Clinical Trial Protocol

Clinical Trial Protocol Number	MS201618-0013
PPD	PPD
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
Phase	I
IND Number	Not Applicable
EudraCT Number	Not Applicable
Principal Investigator	PPD PPD PPD PPD Phone: PPD Mobile: PPD And PPD PPD PPD PPD Phone PPD Mobile: PPD Email: PPD
Funding Sponsor	Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany Medical Responsible: PPD Merck KGaA Frankfurter Strasse 250, F130/005, 64293 Darmstadt, Germany Phone: PPD Email: PPD

Local Sponsor	PPD PPD
Clinical Trial Protocol Version	17 December 2018 / Version 5.0 including Amendment 4
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[redacted]

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List of Abbreviations

CCI [redacted]	
ADME	Absorption, distribution, metabolism and excretion
AE(s)	Adverse event(s)
AESI(s)	Adverse event(s) of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the blood concentration-time curve
AUC_{0-t}	AUC from time zero to the last sampling time at which the concentration is at or above LLOQ
$AUC_{0-t,overall}$	AUC from time zero to the last sampling time at which the concentration is at or above LLOQ, over the entire multiple dosing period
$AUC_{0-t,overall}$/Dose	Dose-normalized $AUC_{0-t,overall}$
$AUC_{0-\infty}$	AUC from time zero extrapolated to infinity
$AUC_{0-\infty, overall}$	AUC from time zero extrapolated to infinity over the entire multiple dosing period
$AUC_{0-\infty,overall}$/Dose	Dose-normalized $AUC_{0-\infty,overall}$
$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$
AUC_{0-24h}	AUC from time zero to 24 hours
AUC_{0-24h}/Dose	Dose-normalized AUC_{0-24h}
AUC_{0-144h}	AUC from time zero to 144 hours
AUC_{0-144h}/Dose	Dose-normalized AUC_{0-144h}
$AUC_{0-144h,overall}$	AUC from time zero to 144 hours in Part B, ie, from time zero (dosing time) on Day 1 until 144 hours after the Day 1 dose
$AUC_{0-144h,overall}$/Dose	Dose-normalized $AUC_{0-144h,overall}$
BMI	Body mass index
CCI [redacted]	
BP	Blood pressure
C_{av}	Average concentration over the dosing interval
CI	Confidence interval
CL/f	Total body clearance of drug from blood following oral administration

$CL/f_{overall}$	Total body clearance of drug from blood following oral administration. This will be calculated over the entire dosing and PK sampling period in Part B
C_{max}	Maximum blood concentration observed
C_{max}/Dose	Dose-normalized C_{max}
C_{min}	Minimum blood concentration observed
CRO	Contract Research Organization
CV%	Coefficient of variation
CYP	Cytochrome P450
DBS	Dried blood spot
CCI [redacted]	
EC_{50}	Half maximal effective concentration
CCI [redacted]	
eCRF(s)	Electronic case report form(s)
ED	Efficacious dose(s)
eEF2	Eukaryotic translation elongation factor 2
E_{max}	The maximum observed effect
E_{tmax}	The time at which E_{max} is observed
F_e	Fraction(s) of dose excreted
FIH	First-in-Human
FSH	Follicle-stimulating hormone
G6PD	Glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
GDP	Guanosine diphosphate
GeoMean	Geometric mean
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GTP	Guanosine triphosphate
HDL	High-density lipoprotein
HED	Human equivalent dose
HIV	Human immunodeficiency virus

HREC	Human Research Ethics Committee
HRT	Hormone replacement therapy
IB	Investigator's Brochure
CCI	[redacted]
ICH	International Council for Harmonization
IEC(s)	Independent Ethics Committee(s)
IMP	Investigational medicinal product
In D1	Inoculum Day 1
In D1 – In D9	Day of Inoculum administration (In D1) to 9 days post administration of the Inoculum (In D9)
In D9	9 days post administration of the Inoculum
INR	International Normalized Ratio
IV	Intravenous
K_{in}	Production rate constant of zero order input
K_{out}	Elimination rate constant of first order input
λz	Terminal first order (elimination) rate constant
LOQ	Limit of quantification
LLOQ	Lower limit of quantification
LS	Least-squares
MAD	Multiple ascending dose(s)
MC	Monte-Carlo
MDMA	3,4-methylenedioxymethamphetamine
MIC	Minimal inhibitory concentration
MPC	Minimal parasiticidal concentration
mRNA	Messenger ribonucleic acid
MRSD	Maximum recommended starting dose
n	Number of nonmissing observation
NCE	New chemical entity
ND	Nondetectable/not detected
NOAEL	No-observed-adverse-effects-level
PCR	Polymerase chain reaction
PCT	Parasite clearance time

PCt½	The parasite clearance half-life, defined as the time needed for parasitemia to be reduced by half during the log-linear phase of parasite clearance.
CCI [redacted]	
PeEF2	Plasmodium eukaryotic translation elongation factor 2
CCI [redacted]	
PI	Principal Investigator
PICF(s)	Participant Information Consent Form(s)
PK	Pharmacokinetic(s)
PLD	Phospholipidosis
CCI [redacted]	
PPD [redacted]	
CCI [redacted]	
QTS	Qualitative Toxicity Scale
$R_{acc(AUC)}$	Accumulation ratio for $AUC_{0\text{-}24h}$, calculated in Part B as $AUC_{0\text{-}24h}$ on Day 3 divided by $AUC_{0\text{-}24h}$ on Day 1
$R_{acc(Cmax)}$	Accumulation ratio for C_{max}, calculated in Part B as C_{max} on Day 3 divided by C_{max} on Day 1
SAE(s)	Serious adverse event(s)
SAD	Single ascending dose(s)
SAP	Statistical analysis plan
SCID	Severe combined immunodeficient
SE	Standard error
SMC	Safety Monitoring Committee
TEAE(s)	Treatment-emergent adverse event(s)
TEM	Transmission electron microscopy
THC	Tetrahydrocannabinol
t_{max}	Time to reach the maximum blood concentration
$t_{>3\ ng/mL}$	Time above or equal to the predicted M5717 mouse MIC of 3 ng/mL

$t_{>10\ ng/mL}$	Time above or equal to the predicted M5717 mouse MPC of 10 ng/mL
$t_{½}$	Apparent terminal half-life
V_z/f	Apparent volume of distribution during the terminal phase following extravascular administration
$V_z/f_{,overall}$	Apparent volume of distribution during the terminal phase following extravascular administration. This will be calculated over the entire dosing and PK sampling period in Part B
ULN	Upper limit of normal
UV	Ultraviolet
WOCBP	Woman of childbearing potential
WNCBP	Woman/women of nonchildbearing potential

1 Synopsis

Clinical Trial Protocol Number	MS201618-0013
PPD	PPD
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
Trial Phase	I
IND Number	Not Applicable
FDA covered trial	No
EudraCT Number	Not Applicable
Principal Investigator	PPD Phone: PPD Mobile: PPD And PPD Phone PPD or PPD Mobile: PPD Email: PPD
Funding Sponsor	Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany Medical Responsible: PPD Merck KGaA Frankfurter Strasse 250, F130/005, 64293 Darmstadt, Germany Phone: PPD Email: PPD

Local Sponsor	PPD PPD
Trial site/country	PPD PPD
Local Ethics Committee	PPD Phone: PPD
Planned trial period (first subject in-last subject out)	August 2017 up to July 2019
Trial Registry	ClinicalTrials.gov

Objectives:

Part A

Primary

- To investigate the safety and tolerability of single ascending oral doses of M5717.

Secondary

- To investigate the pharmacokinetics (PK) of single ascending oral doses of M5717.

Part B (optional)

Primary

- To investigate the safety and tolerability of multiple (3-day) ascending oral doses of M5717.

Secondary

- To investigate the PK of multiple (3-day) ascending oral doses of M5717.

Part C

Primary

- To characterize the PK/pharmacodynamic (PD) relationship between M5717 PK and parasite clearance in healthy subjects following infection with P. falciparum blood stage parasites during the Induced Blood Stage Malaria (IBSM) challenge by assessment of the PK-to-parasite-reduction ratio (PRR) relationship.

Secondary

- 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: parasite clearance time (PCT), minimal inhibitory concentration (MIC), PCt½, MPC, lag time, and frequency of recrudescence
- To characterize the parasiticidal activity of M5717 on P. falciparum asexual blood stage parasites in the blood of healthy subjects in the IBSM challenge
- To evaluate the safety and tolerability of M5717 in healthy volunteers following infection with P. falciparum blood stage parasites during the IBSM challenge.

Methodology:

Part A

Part A is a double-blind, randomized, placebo-controlled, single ascending dose (SAD) investigation in cohorts of 8 healthy subjects with up to 11 dose levels. The trial will evaluate the safety, tolerability, and PK properties of escalating single doses of M5717 when administered to healthy men and women of nonchildbearing potential under fasted conditions.

Within each cohort, subjects will be randomly assigned to receive a single dose of M5717 or placebo in a ratio of 6:2, respectively. The placebo control will minimize bias. A 6:2 ratio of M5717 versus placebo is an accepted standard used in First-in-Human (FIH) trials.

A single dose of M5717 or matched placebo will be administered as oral capsule(s) (appropriate numbers of placebo, 10 mg, 50 mg, or 200 mg capsules) after at least 8 hours of fasting together with water on Day 1, followed by a 4-hour postdose fast. Water will be allowed up to 2 hours predose and again after 2 hours postdose. The number and strength of capsules to be administered at each dose will be detailed in the pharmacy manual.

The initial dose investigated was 50 mg. This was lower than the maximum recommended starting dose (MRSD) of 100 mg derived from the most sensitive no-observed-adverse-effects-level (NOAEL) with a safety factor of 10. This 50 mg dose was within the range of the initially predicted efficacious dose range, which had been estimated to be between 10 mg and 70 mg.

As this is a FIH trial, a sentinel dosing strategy will be employed for each dose cohort in the SAD and multiple ascending dose (MAD) parts. Under the discretion of the SMC, a sentinel cohort consisting of either 2 (1 active and 1 placebo) or 3 (2 active and 1 placebo) subjects will be dosed first. The Investigator will review blinded safety data up to at least 36 hours after dosing from these sentinel subjects to rule out any initial, severe acute reactions. Provided the safety data are supportive, the remaining 6 (5 active and 1 placebo) or 5 (4 active and 1 placebo) subjects, respectively, in the cohort will be randomized next.

No subject will be a member of more than 1 cohort in any part of the trial. After each cohort has completed 11 days of postdosing observation, the Safety Monitoring Committee (SMC) will evaluate the safety dosing and escalation sequence and make recommendations. The data obtained from each cohort will undergo a formal review by the SMC to confirm that it is reasonable to proceed with the next dose/cohort. A formal report of each cohort, consisting of the data evaluated and a summary of the decisions taken by the SMC, will be provided at the end of each review.

A Screening period will occur from Day -28 to Day -2. Subjects will be admitted to the trial site on Day -2 and will be resident at the trial site under medical supervision until discharge on Day 7. Subjects will need to report to the trial site (Day 9 and Day 11), and will be followed up by phone (Day 8 and Day 10) and will be required to send a photograph of their diary cards on those days. On Day -1, digital 12-lead electrocardiogram (ECG) recordings are included as a baseline for the intrasubject comparison on matching time points with the Day 1 recordings postdose over 24 hours, coinciding with the PK sampling time points, for thorough assessment of QT interval corrected for heart rate (QTc) to reduce expected variability. The digital 12-lead ECG based QTc analysis will only be performed after completion of the trial by an experienced, qualified, and certified cardiologist, provided the compound fulfills the expectation, and reported separately from the clinical trial report.

Follow-up visits will occur on Day 13, Day 15, Day 17, Day 22, and Day 33, and an End of Trial visit on Day 44 (± 2 days). In addition, subjects will be regularly contacted (approximately every 2 to 3 days) by telephone during their ambulatory period. Blood and urine samples will be collected for safety evaluation (hematology, biochemistry, coagulation, urinalysis, and CCI [redacted] and blood samples will be collected for PK analysis [redacted] y period (at time points indicated in the Schedule of Assessments).

The planned total duration of the trial for each subject in the SAD portion will be up to approximately 12 weeks (up to 4 weeks for Screening, 1 day for dosing, 1-week residency at the trial site [discharge on Day 7], and Follow-up through Day 44 [± 2 days]). An Early Termination visit will be conducted for subjects who withdraw, preferably performed around the Follow-up visit, due to the expected long half-life of the compound.

Part B

The MAD part of the trial is optional and will only be conducted if the observed PK profile does not allow administering of a tolerable single dose that will achieve an 8-day period with concentrations well above the predicted minimal parasiticidal concentration (MPC), ie, 10 ng/mL. This assessment will be based on characteristic PK parameters, in particular the elimination half-life, as computed by noncompartmental analysis, of the PK data from Part A. The decision will be made by the SMC following collection and review of the initial PK data and sufficient safety data from the first 2 cohorts of Part A.

Part B is a randomized, double-blind, placebo-controlled MAD trial and will evaluate the safety, tolerability, and PK of multiple oral doses (within ascending dose cohorts) of M5717 or placebo administered over 3 consecutive days. As for Part A, digital 12-lead ECG will be

recorded to allow thorough QTc analysis on matching time points during the day before dosing (baseline), Day 1, and up to 24 hours after the third dosing, evaluated and reported later separately from the clinical trial report.

Multiple ascending doses of M5717 oral CCI in capsules or matched placebo will be administered with water in a ratio of 6:2 after an overnight fast of at least 8 hours, once daily for 3 days (Day 1 to Day 3, inclusive), in a double-blinded fashion, followed by a 4-hour postdose fast. Water will be allowed up to 2 hours predose and again after 2 hours postdose.

Three MAD cohorts of 8 subjects each are planned in Part B. In each dose cohort, sentinel dosing as done in Part A will be included (2 subjects dosed on Day 1, the remaining 6 subjects dosed at least 48 hours later). The SMC will decide on the dosing and escalation sequence.

A Screening period will occur from Day -28 to Day -2. Subjects will be admitted to the trial site on Day -2 and will be resident in the trial site under medical supervision until discharge, which is planned after completion of all trial-related assessments on Day 7 at the discretion of the Investigator. Subjects will need to report to the trial site (Day 9 and Day 11), and will be followed up by phone (Day 8 and Day 10) and will be required to send a photograph of their diary cards on those days.

Follow-up visits will occur on Day 13, Day 15, Day 22, and Day 33, and an End of Trial visit on Day 44 (± 2 days). In addition, subjects will be regularly contacted (approximately every 2 to 3 days) by telephone during their ambulatory period. Blood and urine samples will be collected for safety evaluation (hematology, biochemistry, coagulation, urinalysis, and CCI) and blood samples will be collected for PK analysis throughout the residential and ambulatory period (at time points indicated in the Schedule of Assessments).

Part C

Part C may be initiated once the safety and PK data of at least the first 2 cohorts of Part A, ie, the 50 mg and 100 mg dose groups, or the targeted therapeutic exposure range have been assessed. In case multiple dosing (Part B) is deemed necessary based on the results of Part A, multiple dosing in Part C may be initiated after analysis of 1 or 2 cohorts in Part B (safety data and PK), with the decision to be made by the SMC.

Part C is a single-center, open-label trial using the P. falciparum IBSM human challenge to assess the antimalarial activity of M5717 in healthy subjects infected with malaria under controlled conditions. The trial is planned to be conducted in up to 3 cohorts (n=8 per cohort). A key assumption on which the dose for the first cohort will be selected is that the MPC and MIC value derived from the preclinical severe combined immunodeficient (SCID) mouse efficacy model would be the same in humans, taking into account the observed profile in the human PK data as observed in Part A. The current objective is that the dose of M5717 that will be investigated in the first cohort is a single dose that is expected to lead to levels above the MPC for 8 days. The dose will be estimated using noncompartmental PK analysis. This dose needs to be endorsed by the SMC. Depending on whether the assumed MPC in humans is correct, as well as the extent of parasite reduction observed in the first cohort in this part of the trial, the doses needed to characterize the exposure-response relationship (including doses

leading to recrudescence) will be further refined and decided by the SMC. These dose(s) could be higher or lower than the initially administered dose. Depending on the selected doses, the respective number and strength of capsules will be calculated and administered as specified in the pharmacy manual.

A third cohort will be investigated to further refine and characterize the MIC depending on the level of precision and confidence of the observations in the first 2 cohorts, unless the SMC decides otherwise. Similar scenarios as described for the initial 2 cohorts will be considered for the third cohort, with an alternative dosing time point if deemed necessary, with the intention to further refine the modeling and the Phase II dose predictions.

A maximum of 3 cohorts will be investigated as a single-dose or multiple-dose evaluation in Part C of the trial. The highest dose to be investigated in Part C will not exceed the highest dose administered in Part A or Part B of the trial.

Subjects will be admitted to the trial site for M5717 administration 9 days post administration of the Inoculum (In D9; Day 1). The parasitemia of all subjects at In D9 is expected to be ≥ 5,000 parasites/mL. However, subjects can be administered M5717 at any time point before or after In D9 at the Investigators discretion based on parasitemia and/or clinical symptoms.

Follow-up visits will occur on Day 13, Day 15, Day 17, Day 22, Day 29, and Day 33, and an End of Trial visit on Day 44 (± 2 days). In addition, subjects will be regularly contacted by telephone daily while they are outpatients, from Inoculum Day 2 to Inoculum Day 4, as well as on Day 23 to Day 25. Safety samples will be collected for safety evaluation (hematology, biochemistry, coagulation, and urinalysis) and blood samples for PK and PD analysis will be collected throughout the residential and ambulatory period (at time points indicated in the Schedule of Assessments).

The total duration of participation in Part C of the trial is approximately 80 days for each subject, including a Screening period of up to 28 days, 8 days for the IBSM incubation period, and 44 days of Follow-up after treatment with M5717.

Planned number of subjects:
Total: Up to a maximum of 136 healthy men and women of nonchildbearing potential
Part A: Up to 88 subjects in 11 cohorts of 8 subjects each
Part B (optional): Up to 24 subjects in 3 cohorts
Part C: Up to 24 subjects in 3 cohorts.

Primary endpoints:

Part A

- Nature, incidence, and severity of adverse events (AEs)/serious adverse events (SAEs), including relationship to trial treatment, AEs/SAEs leading to dose modification or discontinuation of trial treatment
- Incidence of clinically significant changes and abnormalities in safety laboratory parameters (hematology, coagulation, biochemistry [specifically alanine aminotransferase (ALT) and aspartate aminotransferase (AST)], and urinalysis)

- Incidence of clinically significant changes and abnormalities in vital signs (body temperature, blood pressure [BP], and heart rate), respiratory rate, and 12-lead ECG.

Part B (optional)

- Nature, incidence, and severity of AEs/SAEs, including relationship to trial treatment, AEs/SAEs leading to dose modification or discontinuation of trial treatment
- Incidence of clinically significant changes and abnormalities in safety laboratory parameters (hematology, coagulation, biochemistry [specifically ALT and AST], and urinalysis)
- Incidence of clinically significant changes and abnormalities in vital signs (body temperature, BP, and heart rate), respiratory rate, and 12-lead ECG.

Part C

- Parasite reduction ratio (PRR) as observed through quantitative polymerase chain reaction (qPCR) analysis
- All M5717 PK parameters as defined in Part A or Part B (depending on dosing regimen in Part C).

Secondary endpoints:

Part A

- PK parameters for M5717.

Part B (optional)

- PK parameters for M5717.

Part C

- PCT, MIC, PCt½, MPC, lag phase, number of subjects with recrudescence
- Malaria Clinical Score
- Nature, incidence, and severity of AEs/SAEs, including relationship to trial treatment, AEs/SAEs leading to dose modification or discontinuation of trial treatment
- Incidence of clinically significant changes and abnormalities in safety laboratory parameters (hematology, coagulation, biochemistry [specifically ALT and AST], and urinalysis)
- Incidence of clinically significant changes and abnormalities in vital signs (body temperature, BP, and heart rate), respiratory rate, and 12-lead ECG.

Efficacy/Pharmacodynamic assessments:

Part A and Part B

Not applicable.

Part C

Parasitical effect of M5717, defined as the reduction and/or clearance of parasitemia as determined by qPCR up to Day 8.

Safety assessments:

The safety profile of M5717 will be assessed through the recording, reporting and analysis of AEs, adverse events of special interest (AESIs), physical examination findings including vital signs, 12-lead ECGs, and safety laboratory tests to be performed at specified time points from Screening until the End of Trial visit.

CCI [redacted]

Pharmacokinetics:

Whole blood concentrations of M5717 from subjects receiving M5717 treatment will be analyzed using noncompartmental methods. The following M5717 whole blood PK parameters will be calculated:

Part A

C_{max}, t_{max}, λ_z, $t_{½}$, AUC ($AUC_{0-\infty}$, AUC_{0-t}, AUC_{0-24h}, and AUC_{0-144h}), $AUC_{extra\%}$, CL/f, V_z/f, and dose-normalized $AUC_{0-\infty}$, AUC_{0-t}, C_{max}, AUC_{0-24h}, AUC_{0-144h}, $t_{>10\ ng/mL}$, and $t_{>3\ ng/mL}$.

CCI [redacted]

CCI [redacted] $t_{>10\ ng/mL}$, and $t_{>3\ ng/mL}$.

Part C

PK blood parameters as calculated for Part A or Part B, depending on the dose regimen used in Part C.

Pharmacodynamics:

PRR, MIC, MPC, PCT, PC$t_{½}$, lag phase.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

Diagnosis and key inclusion and exclusion criteria: Adult men and women of nonchildbearing potential, 18 to 55 years of age (inclusive) with total body weight ≥ 50.0 kg and body mass index (BMI) between 19.0 kg/m^2 and 29.9 kg/m^2 (inclusive), with no history or presence of clinically relevant respiratory, gastrointestinal, renal, hepatic, hematological, lymphatic, neurological, cardiovascular, psychiatric, musculoskeletal, genitourinary, immunological, dermatological, or connective tissue diseases or disorders may be eligible to participate in the trial.

For Part C only, the following additional criteria apply: Subject does not live alone (from the start of the malaria inoculation until at least the end of the antimalarial drug treatment), has to be contactable and available for the duration of the trial, has no history of possible malaria exposure or participation in a malaria vaccine or human malaria challenge trial, and has no intention of traveling to a malaria-endemic region during the course of the trial.

Investigational Medicinal Product: dose/mode of administration/dosing schedule:

Capsules containing 10 mg, 50 mg, or 200 mg of M5717 CCI [redacted] or matched placebo. Depending on the dose to be administered, the exact number and strength of capsules will be calculated as detailed in the pharmacy manual. The maximum dose level which may be administered in this trial was initially set at 600 mg daily and re-evaluated to 1500 mg daily by the SMC.

Part A
A single dose of M5717 capsules or matched placebo to be taken orally under fasting conditions with 250 mL of water.

Part B (optional)
M5717 capsules or matched placebo to be taken orally once daily for 3 days under fasting conditions with 250 mL of water.

Part C
A single intravenous malaria inoculum of approximately 1800 viable human erythrocytes infected with P. falciparum, a single dose or a once daily dose for 3 days of M5717 capsules to be taken orally under fasting conditions with 250 mL of water, and an approved regimen for curative therapy for malaria.

