics: number of participants, percentage, and number of events:

- AEs related to DVI

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

15.2.1 Deaths

The below mentioned deaths information will be tabulated from the "Death" page of CRFs and provided in the summary table.

- Number of Deaths
- Primary Reason of Death (Progressive disease and/or disease related condition, Event unrelated to study treatment, Unknown)

15.2.2 Serious Adverse Events

The following overall frequency tables will be prepared for serious treatment emergent serious adverse events (serious TEAEs) and sorted by alphabetically for primary system organ class and preferred term within each primary system organ class:

- Serious TEAEs
- Serious TEAEs by severity
- Serious TEAEs related to study intervention (M5717 or Placebo)
- Serious TEAEs related to study intervention (M5717 or Placebo) by severity

The listings of SAEs will also be provided.

15.3 Clinical Laboratory Evaluation

Clinical laboratory data will be taken from the Hematology, Biochemistry, Urinalysis and Coagulation) eCRF pages. The Safety laboratory data (including Hematology, Biochemistry, Urinalysis, Coagulation) will be summarized in table as absolute values and changes from baseline to each visit over time for quantitative data and for qualitative data as frequency and percentages as appropriate. Coagulation data will be captured on screening (Day -28 to -2/-6) visit only.

Box-and-whisker plots for the absolute change from baseline by visit, treatment M5717 doses and pooled placebo.

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.

All the clinical laboratory data will be provided in the listing and sorted by treatment, laboratory test, date of test and visits of each participants. the abnormal laboratory values outsides the normal ranges will be flagged in the data listings along with corresponding normal ranges Any out-of-range values that are identified by the investigator as being clinically significant will be shown in a data listing. Listings of abnormal test results (low and high) will be provided. For the allowed time windows for scheduled time points for the laboratory parameter see the protocol section 1.3 (Table 5).

The below mentioned clinical laboratory (Hematology, Coagulation, Biochemistry, Urinalysis) parameters will be used for analysis:

- Hematology:

  [Hemoglobin (mmol/L), Hematocrit (L/L), Erythrocytes (RBC) count (10^12/L), Reticulocytes (10^9/L), Platelet count (10^9/L), Mean Corpuscular Volume (MCV) (fL), Mean Corpuscular Hemoglobin (MCH) (fL), Mean Corpuscular Hemoglobin Concentration (MCHC) (mmol/L), Neutrophils (10^9/L), Lymphocytes (10^9/L), Monocytes (10^9/L), Eosinophils (10^9/L), Basophils (10^9/L)]

- Biochemistry:

  [Aspartate Aminotransferase (AST) (U/L), Alanine Aminotransferase (ALT) (U/L), Alkaline phosphatase (U/L), Gamma-glutamyl-transferase (GGT) (U/L), Lactate dehydrogenase (U/L), Creatine phosphokinase (CPK) (U/L), Total Protein (g/L), Albumin (g/L), Bilirubin (total) (µmol/L), hs Troponin T (ng/L), Amylase (U/L), Lipase (U/L), Uric acid (mmol/L), Blood Urea Nitrogen (mmol/L), Blood Urea Nitrogen (mmol/L), Creatinine (umol/L), Glucose (fasting) (mmol/L), Sodium (mmol/L), Potassium (mmol/L), Chloride (mmol/L), Calcium (mmol/L), Magnesium (mmol/L), Bicarbonate (mmol/L), Phosphate (mmol/L)]

- Urinalysis:

  [Urine Glucose (mmol/L), Urine Bilirubin, Urine Ketone (mmol/L), Urine Specific gravity, Urine Blood (ery/ul), Urine pH, Urine Protein (g/L), Urine Urobilinogen (umol/L), Urine nitrite, Urine leucocytes (leuco/ul), Urine - Erythrocytes (RBC), Urine - Leukocytes (WBC), Urine - Epithelial Cells, Urine – Bacteria, Urine – Crystals, Urine - Casts]

- Coagulation:

  [Prothrombin time (sec), Activated partial thromboplastin time (sec), International Normalized Ratio (INR) (Ratio)]

All the above laboratory parameters having lab original units as per eCRF and these units will be converted into Système International (SI) units at the time of programming. Both original units and SI units will be provided in the SDTM domain.

For all the safety laboratory results in case if we have < or > symbol with result value then < or > symbol will be removed and will use only the numeric result values. Example: If Hemoglobin (mmol/L): < 20 then in worse case scenario it will be considered as 20.

15.4 Vital Signs

Vital signs including Systolic blood pressure (mmHg), Diastolic blood pressure (mmHg), Pulse (beats/min), Respiratory rate (breaths/min) and Temperature (in C) will be assessed according to the trial schedule and taken from "Vital Signs" eCRF pages.