Reference treatment: dose/mode of administration/dosing schedule: Not applicable.

Planned trial and treatment duration per subject:

Part A
Approximately 11 weeks from Screening until the End of Trial visit; including 4 weeks for Screening, 1 week as an inpatient at the trial site for investigational medicinal product (IMP) administration, approximately 5 weeks for Daily visits and Follow-up visits, and approximately 1 week until the End of Trial visit.

Part B (optional)
Approximately 11 weeks from Screening until the End of Trial visit; including 4 weeks for Screening, 1 week inpatient at the trial site for IMP administration, approximately 5 weeks for Daily visits and Follow-up visits, and approximately 1 week until the End of Trial visit.

Part C
Approximately 12 weeks from Screening until the End of Trial visit; including 4 weeks for Screening, 1 week for malaria inoculation, 3 days of confinement at the trial site after IMP administration, approximately 6 weeks for daily and/or twice daily visits to the trial site for monitoring and Follow-up visits, and approximately 1 week until the End of Trial visit.

Statistical methods:

Given the exploratory nature of this trial, the sample size is not based on formal statistical calculations. The sample size is based on experience from previous similar trials which will provide sufficient safety, tolerability, PK and PD data to achieve the objectives of the trial.

Dose cohorts including 8 subjects each are planned in all 3 parts of the trial. In each dose cohort of Part A and Part B, 8 subjects will be randomized in a double-blind fashion to M5717 or placebo in a ratio of 6:2, respectively, such that for the first 2 subjects in the sentinel cohort, 1 subject will receive M5717 and 1 subject will receive placebo. Part C is not placebo controlled.

The results of this trial will be reported using summary tables, figures, and data listings, as appropriate. All data will be summarized by dose level and/or scheduled time point, as appropriate and otherwise specified.

Safety and tolerability endpoints will include AEs/SAEs, laboratory parameters, vital signs and 12-lead ECG. All data will be descriptively summarized as appropriate. In Part A and Part B, subjects receiving placebo will be pooled across dosing cohorts for summary purpose. CCI [redacted]

All PK blood concentrations and PK parameters will be descriptively summarized CCI [redacted]

CCI [redacted]

In Part C, the primary PD variable is the PRR of asexual parasites based on qPCR analysis after administration of M5717. All PD endpoints will be descriptively summarized. The number and percentage of subjects with absence of parasitemia (measured by qPCR) as well as the number and percentage of subjects with recrudescence will be summarized.

Table 1 Schedule of Assessments: Part A (Single Ascending Dose)

Activity	Screening		On Treatment Visits																				Ambulatory Visits				Follow-up Visits					End of Trial Visit
Trial Week			1																				2				3			4	6	7
Trial Day		-2	-1	1													2		3		4	5	6	7	8	9	10	11	13	15	17	22	33 ± 2	44 ± 2
Hour after IMP administration				Pre	0	0.5	1	1.5	2	4	6	8	10	12	16	20	24	30, 36, 42	48	60	72	96	120	144	168	192	216	240	288	336	384	504	768	1032
Informed Consent	X																																
Demographic and medical history	X																																
Residency		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[a]									
Outpatient visit																									X	X	X	X	X	X	X	X	X
Inclusion and exclusion criteria check/ recheck	X		X																														
Physical examination[b]	X																							X						X			X
Serology	X																																
Concomitant medication		Throughout the period																															
Adverse events		Throughout the period																															

Activity	Screening			On Treatment Visits																			Ambulatory Visits				Follow-up Visits					End of Trial Visit
Trial Week				1																			2				3			4	6	7
Trial Day		-2	-1	1												2		3	4	5	6	7	8	9	10	11	13	15	17	22	33 ± 2	44 ± 2
Hour after IMP administration				Pre	0	0.5	1	1.5	2	4	6	8	10	12	16	20	24	30, 36, 42	48	60	72	96	120	144	168	192	216	240	288	336	384	504	768	1032
Alcohol breath test	X	X																														
Urine drugs of abuse	X	X																														
FSH (females only)	X																															
Randomization				X																												
IMP administration					X																											
Diary cards[c]																						X	X[d]	X	X[d]	X	X	X	X	X	X	X
CCI																																
Safety laboratory tests[e]	X		X	X													X		X		X	X[f]		X[f]		X		X[f]		X	X	X
Safety biochemistry	X		X	X													X		X	X	X	X		X		X	X	X		X	X	X
Vital signs, respiratory rate[g]	X		X	X			X		X	X	X	X	X	X	X[h]	X[h]	X		X		X	X				X			X	X	X	X
12-lead ECG (triplicates)	X		X[i]	X			X		X	X	X	X	X	X	X		X		X		X					X				X	X	X

Document No CCI [redacted]
Object No. CCI [redacted]

Activity	Screening			On Treatment Visits																		Ambulatory Visits				Follow-up Visits					End of Trial Visit
Trial Week				1																		2				3			4	6	7
Trial Day		-2	-1	1												2		3	4	5	6	7	8	9	10	11	13	15	17	22	33 ± 2	44 ± 2
Hour after IMP administration				Pre	0	0.5	1	1.5	2	4	6	8	10	12	16	20	24	30, 36, 42	48	60	72	96	120	144	168	192	216	240	288	336	384	504	768	1032
PK sampling[i]				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		X		X			X	X	X	X
CCI																																
CCI																																
CCI																																

CCI ; eCRF = electronic case report form; ECG = electrocardiogram; FSH = follicle-stimulating hormone; IMP = investigational medicinal product; CCI PK = pharmacokinetic(s); CCI Pre = predose.

a Discharge of subjects may occur at the discretion of the Investigator after all scheduled assessments on Day 7 have been completed.

b A standard full physical examination, including examination of all body systems, will be performed at Screening and the End of Trial visit (Day 44 ± 2 days), including general appearance, skin, head, neck (including thyroid), eyes, ears, nose, throat, cardiovascular and pulmonary system, abdomen, neurological, peripheral vascular, and musculoskeletal system. At other time points an abbreviated physical examination must be performed. Additional physical examinations may be performed as deemed necessary, per the Investigator's discretion.

c Diary cards will be provided to subjects for collection of data relating to their daily physical activity, daily use of sunscreen/other methods of sun protection, daily alcohol consumption, and fi applicable, their oral (sublingual) temperature. Subjects will bring their completed diary cards with them to the trial site for all ambulant, Follow-up, and End of Trial visits.

d On Day 8 and Day 10, subjects may be contacted by the trial site via a phone call or subjects may text a photo of their completed diary card instead of visiting the trial site.

e Only hematology, coagulation, and urinalysis (dipstick).

f Coagulation not required on Day 7, Day 9, and Day 15.

g On Day 1, a time window of 60 minutes is allowed for blood pressure measurements.

h In case the subject is unable to stand up at the 16 hours and 20 hours postdose time points due to dizziness, the vital signs may be assessed in the supine position.

i Time points on Day -1 will match the time points on Day 1.

j Allowed time windows on PK sampling times are defined in Table 4.

C [redacted]

l From this time point on urine only.

C [redacted]

General: At visits where assessment time points coincide with each other, the following procedure should be followed: perform vital signs assessments slightly before the specific time point, ECG assessments on time, PK blood sampling directly following ECG. Use of agreed upon time windows will be allowed (specified in Table 4).

Time window (see Table 4): Samples and assessments obtained within the allowed time window from dosing will not be captured as a protocol deviation, as long as the exact time of the assessment/sample collection is noted on the source document and data collection tool (eg, eCRF).

For the different biological samples, the required total amount of blood, CCI [redacted] is specified in the laboratory manual.

Table 2 Schedule of Assessments: Part B (Optional; Multiple Ascending Dose)

Activity	Screening		On Treatment Visits																				Ambulatory Visits				Follow-up Visits			End of Trial Visit
Trial Week			1																				2				3	4	6	7
Trial Day		-2	-1	1										2	3				4	5	6	7	8	9	10	11	13	15	22	33 ± 2	44 ± 2
Hour after IMP administration				Pre	0	0.5	1.5	2	4	6	8	12	16	24	48	49	52	56	60	64	72	96	120	144	168	192	214	240	288	336	504	768	1032
Informed Consent	X																														
Demographic and medical history	X																														
Residency		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[a]								
Outpatient visit																								X	X	X	X	X	X	X	X
Inclusion and exclusion criteria check/ recheck	X		X																												
Physical examination[b]	X																					X						X			X
Serology	X																														
Concomitant medication		Throughout the period																													
Adverse events		Throughout the period																													

Activity	Screening			On Treatment Visits																				Ambulatory Visits				Follow-up Visits			End of Trial Visit
Trial Week				1																				2				3	4	6	7
Trial Day		-2	-1	1										2	3					4	5	6	7	8	9	10	11	13	15	22	33 ± 2	44 ± 2
Hour after IMP administration				Pre	0	0.5	1.5	2	4	6	8	12	16	24	48	49	52	56	60	64	72	96	120	144	168	192	214	240	288	336	504	768	1032
Alcohol breath test	X	X																														
Urine drugs of abuse	X	X																														
FSH (females only)	X																															
Randomization				X																												
IMP administration					X									X	X																	
Diary cards[c]																								X[d]	X	X[d]	X	X	X	X	X	X
CCI																																
Safety laboratory tests[e]	X		X	X										X	X						X	X		X[f]		X[f]		X		X[f]	X	X	X
Safety biochemistry	X		X	X										X	X						X	X		X		X		X	X	X	X	X	X
Vital signs, respiratory rate[g]	X		X	X							X		X[h]	X	X		X			X	X	X						X			X	X	X
12-lead ECG (triplicates)	X		X[i]	X				X	X	X	X	X	X	X	X			X	X	X		X						X			X	X	X

Activity	Screening			On Treatment Visits																				Ambulatory Visits				Follow-up Visits				End of Trial Visit
Trial Week				1																				2				3	4	6	7
Trial Day		-2	-1	1									2	3							4	5	6	7	8	9	10	11	13	15	22	33 ± 2	44 ± 2
Hour after IMP administration				Pre	0	0.5	1.5	2	4	6	8	12	16	24	48	49	52	56	60	64	72	96	120	144	168	192	214	240	288	336	504	768	1032
PK sampling[j]				X		X	X	X	X	X	X	X	X	X[k,l]	X[l]	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X	X
CCI																																
CCI																																

CCI ; eCRF = electronic case report form; ECG = electrocardiogram; IMP = investigational medicinal product;
CCI PK = pharmacokinetic(s); PLD = phospholipidosis; Pre = predose.

a Discharge of subjects will occur at the discretion of the Investigator after all scheduled assessments on Day 7 have been completed.

b A standard full physical examination, including examination of all body systems, will be performed at Screening and the End of Trial visit (Day 44 ± 2 days), including general appearance, skin, head, neck (including thyroid), eyes, ears, nose, throat, cardiovascular and pulmonary system, abdomen, neurological, peripheral vascular, and musculoskeletal system. At other time points an abbreviated physical examination must be performed. Additional physical examinations may be performed as deemed necessary, per the Investigator's discretion.

c Diary cards will be provided to subjects for collection of data relating to their daily physical activity, daily use of sunscreen/other methods of sun protection, daily alcohol consumption, and if applicable, their oral (sublingual) temperature. Subjects will bring their completed diary cards with them to the trial site for all ambulant, Follow-up, and End of Trial visits.

d On Day 8 and Day 10, subjects may be contacted by the trial site via a phone call or subjects may text a photo of their completed diary card instead of visiting the trial site.

e Only hematology, coagulation, and urinalysis (dipstick).

f Coagulation not required on Day 7, Day 9, and Day 15.

g On Day 1, a time window of 60 minutes is allowed for blood pressure measurements.

h In case the subject is unable to stand up at the 16 hours postdose time point due to dizziness, the vital signs may be assessed in the supine position.

i Time points on Day -1 will match the time points on Day 1.

j Allowed time windows on PK sampling times are defined in Table 4.

k Additional PK samples to be collected at 36 hours and 40 hours postdose on Day 2.

l PK samples are to be collected predose on IMP administration days (at 24 hours on Day 2 and at 48 hours on Day 3).

C [redacted]

General: At visits where assessment time points coincide with each other, the following procedure should be followed: perform vital signs assessments slightly before the specific time point, ECG assessments on time, PK blood sampling directly following ECG. Use of agreed upon time windows will be allowed (specified in Table 4).

Time window (see Table 4): Samples and assessments obtained within the allowed time window from dosing will not be captured as a protocol deviation, as long as the exact time of the assessment/sample collection is noted on the source document and data collection tool (eg, eCRF).

For the different biological samples, the required total amount of blood, CCI [redacted] is specified in the laboratory manual.

Table 3 Schedule of Assessments: Part C (Induced Blood Stage Malaria Challenge Model, Assuming Single Dosing)

Activity	Screening	Inoculation Visits						On Treatment Visits																								Ambulatory Visits				Follow-up Visits					End of Trial Visit
Trial Week								1																								2				3		4	5	6	7
Trial Day		In D1[a] AM	In D5 AM	In D6 AM, PM	In D7 AM, PM	In D8 AM	In D8 PM	1												2			3		4				5	6	7	9	11	13	15	17	22	29	33 ± 2	44 ± 2
Hour after IMP admin								Pre	0	0.5	1	1.5	2	4	6	8	10	12	16	20	24	30	36, 42	48	54, 60, 66	72	84	96	120	144	192	240	288	336	384	504	672	768	1032
Informed Consent	X																																						
Demographic and medical history	X																																						
Residency								X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]														
Outpatient visit		X	X	X	X	X	X																			X	X	X	X	X	X	X	X	X	X[c]	X	X	X
Inclusion and exclusion criteria check/ recheck	X	X						X																															
G6PD status/ testing	X																																						
Physical examination[d]	X	X						X																	X				X				X						X

Activity	Screening	Inoculation Visits						On Treatment Visits																										Ambulatory Visits									Follow-up Visits							End of Trial Visit
Trial Week								1																												2							3			4	5	6	7
Trial Day		In D1[a] AM	In D5 AM	In D6 AM, PM	In D7 AM, PM	In D8 AM	In D8 PM	1																2			3		4							5	6	7	9	11	13	15	17	22	29	33 ± 2	44 ± 2
Hour after IMP admin								Pre	0	0.5	1	1.5	2	4	6	8	10	12	16	20	24	30	36, 42	48	54, 60, 66	72	84	96	120	144	192	240	288	336	384	504	672	768	1032										
Serology	X																																										X			
Concomitant medication		Throughout the period																																													
Adverse events		Throughout the period																																												
Alcohol breath test	X	X						X																																						
Urine drugs of abuse	X	X						X																																						
FSH (females only)	X																																												
IV Malaria Inoculum		X																																											
IMP administration									X												X[e]			X[e]																						
Diary cards[f]		X	X	X	X	X	X																				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI																																														

Activity	Screening	Inoculation Visits						On Treatment Visits																												Ambulatory Visits									Follow-up Visits						End of Trial Visit
Trial Week								1																														2							3			4	5	6	7
Trial Day		In D1[a] AM	In D5 AM	In D6 AM, PM	In D7 AM, PM	In D8 AM	In D8 PM	1												2			3			4			5	6	7	9	11	13	15		17	22	29	33 ± 2	44 ± 2
Hour after IMP admin								Pre	0	0.5	1	1.5	2	4	6	8	10	12	16	20	24	30	36, 42	48	54, 60, 66	72	84	96	120	144	192	240	288	336		384	504	672	768	1032
Safety laboratory tests[g]	X	X				X		X												X			X				X		X[h]	X[h]	X		X[h]			X	X	X	X
Safety biochemistry	X	X				X														X			X		X		X		X	X	X					X		X	X
Red blood cell antibodies[i]	X																																			X				
Vital signs, respiratory rate[j]	X	X[k]					X	X							X	X	X	X	X[l]		X			X		X		X			X				X		X	X		X	X
12-lead ECG (triplicate)	X	X						X							X	X	X	X	X		X			X				X				X					X		X	X
CCI																																									
PK sampling[q]								X[r]		X	X[r]	X	X[r]	X	X[r]	X	X[r]	X	X[r]	X	X[r, s]	X	X[r]	X[r, s]		X		X[r]	X	X[r]	X	X[r]			X	X[r]		X	X[r]
Rescue medication[t]																																				X				

Activity	Screening	Inoculation Visits						On Treatment Visits																										Ambulatory Visits			Follow-up Visits				End of Trial Visit
Trial Week								1																												2			3		4	5	6	7
Trial Day		In D1[a] AM	In D5 AM	In D6 AM, PM	In D7 AM, PM	In D8 AM	In D8 PM	1										2			3		4		5	6	7	9	11	13	15	17	22	29	33 ± 2	44 ± 2						
Hour after IMP admin								Pre	0	0.5	1	1.5	2	4	6	8	10	12	16	20	24	30	36, 42	48	54, 60, 66	72	84	96	120	144	192	240	288	336	384	504	672	768	1032						
Follow-up via phone call[u]		X[u]																																		X[u]						
Inoculum safety sample[v]		X																																		X						X

eCRF = Electronic case report form; ECG = electrocardiogram; FSH = follicle-stimulating hormone; G6PD = glucose-6-phosphate dehydrogenase; IMP = investigational medicinal product; IV = intravenous; In D1 to In D9 = Day of Inoculum administration (In D1) to 9 days post administration of the Inoculum (In D9); mRNA = messenger ribonucleic acid; CCI [redacted] PK = pharmacokinetic(s); Pre = predose; SMC = Safety Monitoring Committee; qPCR = quantitative polymerase chain reaction.

a The schedule assumed treatment on In D9 = Trial Day 1.

b Discharge of subjects can occur between Day 4 to Day 7 at the discretion of the Investigator on advice of the SMC (based on experience with Part A).

c In Part C, an ambulant visit will be performed on Day 22 for subjects with breakthrough infections for the administration of rescue medication.

d A standard full physical examination, including examination of all body systems, will be performed at Screening and the End of Trial visit (Day 44 ± 2 days), including general appearance, skin, head, neck (including thyroid), eyes, ears, nose, throat, cardiovascular and pulmonary system, abdomen, neurological, peripheral vascular, and musculoskeletal system. At other time points an abbreviated physical examination must be performed. Additional physical examinations may be performed as deemed necessary, per the Investigator's discretion.

e IMP administration on Day 2 and Day 3 in case Part C will be evaluated with multiple doses based on PK data from Part A and B.

f Diary cards will be provided to subjects for collection of data relating to their daily physical activity, daily use of sunscreen/other methods of sun protection, daily alcohol consumption, and if applicable, their oral (sublingual) temperature. Subjects will bring their completed diary cards with them to the trial site for all ambulant, Follow-up, and End of Trial visits.

g Only hematology, coagulation, and urinalysis (dipstick).
h Coagulation not required on Day 7, Day 9, and Day 15.
i Samples will be collected and analyzed for the detection of seroconversion against some rare blood stage pathogens or red blood cell antibodies.
j On Day 1, a time window of 60 minutes is allowed for blood pressure measurements.
k Vital signs assessments prior to administration of malaria inoculum (In D1) as well as 1 hour post inoculation (In D1).
l In case the subject is unable to stand up at the 16 hours postdose time point due to dizziness, the vital signs may be assessed in the supine position.

CCI [redacted]

q At visits where assessment time points coincide with each other, the following procedure should be followed: perform vital signs assessments slightly before the specific time point, ECG assessments on time, PK blood sampling directly following ECG. Use of agreed upon time windows will be allowed (specified in Table 4).
r Including dried blood spot assessments at alternate samples (predose, 1, 2, 6, 10, 16, 24, 36, 48, 96, 144, 240, 504, and 1032 hours).
s In case Part C will be evaluated with multiple doses based on PK data from Part A and B, PK samples are to be collected predose on IMP administration days (at 24 hours on Day 2 and at 48 hours on Day 3).
t Riamet and Primacin. If rescue medications are required prior to Day 22, safety assessments must be performed pre administration of Riamet. This assessment will include hematology, biochemistry, ECG, vital signs, physical examination, coagulation profile, and urinalysis. However, red blood cell auto-antibodies, and serum storage collection will still be collected at Day 22 regardless of the trial day that rescue medications are administered. Administration of rescue medications prior to Day 22 will be determined at the Investigators discretion using the following criteria:
  - Failure of clearance: defined as failure to clear parasitemia by at least 10-fold at 72 hours post IMP administration
  - Recrudescence: defined as ≥ 5000 blood stage parasites/mL and a 2-fold parasitemia increase within 48 hours, or re-occurrence of malaria symptoms with a malaria clinical score > 6.
u Subject will be contacted daily via phone calls while outpatient, from Inoculum Day 2 to Inoculum Day 4, as well as on Day 23 to Day 25, for a safety check and compliance of rescue medication use.
v Serum samples will be collected at Inoculum Day 1 (pre inoculation), Day 22 (pre Riamet treatment) and the End of Trial visit (Day 44 [± 2 days]). These samples will be stored and will be used only in case any safety concerns arise and additional safety parameter testing is required.

Time window: Samples and assessments obtained within the allowed time window from dosing will not be captured as a protocol deviation, as long as the exact time of the assessment/sample collection is noted on the source document and data collection tool (eg, eCRF).

Table 4 Allowed Time Windows

Time Point	Tolerance Window
Pharmacokinetic[redacted] (blood samples)	
Predose	- 60 min to 0 h
0.5 h to 1.5 h post	± 3 min
2 h post	± 3 min
4 h to 20 h post	± 5 min
24 h to 72 h post	± 10 min
84 h to 144 h post	± 2 h
192 h to 384 h post	± 6 h
504 h post	± 24 h
768 h post	± 48 h
1032 h post	± 48 h
12-Lead Electrocardiogram/Vital Signs/Respiratory Rate/Temperature/Safety Laboratory Samples	
Predose	- 90 min to 0 h
0.5 h to 1.5 h post	± 10 min
2 h post	± 10 min
4 h to 20 h post	± 10 min
24 h to 72 h post	± 20 min
84 h to 144 h post	± 2 h
192 h to 384 h post	± 6 h
504 h post	± 24 h
768 h post	± 48 h
1032 h post	± 48 h
Blood Pressure Measurements	
Day 1	± 60 min

2 Sponsor, Investigators and Trial Administrative Structure

This clinical trial will be funded and sponsored by Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany. The local sponsor will be

The trial will be conducted at 1 trial site,

The Contract Research Organization (CRO) responsible for all other tasks (eg, monitoring, data management, medical writing pharmacokinetic (PK) parameter and analysis, and statistical analysis) will be Subjects will be recruited from the database of healthy participants and through trial specific advertisement including radio, print-, social-, and online media, as approved by the Human Research Ethics Committee (HREC).

A Safety Monitoring Committee (SMC) will be established for review of all safety data on a regular basis. The SMC will provide recommendations regarding stopping, modifying, or continuing the trial. The SMC will consist of core voting and nonvoting members: Global Patient Safety Product Leader, Medical Responsible, Representative from Clinical Pharmacology and Statistician from the Sponsor, the Principal Investigator (PI) and CRO Medical Monitor. Extended SMC members may include an external expert or any other ad hoc SMC member who may contribute to the SMC decision. Ad-hoc members may be invited as needed. The composition and roles of the SMC are detailed in Section 5.2.8. The operational procedures will be described in an SMC charter, which will be established prior to the start of recruitment.

The funding Sponsor will be responsible for investigational medicinal product (IMP) supply and distribution.

The Sponsor's Global Patient Safety department or its designated representatives will supervise drug safety and the timeline for reporting of adverse events (AEs), adverse events of special interest (AESIs), and serious adverse events (SAEs) to all concerned parties in accordance with the applicable guidance, laws, and regulations as described in the Safety Management Plan.

[redacted]

Laboratory sample processing, handling, and storage instructions, as well as dose preparation and dispensing details, will be presented in separate manuals that will be prepared by the CRO and/or the testing laboratories in coordination with the Sponsor.

[redacted]

Signature pages for the Protocol Co-Leads and the PI, as well as a list of Sponsor responsible persons, are in Appendix IX.

The trial will appear in the following clinical trial registries: ClinicalTrials.gov.

Details of structures and associated procedures will be defined in a separate Manual of Operations, which will be prepared under the supervision of the Clinical Trial Leader.

3 Background Information

3.1 Malaria

According to the latest estimates, released in December 2016 by World Health Organization, worldwide there were about 212 million cases of malaria in 2015 (with an uncertainty range of 148 million to 304 million) and an estimated 429,000 deaths (with an uncertainty range of 235,000 to 639,000) (1). Most deaths (70%) occur among children below the age of 5 years, mainly in Africa. Human malaria is caused by 4 Plasmodium parasite species (P. falciparum, P. vivax, P. malariae and P. ovale), transmitted to humans by Anopheles mosquitoes, called "malaria vectors". P. falciparum and P. vivax are the most common. P. falciparum is the deadliest whereas P. vivax triggers a recurrent form of malaria that, if left untreated, may lead to severe illness.

Malaria is an acute febrile illness. In a nonimmune individual, symptoms appear from 7 days up to 15 days after the infective mosquito bite. The first symptoms – fever, headache, chills and vomiting – may be mild and difficult to recognize as malaria. If not treated within 24 hours, P. falciparum malaria can progress from acute clinical disease to severe illness often leading to death. Children with severe malaria frequently develop one or more of the following symptoms: severe anemia, respiratory distress in relation to metabolic acidosis, or cerebral malaria. Also in adults, multiple organs are usually involved. In malaria-endemic areas, persons may develop partial immunity, resulting in > 80% of infections being asymptomatic in regions of high transmission. Non severe malaria of all 4 Plasmodium parasite species can be cured with proper treatment.

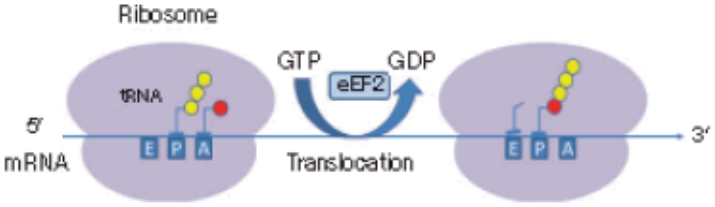
The goal of drug combination therapy for parasitic diseases such as malaria is to prevent the emergence of resistance, while providing additional benefit for the treatment by providing a higher cure rate. The rationale behind the development of artemisinin-based combination therapies was to combine a very fast-acting compound (an artemisinin derivative) that will destroy > 80% of the parasites within the first 24 hours (reducing symptoms rapidly) with a long-acting compound, such

as a 4-aminoquinoline, that will provide some protection against reinfection (post-treatment prophylaxis). Artemisinin derivatives have a very rapid mode of action and kill high numbers of parasites, destroying > 80% of the parasite biomass and as such reduce the probability to select resistance against the long-acting partner compound. Treatment with an artemisinin derivative alone (such as artesunate) requires 7-day dosing due to its short half-life of about 1 hour and often results in incomplete disappearance of the parasites, which may result in resistance. The combination with a long-acting partner synergizes the initial parasite killing rate, while providing prolonged antiparasitic protection and allowing reduction in the treatment course to 3 days.

3.2 M5717, a Plasmodium Eukaryotic Translation Elongation Factor 2 Inhibitor

The external Translational Innovation Platform Malaria Innovation Cluster has in-licensed a drug candidate from the Medicines for Malaria Venture at the preclinical stage. The molecule, named DDD107498, M5717 (this is the name that will be used throughout this document), or Plasmodium eukaryotic translation elongation factor 2 (PeEF2) inhibitor, is a CCI [redacted] targeting PeEF2, which is a critical enzyme involved in protein synthesis. This eEF2 is one of several essential elongation factors required in eukaryotic protein synthesis, by mediating guanosine triphosphate-dependent translocation of the ribosome along messenger RNA (mRNA), as shown in Figure 1.

Figure 1 Schematic Representation of Eukaryotic Translation Elongation Factor 2



eEF2 = Eukaryotic translation elongation factor 2; GDP = guanosine diphosphate; GTP = guanosine triphosphate; mRNA = messenger ribonucleic acid.

M5717 is a highly potent and selective compound that acts on the asexual intraerythrocytic forms of the human malaria parasites P. falciparum and P. vivax as well as on liver and gametocyte forms of the parasites. It is orally bioavailable, and displays PK and PD properties compatible with a long duration of action for the treatment of acute, uncomplicated malaria infections due to P. falciparum and P. vivax. M5717 has the potential to be developed as a single-dose cure and to become the most efficacious antimalarial compound and hence the treatment of choice (best in class) for uncomplicated malaria in combination therapy. In addition, M5717 is a novel agent (first in class) with a mechanism of action different from all other antimalarial drugs, with activity against parasites that have shown resistance to clinically used compounds.

Due to its inhibitory effects on gametocyte formation, it also has the potential to act as a transmission blocker. Finally, due to its predicted long half-life and its activity against pre-erythrocytic stages, M5717 has the potential to be developed in the chemoprotection indication to protect against development of malaria in endemic countries (chemoprevention) and for travelers (chemoprophylaxis).

3.3 Trial Rationale

This is a First-in-Human (FIH) trial with M5717 and consists of 3 parts.

In Part A, the trial will first evaluate the safety, tolerability, and PK properties of single ascending doses (SAD) of M5717 when administered to healthy men and women of nonchildbearing potential (WNCBP) under fasted conditions. Since embryo-fetal toxicity trials have not yet been performed, the trial is restricted to WNCBP.

In Part B, multiple ascending doses (MAD) of M5717 will be administered as 3 consecutive daily doses under the same conditions and in the same population. Part B will only be conducted if the observed half-life in Part A is much shorter (by > 50%) than the 257 hours currently predicted from preclinical data and does not allow for administering a tolerable single dose that covers an 8-day period with concentrations above the minimal parasiticidal concentration (MPC; defined in Table 10) of 10 ng/mL. The characteristic PK parameters, in particular the elimination half-life, as computed by noncompartmental analysis will inform this decision. Three days is the maximum number of daily doses in this therapeutic indication, related to an expected decrease in compliance in the case of a longer duration of daily dosing (2).

Part C will investigate the effects of single or multiple doses (in case the clinical regimen necessitates multiple dosing based on Part A) of M5717 on P. falciparum clearance kinetics in healthy subjects using the Induced Blood Stage Malaria (IBSM) challenge model as described by McCarthy et al (3).

Part A commenced with a starting dose of 50 mg. This 50 mg dose was within the range of the initially predicted efficacious dose (ED) which had been estimated to be between 10 mg and 70 mg. (See Section 5.2.9 for a discussion on the justification for dose.) The daily dose in Part B will not be higher than doses already investigated in Part A. For the IBSM challenge model (Part C), a maximum of 3 cohorts are included, to assess the parasiticidal activity of M5717 followed by an evaluation of the PK/PD relationship.

Additional information is included in the scientific rationale of the trial design (Section 5.2.1) and justification for the dose (Section 5.2.9).

Refer to the Investigator's Brochure (IB) for further information about the nonclinical programs and Guidance for the Investigator.

The Sponsor will immediately notify the PI if any additional safety or toxicology information becomes available during the trial.

This clinical trial will be conducted in compliance with the clinical trial protocol, International Council for Harmonization (ICH) Good Clinical Practice (GCP), and any additional applicable regulatory requirements.

Based on the available nonclinical data to date, the conduct of the trial specified in this protocol is considered justifiable.

3.3.1 Overall Risk Assessment

In line with the current guideline (Committee for Medicinal Products for Human Use Guideline on Strategies to Identify and Mitigate Risks for Clinical Trials with IMP, EMEA/Committee for Medicinal Products for Human Use /SWP/28367/07) a risk assessment was performed for the M5717 molecule regarding its mode of action, nature of the target, and relevance of animal species and models.

The mode of action is new for a molecule effective in malaria, ie, inhibition of PeEF2, which is involved in protein synthesis and therefore no clinical/therapeutic experience from other existing molecules can be gained. However, the compound is highly selective for the Plasmodium elongation factor and does not cross-react with human elongation factors at relevant concentrations. The most relevant animal models for malaria are severe combined immunodeficient (SCID) mice injected with infected human erythrocytes and these models were used to give an estimation of the minimal inhibitory concentration (MIC) and MPC needed to be effective against the parasite. In addition, in standard rat and dog repeat-dose 2-week toxicity trials, little toxicity of the compound was identified and liver, lymphatics, and epithelia of the gastrointestinal tract were identified as the target organs (for details please refer to the IB). One major observation in the rat was adverse liver injury due to phospholipidosis (PLD) symptoms at a dose above the no-observed-adverse-effects-level (NOAEL). Another observation was absorption of ultraviolet (UV) light at 290 nm and 336 nm as well as a positive in vitro phototoxicity (3T3) assay.

In summary, in reference to the mode of action, the nature of the target with high specificity for PeEF2, and the availability of toxicity data from 2 relevant animal species, M5717 was not classified as a high-risk molecule and the NOAEL approach was applied to support the starting dose. The predicted long half-life of the compound does influence the design of the FIH trial, warranting a longer duration of observation than is typical in a Phase I trial.

3.3.2 Benefit and Risk (Single Ascending Dose/Multiple Ascending Dose Part)

The benefit-risk relationship has been carefully considered in the planning of the trial. Based on the nonclinical safety profile and the expected high efficacy against Plasmodium, it is anticipated that M5717 will have a positive benefit-risk profile to warrant trials in healthy volunteers if conducted under well-controlled conditions, including in-house confinement periods, extensive monitoring, and protective measures for contraception and phototoxicity. This initial trial in healthy volunteers will be followed by subsequent proof-of-concept trials in malaria-infected patients, where M5717 will be tested as a monotherapy or in combination with a partner molecule.

Healthy subjects participating in this Phase I trial will not derive any clinical benefit from the treatment. However, the planned trial is thought to have a beneficial impact for future patients by generating information that will guide and shorten the time for the identification of ED of M5717 in patients.

3.3.3 Benefit and Risk (Malaria Challenge Model Part)

Potential risks to subjects in the IBSM challenge model (Part C) include development of mild/moderate symptoms associated with malaria infection following the challenge, as well as adverse effects of M5717 and the approved malaria rescue medications artemether/lumefantrine (Riamet® 20 mg/120 mg from Novartis) and primaquine (Primacin™ from Boucher & Muir Pty Ltd). Benefits are mainly to society for the potential to help make available future antimalarial therapies. The clinical trial protocol has been designed such that the risk to subjects in this trial will be minimized by adequate selection of eligibility criteria, and schedule of clinical monitoring, in-house observation, and administration and treatment duration. Since infection with malaria parasites may lead to transient increased levels of liver enzymes in some subjects - especially alanine aminotransferase (ALT) - liver function tests will be monitored regularly and trial subjects will be informed of these possible asymptomatic disturbances. Furthermore, the subjects will be prescribed curative therapy for malaria: Riamet, and Primacin 45 mg (if determined to be gametocytemic) as described in the protocol for final clearance of the parasite at the end of the trial.

A full discussion of the potential risks from Riamet and Primacin may be found in the respective approved manufacturer's prescribing information.

4 Trial Objectives

4.1 Primary Objectives

Part A

- To investigate the safety and tolerability of single ascending oral doses of M5717.

Part B (optional)

- To investigate the safety and tolerability of multiple (3-day) ascending oral doses of M5717.

Part C

- To characterize the PK/CCI relationship between M5717 PK and CCI [redacted]

4.2 Secondary Objectives

Part A

- To investigate the PK of single ascending oral doses of M5717.

Part B (optional)

- To investigate the PK of multiple (3-day) ascending oral doses of M5717.

Part C

- 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, PCt½, MPC, lag time, and frequency of recrudescence.
- To characterize the parasiticidal activity of M5717 on P. falciparum asexual blood stage parasites in the blood of healthy subjects in the IBSM challenge
- To evaluate the safety and tolerability of M5717 in healthy volunteers following infection with P. falciparum blood stage parasites during the IBSM challenge.

CCI [redacted]

CCI

[redacted]

5 Investigational Plan

5.1 Overall Trial Design and Plan

This is a Phase I, FIH, 3-part trial in healthy subjects at a single trial site. The trial is expected to start (first subject's first visit) in August 2017. The last subject's last visit date will depend on the number of cohorts enrolled as determined by the SMC (latest July 2019).

The trial consists of the following parts: SAD (Part A), MAD (Part B) and the IBSM challenge model (Part C).

Up to a maximum of 88 healthy men and women of nonchildbearing potential (WNCBP) (considering up to 11 cohorts of 8 subjects each) in Part A, up to 24 subjects in 3 cohorts in Part B, and up to 24 subjects in Part C), 18 to 55 years of age (inclusive) will participate in this trial. No subject will be a member of more than 1 cohort in any part of the trial.

A detailed schedule of trial procedures/assessments is provided in the Schedule of Assessments (see Table 1 to Table 3).

5.2 Discussion of Trial Design

5.2.1 Scientific Rationale for Trial Design

M5717 is a new chemical entity with high potency against multi-stage forms of P. falciparum, inhibiting a new target, PeEF2. This target is involved in the guanosine triphosphate-dependent translocation of the ribosome and is essential for protein synthesis. Human, Cynomolgus monkey, rat, and mouse eEF2 are highly conserved and only differ by less than 1% from each other, whilst P. falciparum sequence is only 63.7% identical to the mammalian sequences. From the data generated thus far, M5717 seems to be highly selective for the Plasmodium species and as such no effects on protein synthesis in humans are to be expected. The available data from the pivotal Good Laboratory Practice (GLP) toxicology trials in the rat and dog did not suggest otherwise.

In contrast to many current FIH trials, no CCI [redacted] food-effect trial is included in this protocol, since the compound is predicted to be a Biopharmaceutics Classification System Class I/III compound, with a predicted high oral bioavailability (around 90%). Based on literature pertaining to Class I/III compounds, the high predicted bioavailability and a dedicated GastroPlus simulation™ (Simulations Plus, Inc., Lancaster, California, US) (which allows the simulation of the absorption of a compound in fasted and fed conditions, based on the physical and chemical properties of the molecule), a positive food effect is deemed unlikely (4, 5). The risk for patients

in Phase II to show increased exposure and ensuing safety issues in case the medication is accidentally taken with food is thus minimal. In case M5717 proves to be a Class III compound, a negative food effect cannot be excluded. A dedicated, fully powered food-effect trial will be conducted later in development with the final formulation and when more information on the ED and human variability is available.

The intended patient population for M5717 is people infected with P. falciparum, but the FIH trial is performed in healthy volunteers to characterize the safety, tolerability and PK of the compound in humans in the absence of any disease-related and potentially confounding factors. The safety, tolerability, PK and CCI [redacted] data from Part C will support decision-making on whether, and with which dose, to further investigate M5717 in a Phase II/proof-of-concept patient trial where the drug candidate may be evaluated as monotherapy or in combination with a partner molecule.

The trial will be conducted in healthy male and female subjects (WNCBP) who are free from any underlying conditions which could affect interpretation of the safety results. The inclusion criteria were chosen to help ensure the inclusion of only healthy subjects. Additional criteria are in place to ensure the safety and wellbeing of subjects.

CCI [redacted]

Part A and Part B of the trial will be placebo-controlled, to facilitate identification of effects related to administration of M5717. Part C will be open-label and only treat subjects with M5717.

5.2.2 Part A

Part A is a double-blind, randomized, placebo-controlled, SAD investigation in cohorts of 8 healthy subjects with up to 11 dose levels. The trial will evaluate the safety, tolerability, and PK properties of escalating single doses of M5717 when administered to healthy men and WNCBP under fasted conditions.

Within each cohort, subjects will be randomly assigned to receive a single dose of M5717 or placebo in a ratio of 6:2, respectively. The placebo control will facilitate identification of effects related to administration of M5717 rather than the trial procedures or situation, ie, to minimize bias. A 6:2 ratio of M5717 versus placebo is an accepted standard used in FIH trials.

A single dose of M5717 or matched placebo will be administered as oral capsule(s) (appropriate numbers of placebo, 10 mg, 50 mg, or 200 mg capsules) after at least 8 hours of fasting together with water on Day 1, followed by a 4-hour postdose fast. Water will be allowed up to 2 hours predose and again after 2 hours postdose. The number and strength of capsules to be administered at each dose level will be detailed in the pharmacy manual.

The initial dose investigated was 50 mg. This was lower than the MRSD of 100 mg derived from the most sensitive NOAEL with a safety factor of 10. Further details on the calculation of the MRSD and starting dose are given in Section 5.2.9. This 50 mg dose was within the initially predicted ED range, which had been estimated to be between 10 mg and 70 mg.

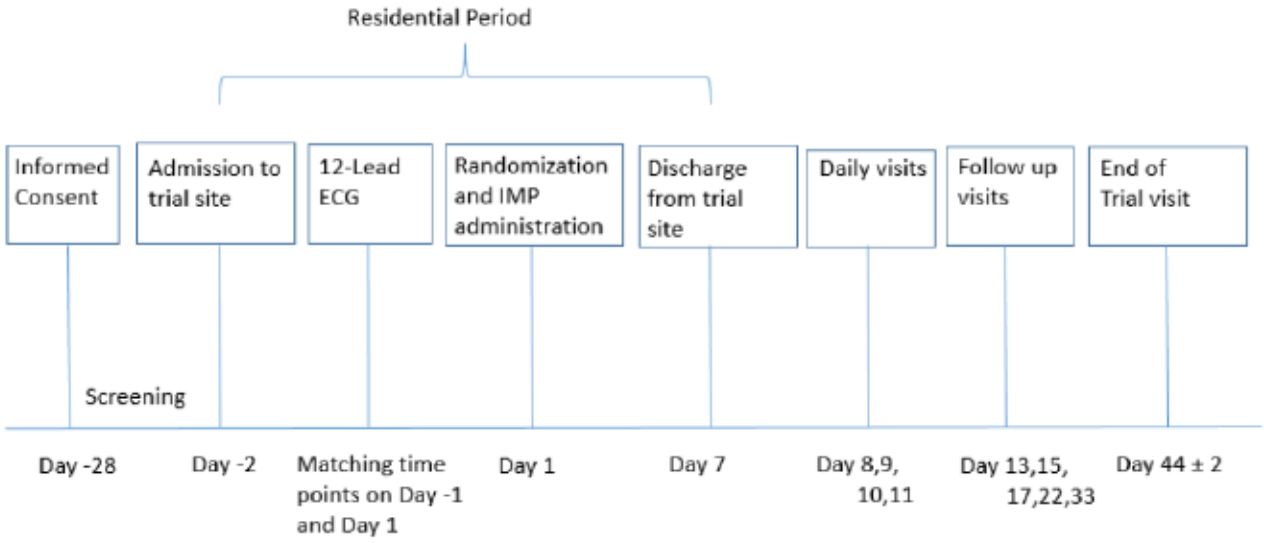
As this is a FIH trial, a sentinel dosing strategy will be employed for each dose cohort in Part A and Part B, except in case subjects are administered a similar or lower dose than an already administered dose. Under the discretion of the SMC, a sentinel cohort consisting of either 2 (1 active and 1 placebo) or 3 subjects (2 active and 1 placebo) will be dosed first. The Investigator will review blinded safety data up to at least 36 hours after dosing (t_{max} is expected to be around 16 hours) from these sentinel subjects to rule out any initial, severe acute reactions. Provided the safety data are supportive, the remaining 6 (5 active and 1 placebo) or 5 (4 active and 1 placebo) subjects, respectively, in the cohort will be randomized the following day or later, or divided over several consecutive days, depending on logistic feasibility.

After each cohort has completed 11 days of postdosing observation, the SMC will evaluate the safety dosing and escalation sequence and make recommendations on an ongoing basis. The data obtained from each cohort will be quality-checked before being provided blinded to the SMC. The data obtained from each cohort will undergo a formal review by the SMC to confirm that it is reasonable to proceed with the next dose/cohort. A formal report of each cohort, consisting of the data evaluated and a summary of the decisions taken by the SMC, will be provided at the end of each review.

A Screening period will occur from Day -28 to Day -2. Subjects will be admitted to the trial site on Day -2 and will be resident at the trial site under medical supervision until discharge on Day 7. On Day -1, digital 12-lead ECG recordings are included as a baseline for the intrasubject comparison of matching time points with the Day 1 recordings postdose over 24 hours, coinciding with the PK sampling time points, for thorough QTc assessment to reduce expected variability. The digital 12-lead ECG based QTc analysis will only be performed after completion of the trial by an experienced, qualified, and certified cardiologist, provided the compound fulfills the expectation, and reported separately from the clinical trial report.

A schematic presentation of the Part A trial design for each subject is presented in Figure 2.

Figure 2 Schematic Trial Design – Individual Subject in Part A



ECG = electrocardiogram; IMP = investigational medicinal product.

The predicted half-life of the compound in human was computed by Monte-Carlo (MC) simulations to take into account the uncertainties around the estimates of human clearance and volume of distribution as deduced from standard allometric scaling. The MC simulation resulted in a log-normal distribution with a median value of 257 hours, and 20% and 80% percentiles of respectively 127 hours and 519 hours. It is common practice to have subjects remain in the Phase I unit (trial site) for at least one half-life of a compound, but in this case confinement would be approximately 11 days, which might negatively affect trial compliance and recruitment. On the other hand, due to the minimal findings in the pivotal toxicology trials in which no acute effects were seen, it does not seem necessary to have the subjects in the trial site unit for a long period of time. Instead, having subjects report to the Phase I unit (trial site) on a regular basis should suffice in detecting safety signals. Therefore, subjects may be released from the trial site on Day 7, at the discretion of the Investigator, but they will need to report to the trial site (Day 9 and Day 11), and will be followed up by phone (Day 8 and Day 10) and will be required to send a photograph of their diary cards on those days. In case the actual half-life is shorter than the current prediction, the SMC can advise to shorten the residential period and to release the subjects earlier than Day 7 (after 1 half-life). Follow-up visits will occur on Day 13, Day 15, Day 17, Day 22, and Day 33, and an End of Trial visit on Day 44 (± 2 days). In addition, all efforts will be done by the investigational trial team to regularly contact (approximately every 2 to 3 days) subjects via telephone in between visits during their ambulatory period. Subjects will be instructed to contact the trial site immediately in case of any AEs.