Vital signs parameters will be summarized absolute values and changes from baseline to each visit over time. The listing will be provided by treatment, vital signs parameter, date of test and visits of each participants and abnormal values will be flagged in the listing (Please use the section 18.2 (Appendix 2) reference ranges to identify the abnormal vital signs values).

For the allowed time windows for scheduled time points for the vital sign parameters see the protocol section 1.3 (Table 5).

15.5 12 Lead Electrocardiogram (ECG)

12-lead ECG including Heart rate (bpm), PR duration (msec), QRS duration (msec), QT duration (msec) and the results of ECG (i.e., normal, abnormal not clinically significant and abnormal clinically significant) will be assessed according to the trial schedule and taken from "12-lead ECG" eCRF page.

12-lead ECG parameters will be summarized absolute values and changes from baseline to each visit over time. The listing will be provided by treatment, 12-lead ECG parameter, date of test and visits of each participants and abnormal values will be flagged in the listing (Please use the section 18.2 Appendix 2 reference ranges to identify the abnormal 12-lead ECG values).

For the allowed time windows for scheduled time points for the 12-lead ECG parameters see the protocol section 1.3 (Table 5).

15.6 Physical Examination

The abnormal physical examination will be recorded as medical history and adverse event. For the physical examination data, no separate listing/table will be presented.

15.7 COVID-19 Impact

The listing will be presented COVID-19 related protocol deviations separately.

16 Analyses of Other Endpoints

16.1 Pharmacokinetics

Blood samples for measurement of M5717 concentrations in whole blood will be collected at the assigned time points as per protocol. Metabolite concentrations, as applicable, may also be measured in blood samples. Remaining samples collected for measurement of M5717 may also be used to evaluate metabolites or used for testing of bioanalytical standards.

Actual date and time of the PK sampling, as well as date/time of drug administration, will be recorded in the eCRF. Samples and assessments obtained outside the allowed time window See the protocol section 1.3 (Table 5) from dosing will be captured as a minor protocol deviation, if the exact time of the assessment/sample collection is noted on the source document and data collection tool (e.g., eCRF). If sample collection within or outside the allowed time window, then scheduled timepoints will be used at the time of analysis. For participants randomized to placebo treatment, no PK samples will be analyzed unless deemed necessary by the Investigator and/or Sponsor. Details on blood sample collection, preparation for processing, and shipment was specified in a separate Laboratory Manual (Latest version).

All the pharmacokinetic analysis will be based on the PK analysis population.

16.1.1 Descriptive Statistics of PK Concentration Data

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

Descriptive statistics will only be calculated for n>2 in which a measurement of <LLOQ represents a valid measurement and Values below the lower level of quantification (LLOQ) will be taken as zero for descriptive statistics of PK concentrations.

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.

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

- Mean, Min, Median, Max: 3 significant digits
- SD 4 significant digits
- CV%: 2 decimal places

16.1.2 Descriptive Statistics of PK Parameter Data

PK parameter data will be descriptively summarized using: number of non-missing observations (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median), maximum (Max), geometric mean (GeoMean), the geometric coefficient of variation (GeoCV) and the 95% confidence interval for the GeoMean (LCI 95% GM, UCI 95% GM). For time to reach maximum observed concentration (tmax), only n, Min, Median, and Max will be reported.

Descriptive statistics will only be calculated for a PK parameter when n>2.

PK parameters read directly from the measurements (i.e., Cmax) will be reported with the same precision as the source data. All other PK parameters will be reported to 3 significant figures. In export datasets, as well as in the Derived PP dataset for SMC, PK parameters will be provided

with full precision and will not be rounded. 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:

- Mean, Min, Median, Max, GeoMean, 95% CI: 3 significant digits
- SD: 4 significant digits
- CV%, GeoCV%: 2 decimal places

16.1.3 General Specifications for PK Concentration and PK Parameter Data Handling

Pre-dose samples which have been taken after the subsequent dosing with M5717 will be reported as protocol deviation. The resulting concentrations will be included in concentration listings but excluded from descriptive statistics of concentrations and from PK parameter estimation of the previous PK profile. This concentration could be included in the subsequent PK profile decided on a case-by case decision.

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

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.

Any PK concentrations or PK parameters excluded from summary statistics will be included in participant listings and flagged.

PK concentrations and PK parameters excluded from summary statistics will not be included in individual and mean figures. Mean plots will only contain averages when n>2.