Incidence, nature, and severity of all AEs, including changes in clinical laboratory results and vital signs, will be collected throughout the trial. Vital signs include body temperature, blood pressure (BP), heart rate, respiration rate, and ECG pattern (12-lead ECG). CCI [redacted]

CCI [redacted]

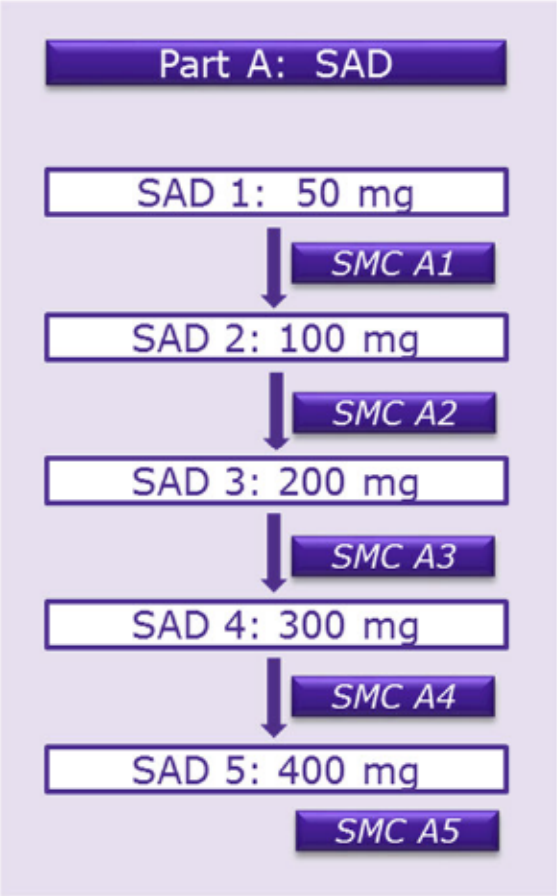
Blood and CCI samples will be collected for safety evaluation (hematology, biochemistry, coagulation, CCI [redacted]

CCI [redacted]

CCI [redacted]

The planned total duration of the trial for each subject in the SAD part will be up to approximately 12 weeks (up to 4 weeks for Screening, 1 day for dosing, 1-week residency at the trial site [discharge on Day 7], and Follow-up through Day 44 [± 2 days]) based on the 5-times expected terminal half-life of 11 days. If available PK data would indicate to a longer half-life, and/or safety data would necessitate a longer observation time beyond 44 days postdose, this will be evaluated and decided by the SMC. An Early Termination visit will be conducted for subjects who withdraw, preferably performed around the Follow-up visit, due to the expected long half-life of the compound.

Figure 3 Schematic Trial Design Cohorts Part A



SAD = Single ascending dose(s); SMC A1 to A5= Safety Monitoring Committee Part A Cohort 1 to Cohort 5.
The SMC may decide, on the basis of supportive safety and PK data, to increase the dose in Cohort 4 (SAD 4) to 400 mg (instead of 300 mg), and in Cohort 5 (SAD 5) to 600 mg (see also Section 5.2.9). During the conduct of the trial, the SMC recommended to add 2 additional SAD cohorts of 1,000 mg and 1,500 mg to Part A. Accordingly, SMC review meetings will be also performed after each cohort (SAD 6, and SAD 7).

Following completion of the first 2 cohorts (50 mg and 100 mg), the SMC will review all safety data up to at least Day 11 (AEs, safety laboratory results, and vital signs) and any other available data (including PK data up to at least 144 hours postdose) in a double-blind fashion, to determine whether the predicted PK and the observed PK are in line with simulations and whether escalation to the next dose level is appropriate. As the PK is predicted to be dose-linear and since the compound is expected to be BCS Class 1/3 with high bioavailability, no further on line PK data will be evaluated for SMC decisions, unless PK observations warrant this.

If the PK parameters of the first 2 cohorts are in line with the prediction, further sequential dosing of eg, 200 mg, 300 mg, and 400 mg (or 200 mg, 400 mg, and 600 mg) can be initiated, with an SMC review of safety data covering at least 11 days after each dosing cohort, with additional PK data of the preceding cohort(s), as applicable. If PK parameters are higher or lower than predicted, the dose escalation scheme can be adjusted by the SMC based on ongoing safety findings. Trial stopping rules are defined in Section 5.5.3.

During the conduct of the trial, the observed exposure was much lower (factor of 11 to 19) than predicted. The prediction of the efficacious dose was updated to 700 mg (range 600 to 800 mg). Based on the accumulated safety and PK data, the SMC recommended to add 2 additional SAD cohorts of 1,000 mg and (dependent on SMC review) 1,500 mg. Due to observations of transient, increases in liver enzymes above ULN in 4 of 8 subjects (one subject Grade 2 ALT and Grade 1 AST, two subjects Grade 1 for both ALT and AST, and one subject Grade one for ALT – according to Toxicity Grading Scale for healthy volunteers) of the 1,000 mg SAD cohort, the SMC decided to dose the next cohort with an intermediate dose of 1,250 mg.

In case no clinically significant deviations of safety parameters or appearance of any moderate/severe IMP-related TEAEs are observed, the SMC may decide to explore higher doses.

It is envisaged to explore a dose (exposure) up to around 2,400 mg, assuming 3 times the highest anticipated therapeutic dose (exposure) of 800 mg, if feasible without jeopardizing the safety of the subjects in the study.

The SMC will convene at an appropriate time to allow for the compilation of the required data for review. The interval between the completion of IMP administration in one cohort and the initiation of IMP administration in the next cohort of subjects will therefore be minimally 25 days. This will allow sufficient time for an SMC review and the final decision to be communicated to the trial site. Initiation of a higher-dose cohort will only occur if the previous dose level was deemed to be generally safe and well-tolerated and is predicted not to exceed the maximum exposure (see Section 5.5).

5.2.3 Part B

The MAD part of the trial is optional and will only be conducted if the observed PK profile does not allow administering of a tolerable single dose that will achieve an 8-day period with concentrations well above the predicted MPC, ie, 10 ng/mL. This assessment will be based on characteristic PK parameters, in particular the elimination half-life, as computed by noncompartmental analysis, of the PK data from Part A. The decision will be made by the SMC following collection and review of the initial PK data and sufficient safety data from the first 2 cohorts of Part A.

Part B is a randomized, double-blind, placebo-controlled MAD trial and will evaluate the safety, tolerability, and PK of multiple oral doses (within ascending dose cohorts) of M5717 or placebo administered over 3 days. CCI [redacted]

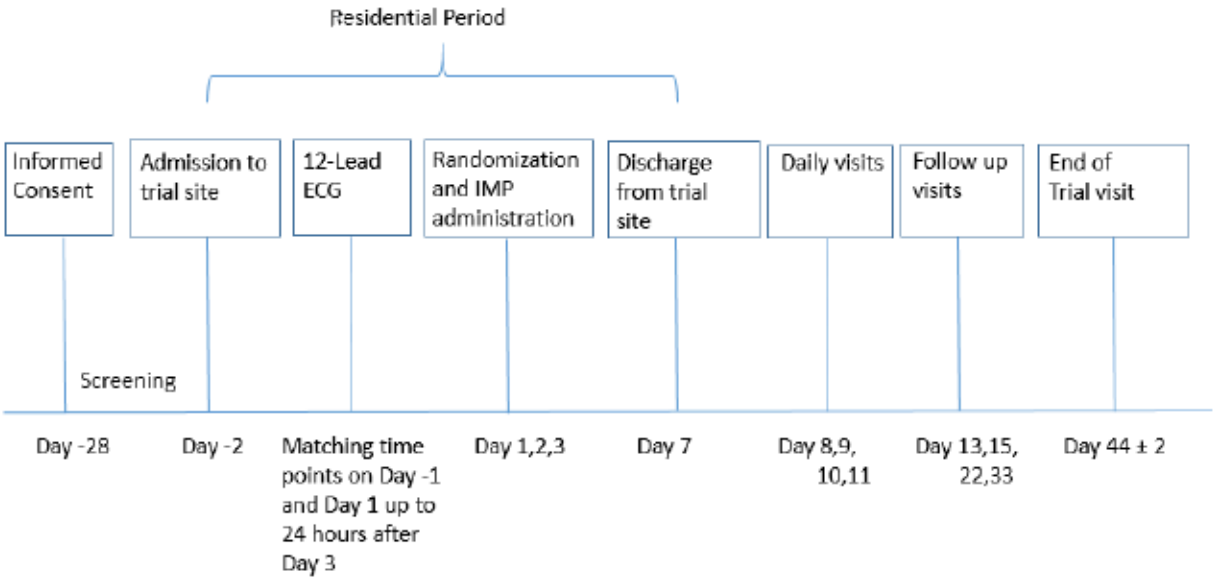
Multiple ascending doses of M5717 oral CCI [redacted] in capsules or matched placebo will be administered with water in a ratio of 6:2 after an overnight fast of at least 8 hours, once daily for 3 days (Day 1 to Day 3, inclusive), in a double-blinded fashion, followed by a 4-hour postdose fast. Water will be allowed up to 2 hours predose and again after 2 hours postdose.

Three MAD cohorts of 8 subjects each are planned in Part B. In each dose cohort, sentinel dosing as done in part A will be included (2 subjects dosed on Day 1, the remaining 6 subjects dosed at least 24 to 48 hours later). The SMC will decide on the dosing and escalation sequence.

A Screening period will occur from Day -28 to Day -1. Subjects will be admitted to the trial site on Day -2 and will be resident in the trial site under medical supervision until discharge, which is planned after completion of all trial-related assessments on Day 7 at the discretion of the Investigator. Subjects will need to report to the trial site (Day 9 and Day 11), and will be followed up by phone (Day 8 and Day 10) and will be required to send a photograph of their diary cards on those days.

Follow-up visits will occur on Day 13, Day 15, Day 22, and Day 33, and an End of Trial visit on Day 44 (± 2 days) (Figure 4). In addition, subjects will be regularly contacted (approximately every 2 to 3 days) by telephone during their ambulatory period. Blood and urine samples will be collected for safety evaluation (hematology, biochemistry, coagulation, urinalysis, and CCI) as will blood samples for PK analysis throughout the residential and ambulatory period (at time points indicated in Table 2).

Figure 4 Schematic Trial Design - Individual Subject in Part B



ECG = electrocardiogram; IMP = investigational medicinal product.

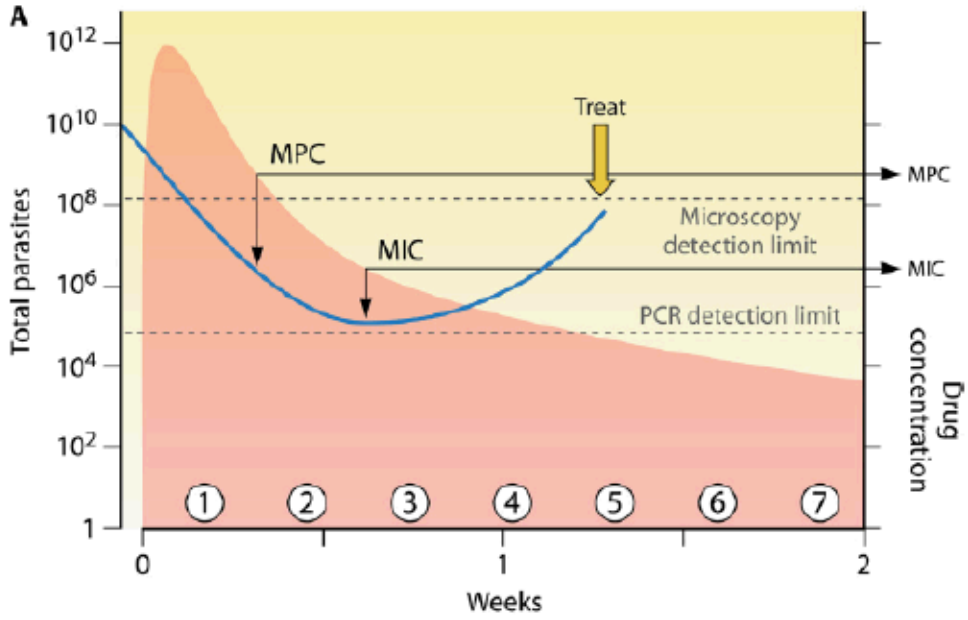
5.2.4 Part C

The objective of this trial part is to evaluate the PK/PD relationship between M5717 PK and parasite clearance. The evolution of the parasitemia will be followed and measured by quantitative polymerase chain reaction (qPCR) over time, following the inoculation and the treatment with M5717. This allows a calculation or modeling of the parasite reduction ratio (PRR), parasite clearance half-life, MIC, and MPC of M5717 for P. falciparum in the human malaria challenge model and will be used to inform on the dose range in patient populations.

The primary objective variable is PRR of asexual parasites based on qPCR after administration of M5717. The PRR for asexual parasites will be estimated using the slope of the optimal fit of the log-linear relationship of the parasitemia decay.

The MIC is defined as the drug concentration at which the relative rate of change in parasitemia is equal to zero (see Figure 5); the MPC represents the lowest drug concentration above which parasites decline at a maximal rate. In other words, the MIC is the drug concentration at which the rate of parasite killing is equal to the rate of parasite reproduction and represents a "steady state". Implicit in this definition is the assumption that the MPC and MIC values are invariant of the dose administered. An approximation of the MPC and MIC values in healthy subjects infected with low numbers of parasites will help in identifying the optimal dose of M5717 for subsequent Phase II trials in patients and will reduce the number of patients in the Phase II trials by reducing the number of doses that will need to be investigated. The MPC and MIC values will be the major parameters to consider in planning for a future combination antimalarial regimen.

Figure 5 **Illustration of Relation between Drug Concentration, Parasitemia Levels, Minimal Parasiticidal Concentration and Minimal Inhibitory Concentration**



MIC = Minimal inhibitory concentration; MPC = minimal parasitacidal concentration; PCR = polymerase chain reaction.

Part C may be initiated once the safety and PK data of at least the first 2 cohorts of Part A, ie, the 50 mg and 100 mg dose groups, or the targeted therapeutic exposure range have been assessed. In case multiple dosing (Part B) is deemed necessary based on the results of Part A, multiple dosing in Part C multiple dosing may be initiated after analysis of 1 or 2 cohorts in Part B (safety data and PK), with the decision to be made by the SMC.

Part C is a single-center, open-label trial using the P. falciparum IBSM human challenge to assess the antimalarial activity of M5717 in healthy subjects infected with malaria under controlled conditions. The trial is planned to be conducted in up to 3 cohorts (n=8 per cohort). CCI

[redacted]

The following options may be considered:

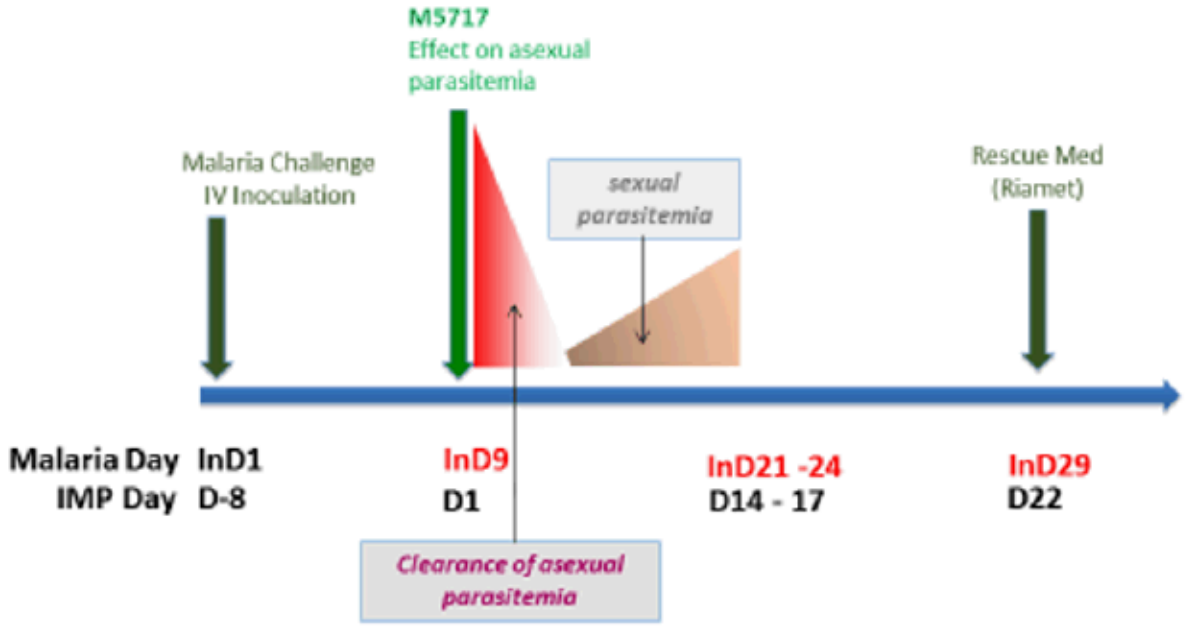
- If the initial dose leads to a complete reduction of parasitemia and does not lead to observed recrudescence in any subjects, then a lower dose will be used for the second cohort
- If recrudescence is observed in an insufficient number of subjects, so that the MIC cannot be derived, then a second cohort with a lower dose should be initiated
- If recrudescence is observed in enough subjects so that the MIC can be derived, then the need for a higher dose will be evaluated and decided by the SMC.

CCI

[redacted]

Figure 6 presents an illustration of the time schedule for Part C.

Figure 6 **Illustration of Time Schedule for Challenge Model**



In D1 to In D9 = Day of Inoculum administration (In D1) to 9 days post administration of the Inoculum (In D9); IMP = investigational medicinal product; IV = intravenous.

This example assumes that the IMP is administered on Inoculum Day 9.

In order to be able to observe the MIC and model the MPC, one needs to assess the drug concentration at the time that parasite count is at its lowest level. This implies that the lowest parasite count must be observed. Provided that a high enough dose is administered, the MIC should be reached after the subject has recovered from any clinical symptoms of malaria, and when parasite densities have fallen below the level of microscopic detection, as the sensitivity of microscopy is only 50/µL (approximately 10^8 parasites total). Sensitive qPCR methods now allow timely (assay time approximately 4 hours) detection of very low parasitic densities (below 100 parasites/mL, which represents sensitivity up to 1,000 times greater than thick blood smears by microscopy), so it is possible to follow the sub-latent parasitemia levels as they decline and then rise again. Once there is clear evidence by real-time qPCR that parasitemia is rising (parasitemia of $\geq$ 5,000 asexual blood stage parasites and increasing 2-fold within 48 hours), rescue medication will be administered at the decision/discretion of the Investigator. The subject will thus be cured of their infection before or at emergence of advanced clinical symptoms of malaria infection.

CCI [redacted]

All subjects in a given cohort will be inoculated within a period of 60 minutes.

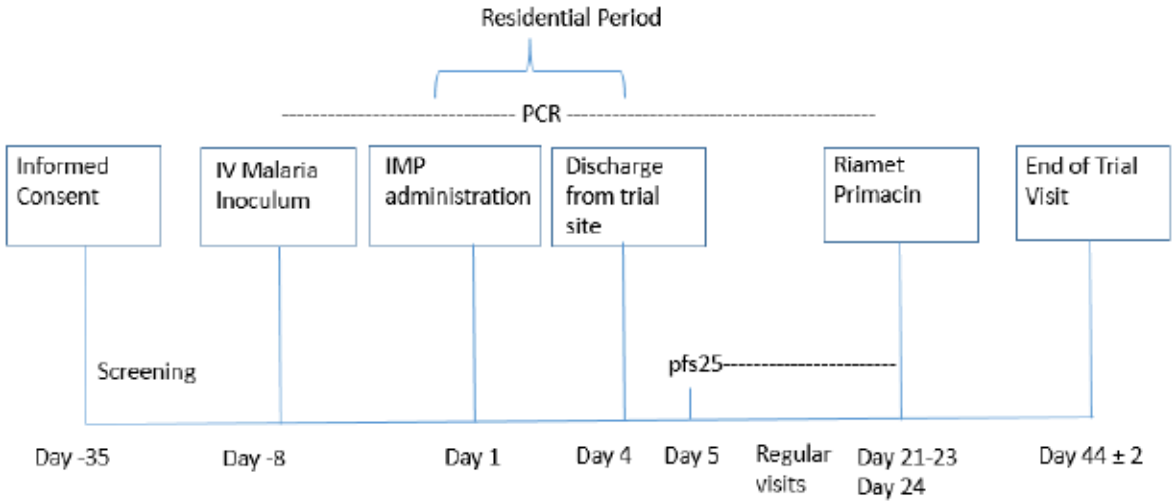
A maximum of 3 cohorts will be investigated as a single-dose or multiple-dose evaluation in Part C of the trial. The highest dose to be investigated in Part C will not exceed the highest dose administered in Part A or Part B of the trial.

Subjects will be admitted to the trial site for M5717 administration 9 days post administration of the Inoculum (In D9; Day 1). The parasitemia of all subjects at In D9 is expected to be ≥ 5,000 parasites/mL. However, subjects can be administered M5717 at any time point before or after In D9 at the Investigators discretion based on parasitemia and/or clinical symptoms.

The total duration of participation in Part C of the trial is approximately 80 days for each subject, including a Screening period of up to 28 days, 8 days for the IBSM incubation period, and 44 days of Follow-up after treatment with M5717.

A schematic presentation of the Part C trial design is presented in Figure 7.

Figure 7 Schematic Trial Design Part C



IMP = Investigational medicinal product; IV = intravenous; PCR = polymerase chain reaction.

Figure 8 displays the possible relationships between Part A and Part C of the trial, in case PK, safety, and tolerability data from the first 2 cohorts support administering a tolerable single dose that covers an 8-day period with concentrations well above the MPC, ie, 10 ng/mL. The SMC will assess on the basis of accumulated exposure and safety data, if Part C can be initiated after the second cohort in Part A (SAD 2: 100 mg), or if further single dose(s) in Part A need to be investigated before initiation of Part C at the appropriate, to be determined, predicted ED.

Figure 8 Schematic Trial Design Cohorts Part C and Relation to Part A

C = Cohort; ED = efficacious dose; IBSM = Induced Blood Stage Malaria; SAD = single ascending dose(s); SMC A1 to A5= Safety Monitoring Committee Part A Cohort 1 to Cohort 5; SMC C1 to C3 = Safety Monitoring Committee Part C Cohort 1 to Cohort 3.

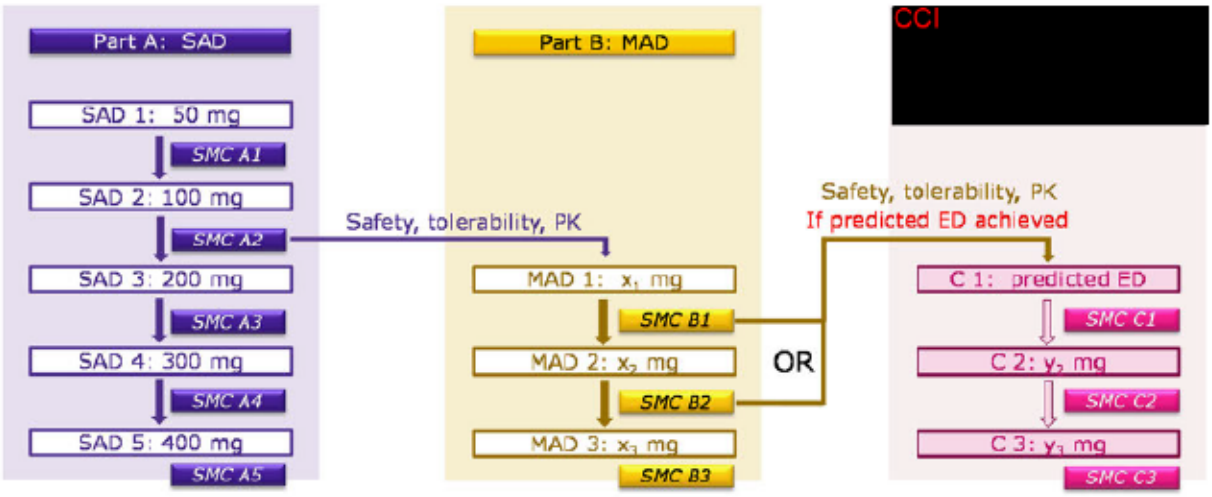
The SMC may decide, on the basis of supportive safety and PK data, to increase the dose in Part A Cohort 4 (SAD 4) to 400 mg (instead of 300 mg), and in Cohort 5 (SAD 5) to 600 mg (see also Section 5.2.9).
During the conduct of the trial, the SMC recommended to add 2 additional SAD cohorts of 1,000 mg and 1,500 mg to Part A. Accordingly, SMC review meetings will also be performed after each cohort (SAD 6, and SAD 7).

Subjects will be injected with the malaria inoculum at approximately Day -8 (Inoculum Day 1). Blood (2 mL) for qPCR will then be collected at Day -8, and then daily from the morning of Day -4 (Inoculum Day 5) until the qPCR is positive. Subjects will be contacted daily via phone to ensure their safety from Inoculum Day 2 to Inoculum Day 4, as well as on Day 23 to Day 25, for a safety check and compliance of rescue medication use. Once the qPCR is positive, blood will be collected twice daily (morning and evening) until the day when the treatment threshold is reached, ie, Day 1 (baseline; that is day of treatment with M5717). Follow-up visits will occur on Day 13, Day 15, Day 17, Day 22, Day 29, and Day 33, and an End of Trial visit on Day 44 (± 2 days). In addition, subjects will be regularly contacted by telephone daily while they are outpatients, from Inoculum Day 2 to Inoculum Day 4, as well as on Day 23 to Day 25. Safety samples will be collected for safety evaluation (hematology, biochemistry, coagulation, and urinalysis) and blood samples for PK and PD analysis will be collected throughout the residential and ambulatory period (at time points indicated in the Schedule of Assessments, Table 3).

During confinement and subsequent visits, blood for qPCR analysis will be collected prior to dosing and then at the time points indicated in the Schedule of Assessments (Table 3). Once the parasitemia is around < 500 parasites, at the Investigator's discretion, the sampling may revert to daily until the qPCR is negative for 48 hours, and then approximately 3 times per week at the Investigator's discretion until Day 22, coinciding with PK time points where possible (see Table 3). In the case of recrudescence, additional blood sample(s) will be collected to investigate for the potential emergence of resistance.

Figure 9 displays the possible relationships between the cohorts in Part A, Part B and Part C of the trial in case it is necessary to explore the multiple dosing part (Part B), ie, if the observed PK profile does not allow administration of a tolerable single dose that covers an 8 day period with concentrations well above the predicted MPC, ie, 10 ng/mL. In this case, the SMC will assess and decide on the basis of accumulated exposure and safety data from Part A (SAD) and Part B (MAD) cohort(s), if Part C can be initiated with multiple dosing at the appropriate, to be determined, predicted ED.

Figure 9 **Schematic Trial Design Cohorts Part C and Relation to Part A and Part B (if applicable)**



C = Cohort; ED = efficacious dose; IBSM = Induced Blood Stage Malaria; MAD = multiple ascending dose(s); SAD = single ascending dose(s); SMC A1 to A5= Safety Monitoring Committee Part A Cohort 1 to Cohort 5; SMC B1 to B3 = Safety Monitoring Committee Part B Cohort 1 to Cohort 3; SMC C1 to C3 = Safety Monitoring Committee Part C Cohort 1 to Cohort 3.

The SMC may decide, on the basis of supportive safety and PK data, to increase the dose in Part A Cohort 4 (SAD 4) to 400 mg (instead of 300 mg), and in Cohort 5 (SAD 5) to 600 mg (see also Section 5.2.9).
During the conduct of the trial, the SMC recommended to add 2 additional SAD cohorts of 1,000 mg and 1,500 mg to Part A. Accordingly, SMC review meetings will also be performed after each cohort (SAD 6, and SAD 7).

5.2.5 Rescue Medication for Breakthrough Infections

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 trial. All subjects will receive Riamet; in addition, Primacin 45 mg will be administered to those subjects who have evidence of gametocytemia. P. falciparum 3D7, the parasite strain constituting the inoculum, is fully sensitive to both Riamet and Primacin. Loss of sensitivity is regularly checked in vitro.

The curative/rescue drugs will be inventoried prior to the beginning of trial enrollment on trial accountability logs, to document condition upon receipt, including lot numbers. The Investigator or qualified trial personnel designated by the Investigator will ensure that the received drugs are the specified formulation. The trial site Pharmacist or a nominee designated by the Investigator is

responsible for maintaining an accurate inventory and accountability record of drug supplies for this trial.

- Riamet (20 mg artemether and 120 mg lumefantrine) oral tablets. A course of treatment comprises 6 doses of 4 tablets each (total course of 24 tablets) given over a period of 60 hours. Four oral tablets are administered as a single-dose, administered twice daily at 12 hour intervals, ie, time 0, 12 hours, 24 hours, 36 hours, 48 hours, and 60 hours. Each dose of tablets administered orally should be consumed with food
- Primacin (7.5 mg primaquine phosphate) oral tablets: To clear gametocytes of P. falciparum, subjects will receive 45 mg as a single dose with food at the end of their Riamet treatment if gametocytes are identified by gametocyte-specific PCR.

Compulsory commencement of clearance medication will occur no later than 21 days after the last dose of M5717. Administration of rescue medications prior to Day 22 will be determined at the Investigator's discretion using the following criteria:

- Failure of clearance: defined as failure to clear parasitemia by at least 10-fold at 72 hours post IMP administration
- Recrudescence: defined as ≥ 5000 blood stage parasites/mL and a 2-fold parasitemia increase within 48 hours, or re-occurrence of malaria symptoms with a malaria clinical score > 6.

Early intervention can occur if either poor responses or fast responses are seen following M5717 treatment. This flexibility is designed to ensure subject safety and to avoid subject inconvenience if useful data cannot be obtained. However, pre-emptive rescue treatment can commence whenever deemed necessary by the Investigator.

Subjects will be monitored, either in the trial site, or by telephone for 3 days to ensure adherence to the rescue medication therapy. In any case, safety assessments should be performed prior to administration of the rescue medication and recorded in the eCRF.

Blood and urine samples will be collected for safety evaluation (hematology, biochemistry, coagulation, urinalysis, and CCI) as will blood samples for PK throughout the residential and ambulant period (at time points indicated in Table 3). This will include hematology, biochemistry, ECG, vital signs, physical examination, coagulation profile and urinalysis. However, serology, red blood cell auto-antibodies, and serum storage collection will still be collected at Day 22 regardless of the study day that rescue medications are administered.

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5.2.8 Safety Monitoring Committee and Decision Criteria

The SMC will be set up as described in the SMC charter.

The SMC will determine:

- Dose escalation/de-escalation
- Termination of further dose escalation in Part A if it is expected that further escalation will not be tolerated or if it is determined that a maximum exposure may be reached (Section 5.5.3)
- The need to start a multiple dosing regimen in Part B
- The timing to start Part C
- The respective dose(s) and dose escalations to be evaluated in Part B and Part C
- Request unblinding of data, if deemed necessary
- Suspension of enrollment, trial modification, or trial termination.

Part A and Part B

The SMC will regularly meet at approximately Day 25 after all subjects in a given SAD/MAD cohort have received administration of M5717 or matching placebo. A medical monitoring report summarizing all safety and tolerability data (AEs, safety laboratory data, ECG, and vital signs) collected from minimally 6 subjects up to and including Day 11 (around 1 median half-life) for SAD cohorts will be provided to the SMC for review. The medical monitoring report may also include a summary of the safety data for all previous dose cohorts, when appropriate. The first 2 SMC meetings in the SAD part (Part A) will also contain PK data from 6 subjects up to 144 hours postdose. For later SMC meetings, PK data of the preceding cohort(s) will be reviewed as applicable to support the safety and tolerability assessment, as deemed necessary by the SMC. Safety laboratory and PK data included in the monitoring report to be provided to the SMC will undergo quality control by the respective laboratory(ies) responsible for this data.

In addition, the SMC can modify PK sampling times and/or ECG recording times based on new information received (eg, to better align with timing of t_{max}) but is not allowed to increase the number of PK sampling points unless by amending the clinical trial protocol.

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In case of a safety concern, the SMC members are allowed to request immediate unblinding of the data. In the pivotal toxicology studies, vomiting and diarrhea were identified as dose-limiting events, so these events will be carefully monitored. The SMC may also request access to unblinded PK data in case the need arises, to evaluate the correlation between exposure and safety data reviewed by the SMC.

Once the SMC has defined a dose, based on safety data, that does not allow further escalation of the dose, the SMC may recommend testing lower doses according to the same Schedule of Assessments as for the other cohorts, if this is deemed necessary to better characterize the safety and/or PK profile of M5717 prior to termination of Part A.

Part C

The SMC will review all available safety (up to at least Day 11) and PK/PD data (up to at least Day 9) after subjects of each cohort have been treated and will decide whether an additional cohort needs to be included, as well as the dose to be investigated in that cohort. In principle, a maximum of 3 doses are foreseen to accurately describe the PK/PD correlation. In addition, the SMC may modify PCR sampling times and the number of samples based on new information received (eg, to better align with timing of the PRR).

5.2.9 Justification for Dose

In reference to its mode of action, the selectivity of the eEF2 target for Plasmodium and the availability of data from a relevant animal species model for predicting human responses, M5717 was not classified as a high-risk molecule and the NOAEL approach was applied to support the starting dose.

The starting dose for the first human use of M5717 was determined based on the following factors which are detailed in the following sections:

- Identification of a MRSD, using the NOAEL identified in pivotal GLP toxicology studies in the most sensitive species, as recommended by the FDA Guidance Estimating the Maximum

Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers 2005 (7)

- Consideration of NOAEL exposures reached in animal toxicity studies
- PK/PD modeling of preclinical data for the purpose of predicting the ED range in humans.

In the 14-day toxicology trial in dogs, M5717 was administered orally 2 times for a period of 3 days with 2 days in between, followed by 4 days of treatment. In the 14-day toxicology trial in rats, M5717 was administered orally 2 times for a period of 3 days, with 6 days in between. An extensive summary of all toxicology findings is given in the IB. The main observations are summarized in Table 5 along with the plan how to adequately monitor these potential findings.

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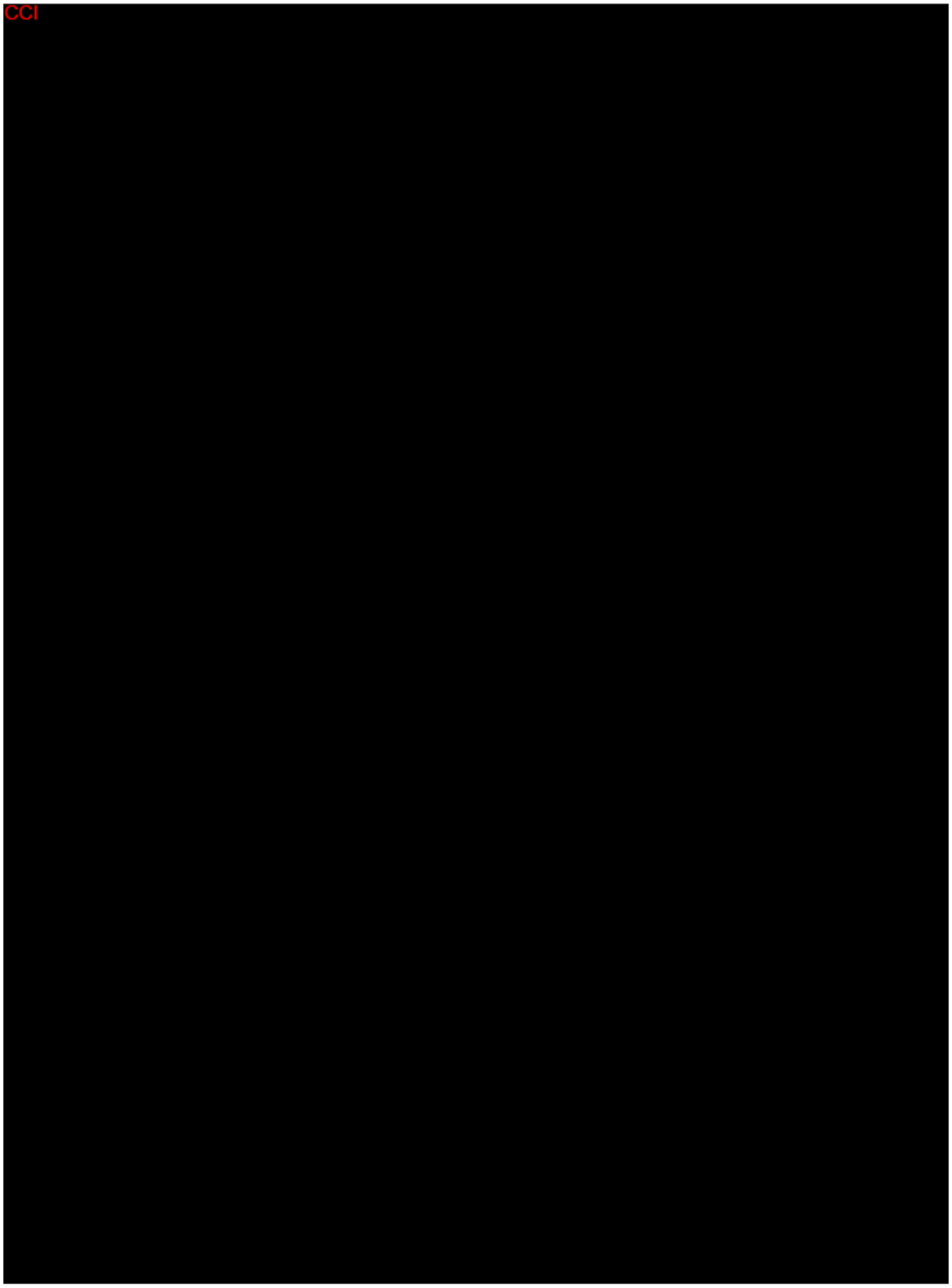

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and glomerular podocytes occurs frequently, with the development of the renal toxicities of aminoglycosides and chloroquine, respectively.

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5.2.10 Inclusion of Special Populations

Not applicable.

5.2.11 Rationale for Endpoints

Standard safety, tolerability and PK of M5717 will be determined using the following parameters:

- Nature, incidence, and severity of AEs/SAEs, including relationship to trial treatment, AEs/SAEs leading to dose modification or discontinuation of trial treatment
- Safety laboratory parameters (hematology, coagulation, biochemistry [specifically ALT and AST], urinalysis, and CCI)

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- Vital signs (body temperature, BP, heart rate), respiratory rate, and 12-lead ECG. The digital 12-lead ECG will be used for concentration QTc analysis
- Blood concentrations of M5717 will be used to determine the standard PK parameters in each trial part
- PRR, PCT, and MIC are validated endpoints for PK/PD analysis of malaria compounds

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5.3 Selection of Trial Population

Only persons meeting all inclusion criteria and none of the exclusion criteria may be enrolled into the trial as subjects. Prior to performing any trial assessments not part of the subject's routine medical care, the Investigator will ensure that the subject has provided written informed consent following the procedure described in Section 9.2.

Inclusion and exclusion criteria are to be checked at Screening and Day -1/ Day -2 of Part A and Part B unless otherwise stated.

For Part C the criteria have to be checked at Screening, prior to inoculation and again prior to IMP administration.

5.3.1 Inclusion Criteria

1. Adult men and WNCBP, 18 to 55 years of age (inclusive), with total body weight ≥ 50.0 kg and body mass index (BMI) between 19.0 kg/m^2 and 29.9 kg/m^2 (inclusive).
2. A female subject is eligible to participate if she is not breastfeeding and not a woman of childbearing potential (WOCBP as defined in Appendix I) confirmed at Screening by fulfilling one of the following criteria:

    a. Postmenopausal defined as having amenorrhea for ≥ 12 consecutive months following cessation of all exogenous hormonal treatments, and increased follicle-stimulating hormone (FSH) > 40 mIU/mL.

    b. Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy. Tubal ligation alone is not sufficient.

3. A male participant must agree to use a condom with or without spermicide during sexual activity with a female partner of childbearing potential and to have their female partner use a highly effective contraception (ie, methods with a failure rate of less than 1 % per year) as detailed in Appendix I of this protocol, during the treatment period and for at least 20 weeks after the last dose of IMP administration and to refrain from donating sperm during this period.
4. Healthy as assessed by the Investigator with no clinically significant abnormality identified on physical examination or laboratory evaluation and no active clinically significant disorder, condition, infection or disease that would pose a risk to subject safety or interfere with the trial evaluation, procedures, or completion.

5. Stable nonsmokers for at least 6 months preceding Screening.
6. Able and willing to comply with restrictions on exposure to sunlight and to give written informed consent.
7. Part C additional: Do not live alone (from start of malaria inoculation until at least the end of the antimalarial drug treatment), willing to provide contact details of a person living with them, and be contactable and available for the duration of the trial; no history of possible malaria exposure.

5.3.2 Exclusion Criteria

5.3.2.1 Part A, Part B, and Part C

1. History or presence of clinically relevant respiratory, gastrointestinal, renal, hepatic, hematological, lymphatic, neurological, cardiovascular, psychiatric, musculoskeletal, genitourinary, immunological, dermatological, connective tissue diseases or disorders.
2. History of any malignancy except surgically cured skin cancers.
3. History of relevant drug hypersensitivity, ascertained or presumptive allergy/hypersensitivity to the active drug substance and/or formulation ingredients; history of serious allergic reactions leading to hospitalization or any other allergic reaction in general, which the Investigator considers may affect the safety of the subject and/or outcome of the trial.
4. History of alcoholism or drug abuse.
5. Liver functions tests:
    a. above the laboratory reference range the day before IMP administration (Day -1) for Part A and Part B
    b. $\geq 3 \times$ ULN for Inoculum Day 8 in Part C.
6. Creatinine clearance < 90 mL/min as estimated using the Cockcroft and Gault equation at Screening.
7. Semi-supine BP > 140/90 mmHg at Day -1 (this may be repeated once).
8. Electrocardiogram shows a QT interval corrected for heart rate according to Fridericia's formula (QTcF) > 450 ms, PR > 210 ms, QRSD > 120 ms at Screening and predose.
9. Consumption of an average weekly intake of > 14 drinks/week for men or > 7 drinks/week for women. One drink is equivalent to 12 g alcohol = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) or 80-proof distilled spirits.
10. Positive for hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody or human immunodeficiency virus (HIV) I and II tests at Screening.
11. Positive for drugs of abuse, nicotine/cotinine or alcohol on Screening or (each) admission.
12. Use of any investigational drug in any clinical trial within 90 days from the last administration, or on extended follow-up in a clinical trial, even if the last administration of an IMP was > 90 days ago.

13. Donation or loss of more than 450 mL of blood in the 90 days prior to Screening.
14. Excessive consumption of xanthine-containing food or beverages (> 5 cups of coffee per day or equivalent) or inability to stop consuming caffeine, from 48 hours prior to IMP administration until 48 hours after IMP administration.
15. Intake of grapefruit, Seville oranges, cranberries, star fruit or juices of these fruits, as well as quinine-containing food/beverages (eg, tonic water, bitter lemon), within 14 days prior to IMP administration until the end of the residential period.
16. Ingestion of any poppy seeds within 24 hours prior to each Drug Abuse Screening.
17. Use of any prescribed medicine or over-the-counter drug (other than occasional ibuprofen [< 1 g] or paracetamol [< 1 g], or vitamins and minerals) within 2 weeks/5 times the half-life of the respective drug, whichever is the longer, prior to the first administration of IMP. See Section 6.5 for details regarding permitted/prohibited medications throughout the duration of the trial.
18. Use of drugs and herbal remedies with enzyme inducing properties such as St. John's Wort, within 4 weeks before the first administration of IMP until the End of Trial visit. See Section 6.5 for details regarding permitted/prohibited medications throughout the duration of the trial.
19. Inability to refrain from taking up any new unaccustomed exercise from Screening until the End of Trial visit.
20. Inability to communicate reliably with trial site personnel or considered by the Investigator to be unable to or unlikely to cooperate with the requirements of the trial.
21. Having skin Type I, ie, always burns, never tans (pale peach complexion; blond or red hair; blue eyes; freckles; according to the Fitzpatrick scale in Appendix VI).

5.3.2.2 Additional for Part C

22. Any history of malaria.
23. Participation in a previous malaria vaccine trial.
24. Participation in a previous human malaria challenge trial.
25. Has travelled to or lived (> 2 weeks) in a malaria-endemic area/region during the past 12 months. Malaria-endemicity will be assessed by consulting https://map.ox.ac.uk/country-profiles/#!/.
26. Plan to travel to a malaria-endemic area/region during the course of the trial.
27. Has evidence of increased cardiovascular disease risk (defined as 5-year risk > 10%, for those > 35 years of age, as determined by the Australian Absolute Cardiovascular Disease Risk Calculator. Risk factors include sex, age, systolic BP (mm/Hg), smoking status, total cholesterol and high-density lipoprotein (HDL) cholesterol (mmol/L), and reported diabetes status.
28. Frequent headaches and/or migraine, recurrent nausea, and/or vomiting (> 2 times per month).

29. Presence of acute infectious disease or fever (ie, sublingual temperature ≥ 38.0°C) within the 5 days prior to inoculation with malaria parasites.
30. History of splenectomy.
31. Participant unwilling to defer blood donations for 6 months.
32. Participant who has previously received a blood transfusion and/or tests positive for red blood cell antibodies.
33. Any corticosteroids, anti-inflammatory drugs, immunomodulators or anticoagulants in the past 3 months. Any participant currently receiving or having previously received immunosuppressive therapy, including systemic corticosteroids including adrenocorticotrophic hormone or inhaled steroids in dosages which are associated with hypothalamic-pituitary-adrenal axis suppression or chronic use of inhaled high-potency corticosteroids.
34. Any recent (within 6 weeks from Screening) or current systemic therapy with drugs known to have potential antimalarial activity eg, trimethoprim/sulfamethoxazole, tetracycline, doxycycline, erythromycin, clarithromycin, azithromycin, clindamycin, rifampicin, newer quinolones, benzodiazepines, flunarizine, fluoxetine, methotrexate, chloroquine, hydroxychloroquine.
35. Known allergy or adversity to one of the rescue medication proposed for the challenge trial including known or confirmed deficiency for glucose-6-phosphate dehydrogenase (G6PD).