16.1.4 Estimation of Pharmacokinetic Parameters

Plasma concentrations will be tabulated and summarized using descriptive statistics. PK parameters will be calculated if possible, as appropriate for the respective sampling schemes. All PK parameters will be calculated using standard non compartmental methods and the actual administered dose. Calculations will be performed using a validated software tool as described below.

The following PK parameters will be calculated, when appropriate:

Table 2 PK parameters

Symbol	Definition
$AUC_{0\text{-}tlast}$	Area under the blood concentration-time curve (AUC) from time zero to the last sampling time at which the concentration is at or above LLOQ, calculated according to the mixed log linear trapezoidal rule (i.e., linear up, log down)
$AUC_{0\text{-}\infty}$	The AUC from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at t_{last}, as estimated using the linear regression from λz determination. $AUC_{0\text{-}\infty} = AUC_{0\text{-}tlast} + C_{last}$ pred/ λz
$AUC_{0\text{-}24}$	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. The actual dosing interval calculated from CRF time data should not be used.
$AUC_{0\text{-}168}$	The AUC from time zero (= dosing time) to 168 hours post dose. Calculated using the mixed log linear trapezoidal rule (linear up, log down) using the nominal dosing interval. The actual dosing interval calculated from CRF time data should not be used.
C_{max}	Maximum blood concentration observed
C_{24}	Blood concentration at 24 hours
C_{168}	Blood concentration at 168 hours
t_{max}	Time to reach the maximum blood concentration (1st occurrence in case of multiple/identical C_{max} values)
$t_{1/2}$	Apparent terminal half-life, calculated as ln2/λz
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
CL/f	Total body clearance of drug from blood following oral administration, calculated as Dose/ $AUC_{0\text{-}\infty}$ The predicted $AUC_{0\text{-}\infty}$ should be used.
Vz/f	Apparent volume of distribution during the terminal phase following extravascular administration. The predicted $AUC_{0\text{-}\infty}$ should be used.

$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$.
$AUC_{0-tlast}$/ Dose	The Dose normalized AUC from time zero to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Normalized using the actual dose, using the formula $AUC_{0-tlast}$ /Dose.
$AUC_{0-\infty}$/Dose	The Dose normalized AUC from time zero extrapolated to infinity. Normalized using actual dose and $AUC_{0-\infty}$ using the formula $AUC_{0-\infty}$ /Dose.
C_{max}/Dose	Dose-normalized C_{max}

LLOQ=lower limit of quantification, CRF=case report form.

PK parameters will be evaluated and listed for all participants who provide sufficient concentration time data.

Estimation of Individual PK Parameters:

- Pharmacokinetic parameters will be calculated by TCD and overseen by the Clinical PK/PD Group of Quantitative Pharmacology, Merck Healthcare KGaA, Darmstadt, Germany, using standard non-compartmental methods and the actual administered dose. PK parameters will be calculated using the actual timepoint since dosing, given with a precision of 14 significant digits or the SAS format Best12. When the actual sampling time is missing, calculations will be performed using the scheduled time. Otherwise, there will be no further imputation of missing data.
- Non-compartmental computation of PK parameters will be performed using the computer program Phoenix® WinNonlin® version 6.4, or higher (Certara, L.P., 1699 S Hanley Road, St Louis, MO 63144, USA).
- The statistical software to be used is SAS® (Statistical Analysis System, SAS-Institute, Cary, NC, USA, windows version 9.1 or higher) may be used to produce tables, listings and figures, if appropriate.

16.1.5 Presentation of PK Concentration and PK Parameter Data

Listing of all the PK concentrations data and the PK parameter data by cohort/dose/participants will be provided using subject IDs.

Individual concentration versus time plots will be provided.

16.1.5.1 Listings and Tables

The following PK tables will be produced:

- Individual PK concentrations with descriptive statistics by time points and each cohort/dose and Overall (Sum of all cohort participants).
- Individual estimated PK parameters with descriptive statistics by PK parameters and each cohort/dose (treatment M5717) and Overall (Sum of all cohort participants).
- Individual dose normalized PK parameters with descriptive statistics by dose normalized PK parameters and each dose cohort (treatment M5717) and Overall (Sum of all cohort participants)

The PK concentration estimated PK parameters and dose normalized PK parameters will be presented.

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

16.1.5.2 Graphical Summaries and Individual plots (PK Analysis Population)

Individual concentration versus time plots; linear and semi-log; using the time points on x axis and concentration on y axis by participants and cohort.

Overlaid individual concentration versus time plots; linear and semi-log; using the time points on x axis and concentration on y axis by cohort.

Mean concentration time plots i.e. (Mean±SD concentration-time curves); linear and semi-log ; using the time on x axis and mean response ± SD for linear and only mean response for semi-log on y axis using scheduled (nominal) time points by cohort. Error bars should be included only in the linear plots.