5.4 Criteria for Initiation of Trial Treatment

Subjects who fulfill the eligibility criteria will be enrolled into the trial. Randomization procedures for Part A and Part B are described in Section 8.2.

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal from Trial Treatment

As only a single dose will be given in Part A, subjects cannot be withdrawn from treatment but can be withdrawn from the trial (see Section 5.5.2). In addition to the rules for withdrawal from the trial, subjects in Part B must be withdrawn from further treatment with the IMP if any of the following occurs:

- Meets an exclusion criterion as listed in Section 5.3.2
- Use of a nonpermitted concomitant medication. However, any medications that are considered necessary for the subject's wellbeing may be given at the discretion of the Investigator
- AEs, if discontinuation of IMP is desired or considered necessary by the Investigator and/or the subject
- Protocol noncompliance judged as significant by the Investigator and/or the Sponsor including noncompliance to the required trial considerations (eg, caffeine intake/food/diet requirements)
- Any events that unacceptably endanger the safety of the subject

- ALT or AST > 5 x ULN
- ALT or AST > 3 x ULN and total bilirubin > 2 x ULN or International Normalized Ratio [INR] > 1.5
- ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

M5717 administration will be suspended and a subject will be withdrawn from the IMP for any of the above events and appropriate medical care will be provided. Subjects withdrawn from the IMP must complete the End of Trial visit as described in the Schedule of Assessments (Table 1 to Table 3). In any case, the appropriate electronic case report form (eCRF) section must be completed.

5.5.2 Withdrawal from the Trial

Subjects may withdraw from the trial at any time without giving a reason. Withdrawal of consent will be considered withdrawal from the trial. Wherever possible, subjects will be followed up until 44 days following administration of M5717 and they will be asked to complete the End of Trial visit.

A subject must be withdrawn if any of the following occur during the trial:

- Use of a nonpermitted concomitant medication. However, any medications that are considered necessary for the subject's wellbeing may be given at the discretion of the Investigator
- Protocol noncompliance judged as significant by the Investigator, including noncompliance to the required trial considerations (eg, caffeine intake/food/diet requirements)
- Subject lost to follow-up
- Participation in another clinical trial during the duration of this trial
- Any events that unacceptably endanger the safety of the subject (eg, occurrence of an SAE)
- ALT or AST > 5 x ULN. (Part A and Part B; Part C before IMP administration)
- ALT or AST > 3 x ULN, and total bilirubin > 2 x ULN or INR > 1.5 (Part A and Part B; Part C before IMP administration)
- ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%). (Part A and Part B; Part C before IMP administration).

In case liver function test derangements are observed, the SMC would need to review the data; the subjects who have been treated with M5717 will be followed up and might remain on trial, rather than being withdrawn, unless a decision is made otherwise by the Investigator and/or the SMC.

If a subject has failed to attend scheduled trial assessments, the Investigator must determine the reasons and the circumstances as completely and accurately as possible. If there is a medical reason for the withdrawal, the subject will remain under the supervision of the Investigator until

satisfactory health has returned or care has been transferred to the subject's general practitioner or to a hospital consultant. In case a subject has to be withdrawn from the trial, the Trial Monitor and Clinical Trial Leader at the Local and Funding Sponsors will be informed immediately. The need for replacement of subjects will be discussed with the Sponsor on a case-by-case determination. Further details on subject replacement are provided in Section 8.2.

5.5.3 Trial Stopping Rules

Along with the PK evaluations during dose-escalation in Part A and Part B, stopping rules will be used to determine whether further dose escalation should be stopped. Dose escalation may be stopped if it is determined that the limits of safety and/or tolerability have been reached or when an exposure above the NOAEL is foreseen/reached. This decision will be made after review of the accumulating data by the SMC. The SMC may not overrule the Investigators' decision to stop dose escalation. If dose escalation is stopped due to any of these findings, additional cohorts may receive intermediate doses of M5717 provided these doses are considered by the SMC as likely to be tolerated and to provide additional scientific value.

Dose escalation in Part A and Part B will be suspended and further review conducted by the SMC, if any of the following conditions are met within a given cohort:

- An SAE occurs in 1 or more drug-treated subjects and is shown to be related to IMP
- Two (2) or more drug-treated subjects having Qualitative Toxicity Scale (QTS) Grade 3 (or higher) events in the same organ or body system
- Fifty (50) percent or more of drug-treated subjects having a QTS Grade 2 (or higher) event in the same organ or body system
- Any other event in drug-treated subjects occurs and is deemed to pose an unacceptable risk to subjects.
- If, based on the observed PK data, the group mean AUC_{0-t} (based on total blood concentration) of the next planned dose is projected to exceed the exposure at the NOAEL (320,000 ng × h/mL) that dose might not be explored. Modified doses may be explored if they are not expected to exceed the PK stopping criteria.
- Once it is confirmed by the SMC, after review of the data, that one of these criteria has been met and drug-relatedness has been established, dose-escalation will be stopped.

In case of an SAE, dosing will cease if the SAE is determined to be either drug-related or unknown. Each SAE will be followed until resolution or during 5 half-lives of M5717.

If the trial is terminated, subjects who have received M5717 will be followed for safety assessments as described in the End of Trial visit.

5.6 Premature Termination of the Trial

The clinical trial may be terminated prematurely or suspended at the request of the Sponsor, the PI, the ethics committee, or the SMC in case new safety or efficacy information leads to an

unfavorable risk-benefit judgment for the IMP. Additionally, the Sponsor may discontinue the trial if it becomes unjustifiable for medical or ethical reasons, for poor enrollment, or because of discontinuation of clinical development of the IMP or for safety reasons.

Local Health Authorities (Therapeutic Goods Administration) and the Independent Ethics Committee (IEC) (-HREC) will be informed about the discontinuation of the trial in accordance with applicable regulations.

5.7 Definition of End of Trial

For administrative and safety reporting purposes, the end of trial will be defined as the day of the last subject's last visit.

6 Investigational Medicinal Product and Other Drugs Used in the Trial

The term "IMP" refers to a pharmaceutical form of an active substance or a placebo being tested or used as a reference treatment or therapy in a clinical trial, including products that have a marketing authorization but are formulated, packaged, or administered differently from the authorized form, used for an unauthorized indication, or used to gain further information about the authorized form.

6.1 Description of the Investigational Medicinal Product

M5717: Capsules containing 10 mg, 50 mg, or 200 mg of M5717 . Depending on the dose to be administered, the exact number and strength of capsules will be calculated as detailed in the pharmacy manual.

Placebo: Capsules containing 50 mg of placebo matched to a similar number of capsules with M5717.

M5717 and matching placebo have the .

6.2 Dosage and Administration

M5717 will be administered in each trial part, as indicated below. In each trial part, subjects will fast from 8 hours prior until 4 hours after each dose. Water will be allowed up to 2 hours predose and again after 2 hours postdose. The date and time of each dose administration will be recorded in the eCRF. The maximum dose level which may be administered in this trial was initially set at 600 mg daily and re-evaluated to 1,500 mg daily by the SMC.

Part A: One single oral dose of M5717 or placebo after an 8-hour fasting period, taken together with 250 mL of water, followed by a 4-hour postdose fast. Water will be allowed up to 2 hours predose and again after 2 hours postdose.

Part B: One single oral dose of M5717 or placebo after an 8-hour predose fasting period, taken together with 250 mL of water, followed by a 4-hour postdose fast, on 3 consecutive days (once

daily dosing, ie, 24 hours apart). Water will be allowed up to 2 hours predose and again after 2 hours postdose.

Part C: On In D9 (Day 1), one single oral dose of M5717 after an 8-hour fasting period, taken together with 250 mL of water, followed by a 4-hour postdose fast, on Day 1 or on 3 consecutive days (once daily dosing, ie, 24 hours apart). Water will be allowed up to 2 hours predose and again after 2 hours postdose.

The Challenge inoculum will be administered intravenously on Inoculum Day 1 (In D1). For that purpose, each subject will undergo cannulation with an appropriate gauge cannula. The cannula will be flushed with 5 mL of 0.9% sodium chloride for injection, before and after the administration of the inoculum. The cannula will then be removed, and hemostasis ensured by the use of an appropriate dressing. Inocula will be administered in the morning under the supervision of the Investigator.

6.3 Assignment to Treatment Groups

Subjects will receive their subject identification number (screening number) as soon as they have signed informed consent. For each cohort in Part A and Part B, subjects who meet all the inclusion criteria and none of the exclusion criteria will be randomized in a double-blind fashion to M5717 or placebo in a ratio of 6:2 (Sentinel 1:1 and Remainder 5:1, or Sentinel 2:1 and Remainder 4:1, based on the SMC decision), respectively. The Investigator or designee will allocate a randomization number (created as per the Sponsor's standards) to each subject in sequential order, immediately before the first administration of the IMP (see Section 8.2). The randomization schedules and individual code-break envelopes (for emergency unblinding, see Section 6.11) for Part A and Part B will be created by a randomization Statistician. For each cohort in Part C, eligible subjects will receive the same M5717 dose with no need for randomization.

6.4 Noninvestigational Medicinal Products and Malaria Inoculum to be Used

For a full description of the Malaria Inoculum and the Rescue Medication, see Appendix II.

Part C: Malaria Inoculum

On In D1, frozen blood aliquots will be thawed and used to prepare the challenge inocula at PPD PPD . The syringes containing the inocula of the blood-stage parasites will be prepared at PPD on the enrollment day and the initiation of the trial. The time between preparation of the final inoculum and inoculation will be a maximum of 2 hours, during which time all inocula will be stored on ice. For further information on the inoculum, see Appendix II. All participants within a single cohort will be challenged intravenously within a 60-minute period. The PPD pharmacist will document receipt conditions and time restrictions of use.

Part C: Other Medication

Riamet and Primacin will be acquired by PPD , labeled according to identity, brand or source, and batch number. The supplies will be held in appropriate locked storage conditions at PPD

until required. The contents of the label for drug to be administered to the participants will be in accordance with all applicable regulatory requirements. The inoculum strain (P. falciparum 3D7) used in the challenge model has been proven to be sensitive to the rescue medications.

The rescue drugs, ie, Riamet, Primacin, Malarone and intravenous artesunate will be inventoried prior to the beginning of trial enrollment on trial accountability logs in regards to condition upon receipt, including lot numbers. The Investigator or qualified designee will ensure that the received drugs are the specified formulation. The site pharmacist or qualified designee is responsible for maintaining an accurate inventory and accountability record of drug supplies for this trial.

6.5 Concomitant Medications and Therapies

The Investigator will record all concomitant medications taken by the subject during the trial, from the date of signature of informed consent, in the appropriate section of the eCRF, noting the name, dose, duration and indication of each drug. Concomitant procedures and any changes to a concomitant medication or other intervention should also be recorded in the eCRF.

Medication history (3 months prior to Screening) must be recorded, noting the generic name, galenic form, and dose, route of administration, duration and indication of each drug.

6.5.1 Permitted Medicines

Ibuprofen is the preferred symptomatic treatment for malaria symptoms occurring during the trial. Paracetamol, which may facilitate liver enzyme elevations in the context of malaria inoculation in nonimmune subjects, should be avoided. Doses of paracetamol up to 1 g per day, at the discretion of the Investigator, may be allowed but only if ibuprofen is contraindicated or considered insufficient to treat the symptoms. No other concomitant medication or over-the-counter products should be administered unless deemed necessary by the Investigator. Any medications that are considered necessary to protect subject welfare and will not interfere with the IMP may be given at the Investigator's discretion. Rescue medications may be administered to address adverse reactions or anticipated emergency situations.

6.5.2 Prohibited Medicines

The subjects are prohibited from using prescription medications within 2 weeks or 5 half-lives, whichever is longer, prior to the first IMP administration, during the trial, and until after the Follow-up visit (this includes vitamins, and minerals). Subjects are also prohibited from using drugs/herbal medications, including over-the-counter and natural products, with enzyme-inducing properties, such as St. John's Wort, within 4 weeks prior to the first IMP administration until end of trial and enzyme inhibitors during the trial. Use of any investigational agent is not permitted within 8 weeks before dosing.

6.5.3 Other Interventions

Not applicable.

6.5.4 Special Precautions

The trial will be performed in a Phase I unit (trial site) with direct access to a Hospital Emergency Unit. Equipment and other agents (epinephrine, prednisolone equivalents, etc) will be available at the trial site in case of severe allergic reactions. The subjects will remain at the trial site from Day -2 to Day 7 in Part A and Part B, and from Day 1 to Day 4 in Part C. The subjects' health and wellbeing will be extensively monitored during this time.

Trial subjects should adhere to the following restrictions:

- Male subjects must agree to use and have their female partners use highly effective medically acceptable methods of contraception (according to ICH Guidance M3[R2] – Nonclinical safety studies for the conduct of human clinical trials and marketing authorization of pharmaceuticals) during the period of participation in the trial and for at least 20 weeks after the last IMP administration (Inclusion 3)
- Be stable nonsmokers for the duration of participation in the trial until the End of Trial visit
- Refrain from alcohol use for 1 week prior to trial treatment. After release of confinement from the trial site, subjects will be requested not to consume more than 1 drink (2 units) of alcohol per day until the End of Trial visit
- Use of sunscreen when bare skin is exposed to sun and use of sunglasses
- Refrain from taking up any new unaccustomed exercise from Screening until the End of Trial visit.

Subjects will be required to protect themselves from sun exposure through the use of appropriate clothing (eg, long sleeved shirts and full length trousers), sunscreen, sunglasses, etc and limit their exposure to the sun until the End of Trial visit. Sunscreen, hats, etc will be provided to subjects.

Compliance checks will be performed and documented at each visit following discharge from the trial site.

6.5.5 Management of Specific Adverse Events or Adverse Drug Reactions

No specific measures are proposed at this stage. Standard medical care will be provided at the trial site for all AEs encountered during the trial. In the challenge model, specific attention will be given to ALT increases.

6.6 Packaging and Labeling of the Investigational Medicinal Product and the Challenge Inoculum

M5717 and matching placebo is manufactured and packaged in accordance with applicable regulatory requirements and GMP Guidelines by the contract manufacturing organization CCI Pharma, Craigavon, UK. The labelling is performed by the contract manufacturing organization CCI , Bathgate, UK. M5717 and matching placebo are packaged in CCI

The challenge inoculum syringes will be labeled in accordance with the GMP requirements.

6.7 Preparation, Handling, and Storage of the Investigational Medicinal Product and the Challenge Inoculum

All Parts

The pharmacy or designee will receive the IMP and the challenge inoculum labeled and packaged according to the local regulatory requirements and the storage requirements. M5717 will be shipped in ready to use capsule formulation. The responsible Pharmacist will dispense the necessary amount of the IMP. Detailed guidance will be provided in the pharmacy manual. The IMP supplies will be recorded in an IMP inventory.

M5717 must be carefully stored at the trial site in a closed room or cabinet with restricted access, safely and separately from other drugs and protected from environmental extremes until used in the trial. M5717 and placebo should only be transported and stored in the original package. CCI [redacted] Any deviations from the recommended transport and storage conditions should be immediately reported to the Sponsor, and the IMP should not be used until authorization has been received from the Sponsor. The preparation, handling and storage of the IMP will be documented in the pharmacy manual.

Part C only

On In D1, the frozen blood aliquots will be thawed and used to prepare the syringes containing the challenge inocula at PPD One vial containing the P. falciparum 3D7 challenge inoculum is sufficient to prepare the malaria challenge dose for all subjects per cohort. The time between preparation of the final inoculum and inoculation will be a maximum of 2 hours, during which time all prepared inocula will be stored at the required temperature.

The IMP must not be used for any purpose other than the trial in question.

It must be ensured at the trial site that the IMP and the challenge inoculum is not used after the use-by date. This is to be closely monitored by the responsible Monitor.

Further details may be provided in the pharmacy manual.

6.8 Investigational Medicinal Product Accountability

The Investigator or suitably qualified designee is responsible for ensuring IMP, inoculum, and rescue medications accountability, including reconciliation of drugs and maintenance of records.

- Upon receipt of the IMP/inoculum/rescue medications, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate documentation and returning it to the location specified. A copy will be archived for the Investigator Site File

- IMP/inoculum/rescue medications dispensing will be recorded on the appropriate drug accountability forms so that accurate records will be available for verification at each monitoring visit
- Trial site IMP/inoculum/rescue medications accountability records will include the following
  - Confirmation of IMP/inoculum/rescue medications receipt, in good condition and in the defined temperature range
  - The inventory of IMP/inoculum/rescue medications provided for the clinical trial and prepared at the site
  - The use of each dose by each subject
  - The disposition (including return, if applicable) of any unused IMP/inoculum/rescue medications
  - Dates, quantities, batch numbers, vial numbers, expiry dates, formulation (for IMP/inoculum/rescue medications prepared at the site), and the individual subject trial numbers.

The Investigator site should maintain records, which adequately document that subjects were provided the doses specified in this protocol, and all IMP/inoculum/rescue medications provided were fully reconciled.

Unused IMP/inoculum/rescue medications must not be discarded and/or used for any purpose other than the present trial. No IMP/inoculum/rescue medications that is dispensed to a subject may be redispensed to a different subject.

A Trial Monitor will periodically collect the IMP/inoculum/rescue medications accountability forms.

6.9 Assessment of Investigational Medicinal Product Compliance

The IMP will be administered by the trial site personnel within the confines of the trial site. A mouth and hand check will be performed after each dose administration to ensure that all doses have been swallowed.

6.10 Blinding

The trial will be double-blind in Part A and Part B. Part C will be open-label. Blinding will be maintained throughout the duration of the relevant trial part, ie, until the database lock of Part A and until the database lock of Part B. The randomization list is to be kept strictly confidential, accessible only to authorized persons (eg, randomization statistician, pharmacists, and the bioanalytical laboratories that prepare and analyze relevant samples), until the time of unblinding. Interim PK analyses will be performed blinded (ie, utilizing dummy subject numbers which cannot be linked to the subject identifiers used in the trial site). In addition, data listings (ie, utilizing dummy subject numbers different from those used for the PK analysis) will be provided in a blinded manner to support dose escalation or dose modification decisions by the SMC. After each cohort in Part A and Part B, the SMC will review data on safety and tolerability. Their ensuing

decision will generally be made without breaking the randomization code. If judged necessary by the SMC, an individual subject or the complete cohort may be unblinded during evaluation of the trial data. Before unblinding, the SMC should document the decision to unblind and any planned action to be taken based on the revealed treatment allocation.

Only when the trial (all 3 parts) is completed, database locked, the data file verified, and protocol deviations determined, will the drug codes be broken and made available for data analysis. However, if the Sponsor decides to lock the database corresponding to a trial part (ie, Part A, or Part B, or Part C) for the purpose of a final analysis of that trial part, then that trial part may be unblinded after the data file is verified and protocol deviations determined. Furthermore, if the Sponsor considers it necessary for timely decision-making, a trial-independent statistician/modeler may be directed to receive the randomization code for a trial part after the trial is completed, but prior to database lock, for that trial part. All breaks of the trial blind must be adequately documented.

6.11 Emergency Unblinding

Part A and Part B only

The trial blind may be broken for an individual subject only if knowledge of the IMP is essential for clinical management of the subject. The Investigator or designee will unblind the subject using the individual code-break envelope provided by the randomization statistician. The Investigator must promptly explain the reason for any unblinding of an IMP to the Sponsor without revealing the result to any Sponsor employee except the designated Drug Safety representative (using the Emergency Unblinding Notification Form).

The Investigator must record the date of unblinding and the reason in the eCRF. Contact information for breaking the blind in an emergency is given on the subject emergency card provided to each subject. Under certain circumstances, Drug Safety may be required to unblind the treatment assignment for an individual subject following an SAE or other serious event; for example, if an expedited regulatory report is required.

Once the treatment code has been broken for a subject, administration of IMPs will be stopped and the subject will be withdrawn from the trial. The subject will attend the Early Termination visit.

6.12 Treatment of Overdose

An overdose is defined as any dose greater than the highest daily dose included in a clinical trial protocol or planned for an individual subject enrolled in the trial. Even if it does not meet other criteria for an SAE, any overdose must be recorded in the trial medication section of the eCRF and reported to Drug Safety in an expedited manner using the SAE Report Form, and following the procedure in Section 7.4.

The effects of an M5717 overdose are unknown, and therefore no standard treatment is currently established. In the event of an overdose, the Investigator or treating physician should use appropriate clinical judgment for the evaluation and management of any clinical signs, symptoms, and laboratory results.

Refer to the package inserts of the rescue medication in Appendix VII for details regarding the effects and management of an overdose.

6.13 Medical Care of Subjects after End of Trial

In this trial in healthy subjects, no further treatment or medical care is planned or required after the end of the trial.

7 Trial Procedures and Assessments

Prior to performing any trial assessments, the Investigator will ensure that the subject has provided written informed consent according to the procedure described in Section 9.2.

A subject identifier (see Section 6.3) will be assigned for each subject for whom written informed consent has been obtained.

All efforts should be made to perform assessments as close as possible to the scheduled time points.

Compliance to protocol specific requirements will be checked at each visit and subjects are given reminders each time they leave the trial site.

At visits where assessment time points coincide with each other, the following procedure should be followed: perform vital signs assessments slightly before the specific time point, ECG assessments on time, PK blood sampling directly following ECG.

Samples and assessments obtained within the defined window (see Table 4) from dosing will not be captured as a protocol deviation, as long as the exact time of the assessment/sample collection is noted on the source document and data collection tool (eg, eCRF).

7.1 Schedule of Assessments

The Schedule of Assessments for Part A, Part B, and Part C is provided in Table 1 to Table 3.

7.1.1 Screening Examinations

All subjects will undergo an entry examination to evaluate their health status. This examination will be conducted not more than 28 days prior to the planned first IMP or inoculum administration. Only subjects who meet the inclusion criteria and none of the exclusion criteria will be enrolled in the trial.

Prior to any Screening examinations the subjects have to sign the Participant Information Consent Form (PICF). The assessments to be performed at Screening are indicated in the Schedule of Assessments (Table 1 to Table 3). Safety laboratory assessments with results outside of the normal laboratory range may be repeated once.

Subjects who fail to meet the protocol specified inclusion- or exclusion criteria, or who withdraw their consent in the Screening period are considered screening failures. The following data, as a

minimum, should be recorded for these subjects: date of informed consent, inclusion/exclusion criteria, demographics (including age, sex (gender), weight, and height), AEs (if any) from the date of informed consent until the subject is considered a screen failure by the Investigator, reason for screening failure, and the Investigator's signature.

7.1.2 Treatment Periods

A review and update of the subject's inclusion/exclusion criteria to ensure the subject remains eligible for participation in the trial should be performed prior to admission to the trial site. Eligible subjects will be randomized to active treatment or placebo in Part A and Part B, or enrolled to the challenge and active treatment in Part C. Subjects will be admitted to the trial site on Day -2 for Part A and Part B, and Day 1 for Part C. Subjects will be discharged after completion of the required assessments on Day 7 for Part A and Part B, and between Day 4 to Day 7, at the discretion of the Investigator on advice of the SMC.

The assessments to be performed at specific time points are indicated in the Schedule of Assessments (Table 1 to Table 3).

7.1.3 Ambulant Visits

Ambulant visits will be performed at regular intervals from Day 8 onwards for Part A and Part B. In Part C, ambulant visits will be performed on Inoculum Days prior to IMP administration and at regular intervals from Day 4 onwards. In Part C, an ambulant visit will be performed on Day 22 for subjects with breakthrough infections for the administration of rescue medication.

In addition, subjects will be regularly contacted (approximately every 2 to 3 days) by telephone during their ambulant period.

The assessments to be performed at specific time points are indicated in the Schedule of Assessments (Table 1 to Table 3).

7.1.4 Follow-up Visits

Subjects will be asked to return to the trial site for Follow-up visits on Day 13, Day 15, Day 17 (Part A and Part C), Day 22, Day 29 (Part C only), Day 33, and Day 44 for Part A, Part B, and Part C. The assessments to be performed at these time points are indicated in the Schedule of Assessments (Table 1 to Table 3).

7.1.5 Phone Calls

On Day 8 and Day 10 of Part A and Part B, subjects may be contacted by the trial site via a phone call or subjects may text a photo of their completed diary card instead of visiting the trial site. In Part C, the subject will be contacted daily via phone calls while outpatient, from Inoculum Day 2 to Inoculum Day 4, as well as on Day 23 to Day 25, for a safety check and compliance of rescue medication use.

7.1.6 End of Trial/Early Termination Visit

The End of Trial examination has to verify that all values tested in the Screening have remained within a clinically acceptable range. The relevant tests will be performed on Day 44 (± 2 days) for Part A, Part B, and Part C. The assessments to be performed at these time points are indicated in the Schedule of Assessments (Table 1 to Table 3).

Unacceptable values and AEs will be followed up until they return to baseline/resolved or there is an adequate explanation which is not related to the trial.

7.2 Demographic and Other Baseline Characteristics

At Screening, the following demographic data will be collected: date of birth, sex (gender), race, and ethnicity.

Furthermore, the following will be documented:

- Height, weight, and BMI
- Skin type according to the Fitzpatrick scale (Appendix VI)
- Clinically relevant findings in the medical history are recorded
- Prior medications within 4 weeks (any medication with enzyme inducing or inhibiting properties) or 2 weeks (any prescribed medicine or over-the-counter drug [other than occasional ibuprofen < 1 g or paracetamol < 1 g] or dietary supplement including herbal remedies, vitamins, and minerals
- Smoking status, alcohol intake
- Female status (WNCBP, postmenopausal, sterilization).

7.3 Efficacy Assessments

Clinical endpoints: Part A and B; not applicable.

Clinical endpoints: Part C; Parasitical effect of M5717, defined as the reduction and/or clearance of parasitemia by qPCR up to Day 8, (see Section 5.2.4).

The malaria clinical score is defined in Appendix IV and needs to be assessed in case any malaria-related symptoms are seen.

Surrogate endpoints: Not applicable.

Follow-up: Not applicable.

Efficacy examinations will be scheduled according to the applicable Schedule of Assessments (Table 3).

7.4 Assessment of Safety

The safety profile of the IMP will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings including vital signs, 12-lead ECGs, and safety laboratory tests.

Comprehensive assessment of any apparent toxicity experienced by each subject will be performed from the time of giving informed consent and throughout the trial. The Investigator will report any AEs, whether observed by the Investigator or reported by the subject (see Section 7.4.1.2). The reporting period for AEs is described in Section 7.4.1.3. The expected signs and symptoms of malaria after administration of the inoculum in Part C is detailed in Appendix V.

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, regardless of causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator must assess the severity of AEs according to the QTS as described in the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials", as follows:

Mild (Grade 1): The subject is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate (Grade 2): The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe (Grade 3): Significant impairment of functioning: the subject is unable to carry out his or her usual activities.

Potentially Life-Threatening (Grade 4): Extreme limitation to daily activity. Significant assistance required. Significant medical intervention, hospital or hospice care very likely.

Investigators must also systematically assess the causal relationship of AEs to the IMP or inoculum using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the IMP include, but may not be limited to, temporal relationship between the AE and the IMP,

known (from animal studies) side effects of the IMP, known side effects of the inoculum, medical history, concomitant medication, course of the underlying disease, trial procedures.

Unrelated: Not reasonably related to the IMP or inoculum or rescue medication. AE could not medically (pharmacologically/clinically) be attributed to the IMP/inoculum/rescue medication under investigation in this clinical trial protocol. A reasonable alternative explanation must be available.

Related: Suspected to be reasonably related to the IMP or inoculum or rescue medication. AE could medically (pharmacologically/clinically) be attributed to the IMP/inoculum/rescue medication under investigation in this clinical trial protocol.

The outcome should be entered with terms described below:

- Recovered without sequelae
- Recovered with sequelae
- Ongoing
- Fatal
- Unknown.

In case of a fatality, the cause of death is considered as the SAE, and the death is considered as its OUTCOME.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition must be reported as the AE rather than the abnormal value itself.

Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening. (Note: The term "life-threatening" refers to an event in which the subject is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe)
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

- Is otherwise considered to be medically important. (Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

For the purposes of reporting, any suspected transmission of an infectious agent via an IMP/inoculum is also considered an SAE and should be reported in an expedited manner, as described in Section 7.4.1.4.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to simplify trial treatment or trial procedures (for example, an overnight stay to monitor initiation of treatment with the IMP is not considered an SAE. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (for example, undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial are defined as Baseline Medical Conditions, and are not to be considered AEs.

Adverse Events of Special Interest

The assessments to be performed for assessment of AESIs is detailed in Section 7.4.4.7.

The following are identified as AESIs in this trial:

- Vomiting or diarrhea
- Liver enzyme elevations (ALT/AST/Bilirubin)
- Cutaneous reactions (local tolerability CRF for severity of redness, swelling, induration, bruising, and itching)
- Photosensitivity/light sensitivity
- Pregnancy in a female partner of a male subject.

AESIs for monitoring should be reported following the procedure for an SAE described in Section 7.4.1.4.

7.4.1.2 Methods of Recording and Assessing Adverse Events

At each trial visit, the subject will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject or observed by the Investigator.

Complete, accurate, and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. Among these AEs, all SAEs and all nonserious AESIs must be additionally documented and reported using a Serious Adverse Event Report Form as described in Section 7.4.1.4.

It is important that each AE report include a description of the event, its duration (onset and resolution dates [and times, when it is important to assess the time of AE onset relative to the recorded treatment administration time]), its severity (according to the QTS as described in the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"), its causal relationship with the IMP or rescue medication, any other potential causal factors, any treatment given or other action taken (including dose modification or discontinuation of the IMP), and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

Specific guidance can be found in the eCRF Completion and Monitoring Conventions provided by the CRO in coordination with of the Sponsor.

7.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is initially included in any part (Part A, B, or C) of the trial (date of first signature of informed consent/date of first signature of first informed consent) and continues until the End of Trial visit (Day 44 ± 2 days) for the subject.

7.4.1.4 Procedure for Reporting Serious Adverse Events, Adverse Events of Special Interest and Dose Limiting Toxicities

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the Sponsors, both Funding and the Local Sponsor, or their designee by fax or by e-mail. All written reports should be transmitted using the SAE Report Form, which must be completed by the Investigator following specific completion instructions.

When an SAE (or follow-up information) is reported by telephone, a written report must be sent immediately thereafter by fax or e-mail. Reporting procedures and timelines are the same for any new follow-up information on a previously reported SAE.

Names, addresses, telephone-, and fax numbers for SAE reporting will be included in the trial-specific SAE Report Form.

All written reports should be transmitted with the SAE Report Form, which must be completed by the Investigator following specific completion instructions.

Relevant pages from the eCRF may be provided in parallel (for example, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (for

example, laboratory results, hospital report, autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data on the event that are recorded in the corresponding section of the eCRF.

The Investigator must respond to any request for follow-up information (for example, additional information, outcome, final evaluation, other records where needed) or to any question the Sponsors/designees may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsors to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the responsible Monitor, although in exceptional circumstances the Global Patient Safety department may contact the Investigator directly to obtain further information or to discuss the event.

Adverse Events of Special Interest

In the event of a ***nonserious*** AESI, the Investigator will complete the AESI Report Form and send it to the Sponsors/designees within a maximum of 24 HOURS after becoming aware of the event. Names, addresses, telephone-, and fax numbers for AESI reporting will be included on the Report Form. Serious AESIs have to be reported in an expedited manner as SAEs as outlined above.

7.4.1.5 Safety Reporting to Health Authorities, Independent Ethics Committees/ Institutional Review Boards and Investigators

The Local Sponsor will send appropriate safety notifications to the Local Health Authorities (Therapeutic Goods Administration) in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving trial subjects to the HREC that approved the trial.

In accordance with ICH GCP, the Sponsors/designees will inform the Investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the trial or alter the HREC's approval/favorable opinion to continue the trial." In particular and in line with respective regulations, the Sponsors/designees will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product ("suspected unexpected serious adverse reactions"). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations with regard to Safety Report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsors/designees will provide appropriate Safety Reports directly to the concerned lead HREC and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned HREC of any Safety Reports provided by the Sponsors/designees and of filing copies of all related correspondence in the Investigator Site File.

7.4.1.6 Monitoring of Subjects with Adverse Events

Adverse events are recorded and assessed continuously throughout the trial (see Section 7.4.1.3) and are assessed for final outcome at the End of Trial visit). All SAEs/AESIs ongoing at the End of Trial visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

7.4.2 Pregnancy and In Utero Drug Exposure

Pregnancies in female partners of male subjects are considered to be AEs. All pregnancies with an estimated conception date during the period defined in Section 7.4.1.3 must be recorded by convention in the AE page/section of the eCRF. The Investigator must notify the Sponsors/designees in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting in Section 7.4.1.4.

Investigators must actively follow up, document and report on the outcome of all these pregnancies, even if the subjects are withdrawn from the trial.

The Investigator must notify the Sponsors/designees of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the Serious Adverse Event Report Form will be used if the subject sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event.

Any abnormal outcome must be reported in an expedited manner as described in Section 7.4.1.4, while normal outcomes must be reported within 45 days after delivery.

7.4.3 Clinical Laboratory Assessments

A list of laboratory reference ranges will be provided to the Sponsors/designees before shipment of the IMP. Any change in laboratory reference ranges during the trial will additionally be forwarded to the Sponsors/designees.

All routine laboratory analyses will be done at a laboratory facility local to the trial site, and relevant results should be available before administration of the IMP. The report of the results must be retained as a part of the subject's medical record or source documents. Blood and urine samples will be collected for the laboratory tests specified in Table 8, following the timing noted in the Schedule of Assessments (Table 1 to Table 3). All samples should be clearly identified.

For that purpose of safety laboratory blood sample collection and PK/PD sample collection during the residency periods, each subject will undergo cannulation with an appropriate gauge cannula. The cannula will be flushed with 5 mL of 0.9% sodium chloride before sample collection. The cannula will then be removed, and hemostasis ensured by the use of an appropriate dressing.

The actual date and time of the blood sample collection will be recorded in the subject's eCRF. The details of sample collection, sample tube labelling, sample preparation and processing, storage, and shipping procedures will be described in a separate laboratory manual or manual of operations.

The total blood volume to be drawn from each subject for planned assessments during the trial will not exceed a standard unit of blood (approximately 450 mL).

7.4.3.1 Safety Laboratory Assessments

All laboratory examinations will be carried out under fasting conditions of at least 8 hours for Screening and subsequent biochemistry assessments. The list of safety laboratory examinations is displayed in Table 8.

Some additional parameters might be routinely analyzed by the laboratory after abnormal findings, such as manual differential blood count, direct/indirect bilirubin, creatine phosphokinase myocardial/brain type fraction, haptoglobin, hemolysis index, or miR22 in Part C. Additional laboratory safety examinations during the course of the trial are at the discretion of the Investigator.

Table 8 Clinical Laboratory Evaluations

Biochemistry	Aspartate aminotransferase Alanine aminotransferase Alkaline phosphatase Gamma-glutamyl-transferase Lactate dehydrogenase Creatine phosphokinase[a]	Bilirubin (total)[a] Cholesterol[b] Triglycerides[b] HDL cholesterol[b] Amylase Lipase Uric acid	Sodium Potassium Chloride Calcium Magnesium[b] Bicarbonate	Phosphate Creatinine Urea Glucose (fasting)
Hematology	Hematocrit Hemoglobin Red blood cell count Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration	Platelet count White blood cell count Reticulocyte count	White blood cell differentials and absolute counts[a]: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	
Urinalysis	pH Nitrite Protein Glucose	Ketone bodies Urobilinogen Bilirubin	White blood cell count Microscopic examination[c]	
Urine drug screen	Cocaine Amphetamines Methamphetamines Opiates	Barbiturates MDMA (ecstasy) Benzodiazepine Methadone	THC (cannabinoids) Phencyclidine Tricyclic antidepressants Paracetamol	
Serology	Hepatitis B surface antigen Hepatitis B core antibody Hepatitis C antibody Human immunodeficiency virus (HIV) I and II antibodies Red blood cell antibodies (Part C only)			
Coagulation	Prothrombin time (INR), Activated partial thromboplastin time			
Other tests	Urine cotinine Alcohol breathalyzer Follicle-stimulating hormone (for postmenopausal women) Glucose-6-phosphate dehydrogenase status/testing (Part C only)			

HDL = High-density lipoprotein; INR = International Normalized Ratio:
MDMA = 3,4-methylenedioxymethamphetamine; THC = tetrahydrocannabinol.

a In case of abnormal findings manual differential blood count, direct/indirect bilirubin and creatine phosphokinase myocardial/brain type fraction or other assessments can be requested by the Investigator.

b Screening only.

c Only if blood, protein, nitrite, or white blood cell count are positive on the dipstick.

7.4.3.2 Semi-Quantitative Urinalysis

The list of semi-quantitative urinalysis examinations is displayed in Table 8.

On positive findings or on demand of the Investigator, a subsidiary microscopic examination of the sediment will be performed. Additional laboratory examinations during the course of the trial are at the discretion of the Investigator.

7.4.3.3 Follicle-Stimulating Hormone

FSH will be investigated at Screening to confirm postmenopausal status (females only).

7.4.3.4 Serology

Serology for hepatitis and HIV, including HIV antibodies, HBs-Ag and antibodies against hepatitis C virus will be investigated at Screening. In Part C, samples will be collected and analyzed for the detection of seroconversion against some rare blood stage pathogens or red blood cell antibodies at time points indicated in Table 3.

7.4.3.5 Glucose-6-Phosphate Dehydrogenase Status

In Part C, subjects' G6PD status will be determined at Screening to exclude subjects with known or measured G6PD deficiency.

7.4.3.6 Inoculum Safety Sample

In Part C, serum samples will be collected from each subject at Inoculum Day 1 (pre inoculation), Day 22 (pre Riamet treatment) and the End of Trial visit (Day 44 [± 2 days]). These samples will be stored and will be used only in case any safety concerns arise and additional safety parameter testing is required.

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

7.4.4.1 Vital Signs

Vital signs include body temperature, BP, and heart rate.

Blood pressure will be measured according to the Riva/Rocci method using an automated device, which also indicates the corresponding heart rate in beats per minute. Blood pressure and heart rate will be measured after at least 5 minutes in a recumbent position, except at predose, 8 hours, 16 hours, and 24 hours after dosing, when in addition also orthostatic measurements will be conducted. On Day 1, a time window of 60 minutes is allowed for blood pressure measurements. In case the subject is unable to stand up at the 16 hours (and/or 20 hours for Part A) postdose time point due to dizziness, the vital signs may be assessed in the supine position. Body temperature will be measured orally (sublingual). Vital signs will be measured at scheduled visits according to the applicable Schedule of Assessments (Table 1 to Table 3). Further vital sign measurements during the course of the trial are at the discretion of the Investigator.

7.4.4.2 Physical Examination

A standard full physical examination, including examination of all body systems, will be performed at Screening and the End of Trial visit (Day 44 ± 2 days), including general appearance, skin, head, neck (including thyroid), eyes, ears, nose, throat, cardiovascular and pulmonary system,

abdomen, neurological, peripheral vascular, and musculoskeletal system. At other time points an abbreviated physical examination must be performed.

Respiratory rate will be assessed at time points indicated in the Schedule of Assessments (Table 1 to Table 3).

Physical examinations will be scheduled according to the applicable Schedule of Assessments (Table 1 to Table 3). Further medical examinations during the course of the trial are at the discretion of the Investigator.

7.4.4.3 Alcohol Breath Test

A commercially available breathalyzer test will be used to determine the concentration of alcohol in subject's breath according to the Schedule of Assessments (Table 1 to Table 3).

Additional alcohol breath tests during the course of the trial are at the discretion of the Investigator.

7.4.4.4 Urine Drug Screen

Spot urine will be assessed for recreational drugs according to the Schedule of Assessments (Table 1 to Table 3). The list of urine drug screen examinations is displayed in Table 8.

Additional urine drug screens during the course of the trial are at the discretion of the Investigator.

7.4.4.5 12-Lead Electrocardiogram

The 12-Lead ECG records will be used for on-time cardiac safety monitoring. Before taking the ECG the subject has to remain in a recumbent position for at least 5 minutes. A full standard 12-lead ECG (I, II, III, aVR, aVL, aVF, V1-V6) for about 5 seconds (3 adjacent beats, calibration: 50 mm/sec 10 mm/mV) and a rhythm recording from lead II for 60 seconds (Calibration: 10 mm/sec 12,5 mm/mV) is recorded according to the Schedule of Assessments (Table 1 to Table 3).

Safety 12-lead ECGs will be read locally and monitored in real time. ECG printouts should be signed and dated by the person performing the ECG. The 12-lead ECG will be analyzed, assessed for plausibility and clinical relevance, and signed by the Investigator. The clinical relevance of the ECG will be assessed by the Investigator, but any values outside the "Reference Ranges for AE Reporting" will be assessed as clinically relevant.

Additional ECGs during the course of the trial are at the discretion of the Investigator.

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7.4.4.7 Specific Planned Assessments or Adverse Events of Special Interest

- Vomiting, diarrhea. In case of vomiting subjects should not be re-dosed and they should be kept in the trial, however the Investigator can decide whether to schedule the final Follow-up visit earlier
- Liver enzymes (ALT/AST/Bilirubin)
- Cutaneous reactions (local tolerability CRF for severity of redness, swelling, induration, bruising, and itching)
- Photosensitivity/light sensitivity
- Pregnancy in a female partner of a male subject. Any subject's female partner who becomes pregnant during the trial or in the following 20 weeks after the last dosing should be followed through delivery or termination of the pregnancy. Pregnancy is reported to the Sponsor by completion of the pregnancy form.

7.4.4.8 Diary Cards

Diary cards will be provided to subjects when leaving confinement for collection of data relating to their daily physical activity, daily use of sunscreen/other methods of sun protection, daily alcohol consumption, and if applicable their oral (sublingual) temperature. Subjects will bring their completed diary cards with them to the trial site for all ambulant, Follow-up, and End of Trial visits (Table 1, Table 2, and Table 3).

7.5 Pharmacokinetics

7.5.1 Pharmacokinetic Samples

7.5.1.1 Blood

Blood Samples for Whole Blood Assay

Blood samples for measurement of M5717 concentrations in whole blood will be collected in Part A, Part B, and Part C at the time points indicated in the Schedule of Assessments (Table 1 to Table 3). CCI [redacted]

Actual date and time of the PK sample will be recorded in the eCRF. In case the actual sampling time deviates outside the time window specified, this will be recorded as a protocol deviation.

Volume of blood taken per treatment period and total volume will be listed in a separate laboratory manual.

For PK sample analysis, liquid whole blood levels of M5717 will be analyzed by the analytical laboratory selected under responsibility of the Sponsor, using an appropriate validated bioanalytical method. Full details of the bioanalytical method used will be described in a separate bioanalytical report. For subjects 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 will be specified in a separate laboratory manual.

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Details on sample collection, preparation for processing, shipment, and analysis will be specified in a separate laboratory manual.

7.5.2 Pharmacokinetic Calculations

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Individual whole blood PK parameters will be calculated using actual sampling times, where available. In cases where the actual sampling time is missing (eg, Intermediary SMC reports) calculations will be performed using the scheduled time. The predose samples will be considered as if they had been taken simultaneously with the administration.

7.5.2.1 Whole Blood

For each subject with evaluable whole blood PK data, the following PK parameters will be calculated from M5717 whole blood concentrations generated from the validated bioanalytical assays:

Part A and Part B

Table 9 Definition of Individual Pharmacokinetic Parameters

Parameter	Definition
AUC_{0-t}	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 (ie, linear up/log down). This will be calculated for Part A, and for Day 1 and Day 3 of Part B.
$AUC_{0-t,overall}$	The AUC_{0-t} over the entire dosing time period in Part B, ie, from time zero (dosing time) on Day 1 to the last sampling time at which the concentration is at or above LLOQ on Day 3, calculated according to the mixed log linear trapezoidal rule (ie, linear up/log down).
$AUC_{0-\infty}$	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 λ_z determination. $AUC_{0-\infty}=AUC_{0-t}+C_{last\ pred}/\lambda z$. This will be calculated for Part A.
$AUC_{0-\infty,overall}$	The $AUC_{0-\infty}$ over the entire dosing time period in Part B, ie, from time zero (dosing time) on Day 1, extrapolated to infinity following the dose on Day 3, based on the predicted value for the concentration at t_{last}, on Day 3, as estimated using the linear regression from λ_z determination.
AUC_{0-24h}	AUC from time zero to 24 hours. This will be calculated for Part A, and for Day 1 and Day 3 of Part B.
AUC_{0-144h}	AUC from time zero to 144 hours. This will be calculated for Part A, and for Day 3 of Part B.
$AUC_{0-144h.overall}$	AUC from time zero to 144 hours in Part B, ie, from time zero (dosing time) on Day 1 until 144 hours after the Day 1 dose.
C_{max}	Maximum blood concentration observed. This will be calculated for Part A, and for Day 1 and Day 3 of Part B.
t_{max}	Time to reach the maximum blood concentration. This will be calculated for Part A, and for Day 1 and Day 3 of Part B.
$t_{½}$	Apparent terminal half-life, calculated as $\ln 2/\lambda z$. This will be calculated for Part A and Day 3 of Part B.
λz	Terminal first order (elimination) rate constant. This will be calculated for Part A and Day 3 of Part B.
CL/f	Total body clearance of drug from blood following oral administration. This will be calculated for Part A.
$CL/f_{,overall}$	Total body clearance of drug from blood following oral administration. This will be calculated over the entire dosing and PK sampling period in Part B.
V_z/f	Apparent volume of distribution during the terminal phase following extravascular administration. This will be calculated for Part A.
$V_z/f_{,overall}$	Apparent volume of distribution during the terminal phase following extravascular administration. This will be calculated over the entire dosing and PK sampling period in Part B.
$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$. This will be calculated for Part A. For Part B, this will be calculated for $AUC_{0-\infty,overall}$, and for $AUC_{0-\infty}$ on Day 1 if $AUC_{0-\infty}$ if accurately estimable.
AUC_{0-t}/Dose	Dose-normalized AUC_{0-t}. This will be calculated for Part A, and on Day 1 and Day 3 of Part B.
$AUC_{0-t,overall}$/Dose	Dose-normalized $AUC_{0-t,overall}$. This will be calculated for Part B.
$AUC_{0-\infty}$/Dose	Dose-normalized $AUC_{0-\infty}$. This will be calculated for Part A.
$AUC_{0-\infty,overall}$/Dose	Dose-normalized $AUC_{0-\infty,overall}$. This will be calculated for Part B.