Scatter Plots using subject IDs: For PK parameters: Cmax, C_{24}, C_{168}, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}168}$ and dose normalized PK parameters (AUC/Dose and Cmax/Dose) (including regression line not forced through 0), using the respective PK and dose-normalized PK parameter data on y axis and dose on x axis and with group by dose levels.

Boxplots for PK parameters (Cmax, C_{24}, C_{168}, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}168}$) and dose-normalized PK parameters ($AUC_{0\text{-}tlast}$/Dose, $AUC_{0\text{-}inf}$/Dose and Cmax/Dose), Using the respective PK and dose-normalized PK parameter data on y axis and dose on x axis with group by dose level.

16.2 Pharmacokinetics (PK) and Pharmacodynamics (PD) Relationships

The PK/PD modeling is a part of primary endpoint and will be used to explore the dose-exposure-response relationship of a single oral dose of M5717 administered after DVI of PfSPZ challenge in healthy participants. The analysis will be performed by OCCAMS and overseen by the Merck Pharmacometrician based on the SAF analysis population.

The influence of PK exposure metrics on response will be assessed using logistic regression.

The logistic regression model is as follows:

$$\text{Logit}(p) = \log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 * \text{PK exposure} + \beta_2 * X_2 + \beta_3 * X_3 + \ldots + \beta_n * X_n$$

Where,

P is the probability of response

β0 is the intercept, β1…βn are the regression coefficients for the n covariates (Xn)

PK exposure refers to different exposure metrics that will be assessed. The exposure metrics may also be parametrized as emax model, if allowed by the data.

The response here is binary, i.e., 1 (cured) or 0 (not cured) which will be identified as follows:

- Cured (response= 1): Negative qPCR outcome throughout the study period are referred as cured. A participant with a solitary (single) positive qPCR that is not confirmable in subsequent qPCR tests and remains < 100 /mL and not used rescue medication within 28 days of PfSPZ challenge is also to be classified as cured.
- Not-cured (response= 0): Participants with documented blood stage parasite growth defined as an increase of qPCR measured asexual parasites per mL compared to the first positive parasitemia measurement (defined as equal or greater than 100 asexual parasites per mL of blood) within 28 days of PfSPZ challenge or if a participant receives rescue medication within 28 days of PfSPZ challenge, are referred to as not-cured.

The PK/PD analysis will be performed utilizing logistic regression to model cured, i.e. response on PK exposure metrics AUC0-24, AUC0-168, C24, C168 etc. Additional details will be mentioned in a separate analysis plan. The results of these analysis will be reported in a separate report outside of clinical trial report.

17 References

Clinical Protocol Number: MS201618-0003, Version: 03 December 2020/4.0

Electronic case report form (eCRF): Version: 08 September 2020/4.0

ICH E9 Statistical Principles for Clinical Trials (September 1998)

COVID-19 Guidance on Statistical Methods: Version: 28 August 2020/2.0

18 Appendices

18.1 Appendix 1 – Planned analyses for SMC meetings

Refer to the SMC charter.

18.2 Appendix 2 – Vital Signs and 12-Lead ECG Reference Ranges

	Abnormal (NCS or CS)	Normal	Abnormal (NCS or CS)
Temperature			
Tympanic Temperature (°C)	< 35.4	35.4 – 37.8	> 37.8
Respiratory rate			
Resp Rate (breaths/min)	< 8	8-20	> 20
Pulse rate (supine, resting)			
Pulse Rate (bpm)	< 45	45 - 100	> 100
Blood pressure adults (18-65 years) (supine, resting)			
Systolic (mmHg)	< 90	90 - 140	> 140
Diastolic (mmHg)	< 50	50 - 90	> 90
ECG derived values (supine, resting)			
Heart Rate (bpm)	< 45	45 - 100	> 100
PR (msec)	< 120	120 - 200	> 200
QRS (msec)	N/A	< 120	≥ 120
QTcB/F (msec)	< 370	370 - 450 (M) 370 - 470 (F)	> 450 (M) > 470 (F)

ELECTRONIC SIGNATURES

Document: iap-ms201618-0003

Signed By	Event Name	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Task Completed (Approval eSign): Approved	Technical Approval	15-Mar-2021 14:01
PPD	Task Completed (Approval eSign): Approved	Technical Approval	16-Mar-2021 13:20
PPD	Task Completed (Approval eSign): Approved	Technical Approval	17-Mar-2021 08:31
PPD	Task Completed (Approval eSign): Approved	Technical Approval	19-Mar-2021 07:58