Parameter	Definition
C_{max}/Dose	Dose-normalized C_{max}. This will be calculated for Part A, and for Day 1 and Day 3 of Part B.
AUC_{0-24h}/Dose	Dose-normalized AUC_{0-24h}. This will be calculated for Part A, and for Day 1 and Day 3 of Part B.
AUC_{0-144h}/Dose	Dose-normalized AUC_{0-144h}. This will be calculated for Part A, and for Day 3 of Part B.
$AUC_{0-144h,overall}$/Dose	Dose-normalized $AUC_{0-144h,overall}$. This will be calculated for Part B.
$R_{acc(AUC)}$	Accumulation ratio for AUC_{0-24h}, calculated in Part B as AUC_{0-24h} on Day 3 divided by AUC_{0-24h} on Day 1
$R_{acc(Cmax)}$	Accumulation ratio for C_{max}, calculated in Part B as C_{max} on Day 3 divided by C_{max} on Day 1
$t_{>10\ ng/mL}$	Time above or equal to the predicted M5717 mouse MPC of 10 ng/mL. Calculated for Part A, and for Part B over the entire dosing time period.
$t_{>3\ ng/mL}$	Time above or equal to the predicted M5717 mouse MIC of 3 ng/mL. Calculated for Part A, and for Part B over the entire dosing time period.

LLOQ = Lower limit of quantification; MIC = minimal inhibitory concentration; MPC = minimal parasiticidal concentration.

Additional PK parameters may be calculated.

Part C

If the trial design of Part C is single dose, whole blood PK parameters as described for Part A (Table 9) will be calculated. Alternatively, if the trial design of Part C is multiple dose, whole blood PK parameters as described for Part B (Table 9) will be calculated.

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8 Statistics

8.1 Sample Size

Given the exploratory nature of this trial, the sample size in Part A and Part B is not based on formal statistical calculations. The sample size is based on experience from previous similar Phase I trials which will provide sufficient safety and tolerability data for M5717 to achieve the objectives from Part A and Part B of the trial while exposing as few subjects as possible to the IMP and procedures.

For Part C, the objective is to define the PK/PD relationship of M5717. Historically, 8 participants in a dose cohort have proven sufficient to characterize the effects of a drug on malaria parasite kinetics following induction in healthy volunteers using inoculation with blood stage P. falciparum. Therefore, the sample size of the current trial for P. falciparum infection (n=8 per cohort) is comparable with previous trials, and based on previously published experience (3, 10). Two or 3 cohorts should be sufficient to achieve the objective in Part C, which is to define the PRR, the major PD parameter, and to derive the MIC and MPC of the compound.

As the exact number of subjects showing recrudescence is unknown, 3 cohorts are planned to be able to evaluate a higher or lower dose of IMP to collect sufficient data on subjects showing cure as well as recrudescence.

In Part C, subjects who are withdrawn from the trial by the Investigator due to AEs after the start of the inoculum will generally not be replaced. The final decision will be taken after discussion with the Sponsor.

8.2 Randomization

Part A

Dose cohorts including 8 subjects each are planned in Part A. Dose administration for each dose cohort will proceed with 2 subjects in a sentinel cohort. In each dose cohort, 8 subjects will be randomized in a double-blind fashion to M5717 or placebo in a ratio of 6:2, respectively, such that for the first 2 subjects in the sentinel cohort, 1 subject will receive M5717 and 1 subject will receive placebo.

Depending on available safety data the SMC can decide to start the cohort with 3 sentinel subjects (2 M5717:1 placebo).

The randomization will be generated for each cohort using consecutive randomization codes and subjects will be allocated to M5717 or placebo in a ratio as presented in Table 11.

Table 11 Method of Assigning Subjects to Treatment Groups in Part A

Cohort	Subject Number (Screening Number)	Randomization Number	Replacement Randomization Number	Ratio of Subject Assignment (Active:Placebo)
Cohort 1 Single Ascending Dose	11xx	RA1101-1108	RA1151-1158	6:2 (Sentinel 1:1; Remainder 5:1)
Cohort 2 Single Ascending Dose	12xx	RA1201-1208	RA1251-1258	6:2 (Sentinel 1:1; Remainder 5:1)
Cohort 3 Single Ascending Dose	13xx	RA1301-1308	RA1351-1358	6:2 (Sentinel 1:1; Remainder 5:1)
Cohort 4 Single Ascending Dose	14xx	RA1401-1408	RA1451-1458	6:2 (Sentinel 1:1; Remainder 5:1)
Cohort 5 Single Ascending Dose	15xx	RA1501-1508	RA1551-1558	6:2 (Sentinel 1:1; Remainder 5:1)
Cohort 6 Single Ascending Dose	16xx	RA1601-1608	RA1651-1658	6:2 (Sentinel 1:1; Remainder 5:1)
Cohort 7 Single Ascending Dose	17xx	RA1721-1728	RA1771-1778	6:2 (Sentinel 2:1; Remainder 4:1)

For the additional SAD cohorts, the randomization will be generated based on the SMC decision on the number of subjects in the sentinel group (2 or 3 sentinel subjects).

Part B

Three ascending dose cohorts of 8 subjects each are planned in Part B, should that part of the trial be conducted. Within each dose cohort, 8 subjects will be randomized in a double-blind fashion to

M5717 or placebo in a ratio of 6:2, respectively such that for the first 2 subjects in the sentinel cohort, 1 subject will receive M5717 and 1 subject will receive placebo. The randomization will be generated for each cohort using consecutive randomization codes as presented in Table 12.

Table 12 Method of Assigning Subjects to Treatment Groups in Part B

Cohort	Subject Number (Screening Number)	Randomization Number	Replacement Subject Number	Ratio of Subject Assignment (Active:Placebo)
Cohort 1 Multiple Ascending Dose	21xx	RA2101-2108	RA2151-2158	6:2 (Sentinel 1:1; Remainder 5:1)
Cohort 2 Multiple Ascending Dose	22xx	RA2201-2208	RA2251-2258	6:2 (Sentinel 1:1; Remainder 5:1)
Cohort 3 Multiple Ascending Dose	23xx	RA2301-2308	RA2351-2358	6:2 (Sentinel 1:1; Remainder 5:1)

Subject Replacement for Part A and Part B

Subjects who are withdrawn from the trial by the Investigator due to AEs after the start of administration of the IMP will not be replaced. Subjects who withdraw for any other reason may be replaced after discussion with the Sponsor. In Part A and Part B, replacement subjects, if utilized, will receive the same treatment as the subject they are replacing, using a randomization number incremented by 50 as shown above.

8.3 Endpoints

8.3.1 Primary Endpoints

Part A

- Nature, incidence, and severity of AEs/SAEs, including relationship to trial treatment, AEs/SAEs leading to dose modification or discontinuation of trial treatment
- Incidence of clinically significant changes and abnormalities in safety laboratory parameters (hematology, coagulation, biochemistry [specifically ALT and AST], and urinalysis)
- Incidence of clinically significant changes and abnormalities in vital signs (body temperature, BP, and heart rate), respiratory rate, and 12-lead ECG.

Part B (optional)

- Nature, incidence, and severity of AEs/SAEs, including relationship to trial treatment, AEs/SAEs leading to dose modification or discontinuation of trial treatment
- Incidence and clinically significant changes and abnormalities in safety laboratory parameters (hematology, coagulation, biochemistry [specifically ALT and AST] and urinalysis)
- Incidence and clinically significant changes and abnormalities in vital signs (body temperature, BP, and heart rate), respiratory rate, and 12-lead ECG.

Part C

- PRR as observed through quantitative polymerase chain reaction (qPCR) analysis
- All M5717 PK parameters as defined in Part A or Part B (depending on dosing regimen in Part C).

8.3.2 Secondary Endpoints

Part A

- PK parameters for M5717.

Part B (optional)

- PK parameters for M5717.

Part C

- PCT, MIC, PCt½, MPC, lag phase, number of subjects with recrudescence
- Malaria Clinical Score
- Nature, incidence, and severity of AEs/SAEs, including relationship to trial treatment, AEs/SAEs leading to dose modification or discontinuation of trial treatment
- Incidence of clinically significant changes and abnormalities in safety laboratory parameters (hematology, coagulation, biochemistry [specifically ALT and AST], and urinalysis)
- Incidence of clinically significant changes and abnormalities in vital signs (body temperature, BP, and heart rate), respiratory rate, and 12-lead ECG.

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8.4 Analysis Sets

For purposes of analysis, the following populations are defined:

Table 13 Definition of Statistical Analysis Populations

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

8.5 Description of Statistical Analyses

8.5.1 General Considerations

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The results of this trial will be reported using summary tables, figures, and data listings, as appropriate. All data will be summarized by trial part, dose level and/or scheduled time point, as appropriate and otherwise specified.

For demographic, baseline and safety assessments, continuous measurements will be summarized by means of descriptive statistics (ie, number and percentage of observations, number and percentage of missing observations, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum) and categorical data will be summarized by means of frequency tables (ie, count and percentages), if not stated otherwise.

Given its exploratory nature, no formal statistical hypothesis testing will be performed in this trial. Data will be presented by actual dose or treatment, and subjects receiving placebo will be pooled across dosing cohorts for the purposes of summarizing the safety results (Part A and Part B). Missing data will result in a reduced sample size for that parameter. Since the statistical analyses will be predominantly descriptive presentations in tables and individual data listings, no action will be taken to handle missing data. A subject who withdraws prior to the last planned observation in a trial period will be included in the analyses up to the time of discontinuation.

PK concentrations in blood, and PK and PD parameters will be presented in tables and descriptively summarized by trial part, dose level, trial day, and/or nominal time point, as appropriate, using n, arithmetic mean, standard deviation, median, minimum, maximum, and CV%. Values below the LLOQ will be taken as zero for descriptive statistics of PK concentrations. Descriptive statistics of PK and PD parameters will additionally show the GeoMean, the geometric CV%, and the 95% CI for the GeoMean.

Graphical displays will be given, where appropriate. Details of the statistical analysis will be described in the statistical analysis plan (SAP).

8.5.2 Analysis of Primary Endpoints

8.5.2.1 Safety

Part A and Part B

Safety data analysis will be conducted on the Safety Analysis Set. The number and percentage of subjects experiencing one or more AEs will be summarized by dose level group, relationship to IMP, and severity. AEs will be coded using Medical Dictionary for Regulatory Activities terminology. Laboratory parameters will be summarized using descriptive statistics, by postdose shifts relative to baseline, and data listings of abnormal results as appropriate. Vital signs and ECG data will be summarized for observed and changes-from-baseline values by dose level using descriptive statistics. Clinically noteworthy ECG findings for individual subjects will be listed and summarized as appropriate.

8.5.2.2 Pharmacokinetics

Part C

All PK blood concentrations and PK parameters will be descriptively summarized by trial part, dose level, trial day, and/or nominal time point, as described in Section 8.5.1. For calculation of descriptive statistics of blood concentrations, values below the LLOQ will be set to zero.

The statistical analysis of dose proportionality (and the statistical analysis of linearity and accumulation, if applicable, depending on the trial design of Part C) that is described in Section 8.5.3.1, will be repeated after including applicable PK parameters from Part C.

8.5.2.3 Pharmacodynamics

Part C

The primary PD variable is the PRR of asexual parasites based on qPCR after administration of M5717. Secondary PD variables are PCT, MIC, PCt½, and MPC (calculation to be described in the SAP), clinical score, and the number and percentage of subjects with recrudescence. Statistically, recrudescence is defined as an increase in parasitemia > 1 log, over 2 or more consecutive qPCR results. To be considered recrudescence this increase must occur after the initial decrease in parasitemia post-IMP administration.

The PRR for asexual parasites will be estimated using the slope of the optimal fit of the log-linear relationship of the parasitemia decay based on the PD Analysis Set. The optimal fit can be derived using summarized replicate parasitemia data, which have been cleaned by dealing with potential outliers, values below the limit of detection and nondetectable values (ND). The optimal fit of the log-linear parasitemia-by-time relationship is determined by using left and right censoring to systematically remove the potential lag phase and tail phase of the parasitemia decay. The decay rate, estimated by the slope coefficient from the log-linear decay regression of qPCR data, will be calculated for each subject. The overall cohort-dose specific PRR will be estimated with its 95% CI by calculating the weighted average slope estimate and corresponding standard error (SE) using an inverse-variance method. Only subjects who have optimal regression models with appropriate fit contribute toward the dose-specific PRR.

For any replicate parasitemia values below LLOQ, the value is substituted with LOQ/2. The LOQ is assumed to be 64 parasites/mL of blood, based on published data (9). For any values that were not detected (ND) the value is set to 1, such that when the data is $\log_{10}$ transformed the ND = $\log_{10}$ (1) = 0. If all replicates for a subject within a time point are ND, the first time point with all ND is included in model fitting, and all subsequent time points are set to 'missing', regardless of whether parasitemia values increased afterwards due to potential recrudescence of malaria infection. The data used for all subsequent model selection and fitting calculations is comprised of arithmetic mean of the replicate $\log_{10}$ parasitemia value per time point per subject up to the first time all replicates are ND.

The algorithm to obtain the log-linear decay for each subject is based on the log-linear regression detailed in Equation (1), where Time is the number of hours since administration of antimalarial treatment ($Time = 1, \ldots, m$), and β_0 and β_1 are the intercept and slope estimates, respectively.

$$\log_{10} Parasitemia = \beta_0 + \beta_1 Time \quad (1)$$

Based on the cleaned and processed parasitemia data for each subject, the iterative algorithm to determine the optimal log-linear decay for each subject is summarized below. The iterative algorithm is continued until a minimum of 4 observations are available.

The optimal log-linear regression model for a subject is deemed an appropriate fit if the overall model p-value < 0.001.

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8.5.3 Analysis of Secondary Endpoints

8.5.3.1 Pharmacokinetics

Part A and Part B

All PK blood concentrations and PK parameters will be descriptively summarized by trial part, dose level, trial day, and/or nominal time point, as described in Section 8.5.1. For calculation of descriptive statistics of blood concentrations, values below the lower limit of quantitation of the assay (LLOQ) will be set to zero. CCI [redacted]

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8.5.3.2 Other Secondary Endpoints

Part C

All secondary PD variables, including PCT, MIC, PCt½, MPC, lag phase, and clinical score, will be descriptively summarized. Further details will be provided in the SAP as well as for the number and percentage of subjects with recrudescence. PCT and MIC are defined in Table 10. The MIC is the drug concentration at which the relative rate of change in parasitemia is equal to zero (see Figure 5). In other words, the MIC is the drug concentration at which the rate of parasite killing is equal to the rate of parasite reproduction and represents a "steady state". Implicit in this definition is the assumption that the MIC value is invariant of the dose administered.

Safety data will be similarly analyzed as described for the safety analysis in Part A and Part B in Section 8.5.2.

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8.6 Interim and Additional Planned Analyses

No formal interim statistical analysis is planned. However, to support timely decision-making, the Sponsor may decide to perform a final analysis of a trial part after the completion of a trial part. The data for that trial part will be locked and unblinded as described in Section 6.10.

An SMC will be established according to the SMC charter. Membership, mandate, and processes of the SMC will be detailed in the SMC Charter. Information regarding the SMC decision criteria are provided in Section 5.2.8.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at the site and will ensure that the trial is performed in accordance with this protocol, the ethical principles outlined in the Declaration of Helsinki, the Notes for Guidance on GCP (CPMP/ICH/135/95), as adopted by the Australian Therapeutic Goods Administration (2000) (NHMRC National Statement on Ethical Conduct in Human Research), and any other applicable regulations. The Investigator must ensure that only subjects who have given informed consent are included in the trial.

9.2 Subject Information and Informed Consent

An unconditional prerequisite for each subject prior to participation in the trial is written informed consent, which must be given before any trial-related activities are carried out. Adequate information must therefore be given to the subject by the Investigator or an appropriate designee (if local regulations permit) before informed consent is obtained.

A subject information sheet must be prepared in the local language in accordance with ICH GCP and provided to the subject for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the Investigator or a designate will inform the subject verbally of all pertinent aspects of the trial, using language chosen so that the information can be fully and readily understood by laypersons. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification.

If permitted by national regulations, a person other than the Investigator may inform the subject about the trial and sign the PICF, as above.

After the information is provided by the Investigator, the PICF must be signed and personally dated by the subject and the Investigator.

The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived by the Investigator/designee so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated PICF should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to the subject's consent, the written subject information sheet and any other written information to be provided to the subjects will be revised by the Sponsors/designees and be submitted again to the PPD HREC for review and favorable opinion. The Investigator/designee will explain the changes to the previous version to each trial subject the agreed, revised information will be provided to each subject in the trial for signing and dating.

9.3 Subject Identification and Privacy

A unique subject number will be assigned to each subject at inclusion, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the clinical trial database. All subject data collected in the trial will be stored under this number. Only the Investigator will be able to link the subject's trial data to an individual subject via an identification list kept at the site. For each subject, original medical data will be accessible for the purposes of source data verification by the Monitor, audits and Health Authority inspections, but patient confidentiality will be strictly maintained.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

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9.4 Emergency Medical Support and Subject Card

Subjects will be provided with Emergency Medical Support cards supplied by the trial site for use during trial participation in order to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial and to give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the subject. The information provided on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).

The first point of contact for all emergencies will be the clinical trial Investigator caring for the affected subject. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (for example, unblinding) will follow the standard process established for Investigators.

In cases where the Investigator is not available, the Phase I facility will provide the appropriate means to contact a physician. This includes the provision of a 24-hour contact number at the facility, whereby the health care providers will be given access to an appropriate physician to assist with the medical emergency and to provide support for the potential unblinding of the subject concerned.

9.5 Clinical Trial Insurance and Compensation to Subjects

Insurance coverage will be provided for each country participating to the trial. Insurance conditions shall meet good local standards, as applicable.

9.6 Independent Ethics Committee (Human Research Ethics Committee)

Prior to commencement of the trial at a given site, this clinical trial protocol will be submitted together with its associated documents (eg, the PICF) to the responsible HREC for its favorable opinion or approval, which will be filed in the Investigator Site File. A copy will be filed in the Sponsor Trial Master File at the CRO.

The HREC will provide an approval letter that will clearly identify the trial number and list all documents ant their version numbers that were reviewed and approved by the committee (eg, the clinical trial protocol and PICF).

Amendments to this clinical trial protocol will also be submitted to the concerned HREC, before implementation of substantial changes (see Section 10.5). Relevant safety information will be

submitted to the HREC during the course of the trial in accordance with national regulations and requirements.

9.7 Health Authorities

The clinical trial protocol and any applicable documentation (for example, IMP Dossier and PICF) will be submitted or notified to the Health Authorities in accordance with all local and national regulations for the trial site.

For Australia: the IB, PICF, clinical trial protocol, and Expert toxicology report will be submitted to HREC for approval and after approval, notified to the Health Authorities, using the CTN scheme, in accordance with all local and national regulations for the trial site.

10 Trial Management

10.1 Case Report Form Handling

Refer to the Manual of Operations for eCRF Completion Guidelines.

The main purpose of the eCRF is to obtain data required by the clinical trial protocol in a complete, accurate, legible and timely. The data in the eCRF should be consistent with the relevant source documents.

The Investigator or designee is responsible for ensuring that the data collected in the course of this trial is accurate and documented appropriately on all applicable forms. They will then be processed, evaluated, and stored in anonymous form in accordance with applicable data protection regulations. The Investigator must ensure that the eCRFs and any other associated documents forwarded to Sponsor or its designated organization contain no mention of any subject names.

The data will be entered into a validated database. The Sponsor or its designee will be responsible for data processing, in accordance with the Sponsor's data management procedures. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of the eCRFs will be provided to the Investigators at the completion of the trial.

10.2 Source Data and Subject Files

The Investigator must keep a file (medical file, original medical records) on paper or electronically for every subject in the trial. It must be possible to identify each subject by using this subject file. This file will contain the demographic and medical information for the subject listed below and should be as complete as possible.

- Subject's full name, date of birth, sex, height, weight, and skin type
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Trial identification, that is, the Sponsor trial number for this clinical trial, and subject number

- Dates for entry into the trial (informed consent) and visits to the site
- Any medical examinations and clinical findings predefined in this clinical trial protocol
- All AEs observed in the subject, including severity, relationship and outcome of AEs
- Date that the subject left the trial including any reason for early withdrawal from the trial or IMP (if applicable).

All documents containing source data must be filed, including, but not limited to the original printouts of the data recorded or generated by automated instruments, photographic negatives, ECG recordings, and laboratory results. Such documents must bear the subject number and the date of the procedure. If possible, this information should be printed by the instrument used to perform the assessment or measurement. Information that cannot be printed by an automated instrument will be entered manually. As necessary, medical evaluation of such records should be performed; all evaluations should be documented, signed, and dated by the Investigator.

Electronic subject files will be printed whenever the Monitor performs source data verification. Printouts must be signed and dated by the Investigator, countersigned by the Monitor and kept in a safe place at the site.

10.3 Investigator Site File and Archiving

Upon initiation of the trial, the Investigator will be provided with an Investigator Site File containing all necessary trial documents, which will be completed throughout the trial and updated as necessary. The file must be available for review by the Monitor, during Sponsor audits and for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end of the trial. The documents to be archived include the Subject Identification List and the signed subject PICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsors/designees.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This trial will be monitored in accordance with the ICH GCP and any other applicable regulations. The site Monitor will perform visits to the trial site at regular intervals.

The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data. Representatives of the Quality Assurance unit from the Sponsor or a designated organization, as well as Health Authorities, must be permitted to access all trial documents and

other materials at the site, including the Investigator Site File, the completed eCRFs, all IMP and IMP accountability records, and the original medical records or files for each subject.

10.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in written clinical trial protocol amendments. Major (substantial, significant) amendments will usually require submission to the relevant HREC for approval. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the trial site. They will be submitted to the relevant HREC or to Health Authorities only where requested by pertinent regulations. Any amendment that could affect the subject's agreement to participate in the trial requires additional informed consent prior to implementation following the process as described in Section 9.2.

10.6 Clinical Trial Report and Publication Policy

10.6.1 Clinical Trial Report

After completion of the trial, a clinical trial report will be written by the Sponsors/designees in consultation with the PI following the guidance in ICH Topic E3.

CCI [redacted]

10.6.2 Publication

The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc), either in whole or in part, by Investigators or their representatives will require review by the Sponsor before submission. The Sponsor will not suppress publication, but maintains the right to delay publication in order to protect intellectual property rights.

Posting of data on ClinicalTrials.gov is planned and will occur 12 months after the last visit of the final trial subject or another appropriate date to meet applicable requirements.

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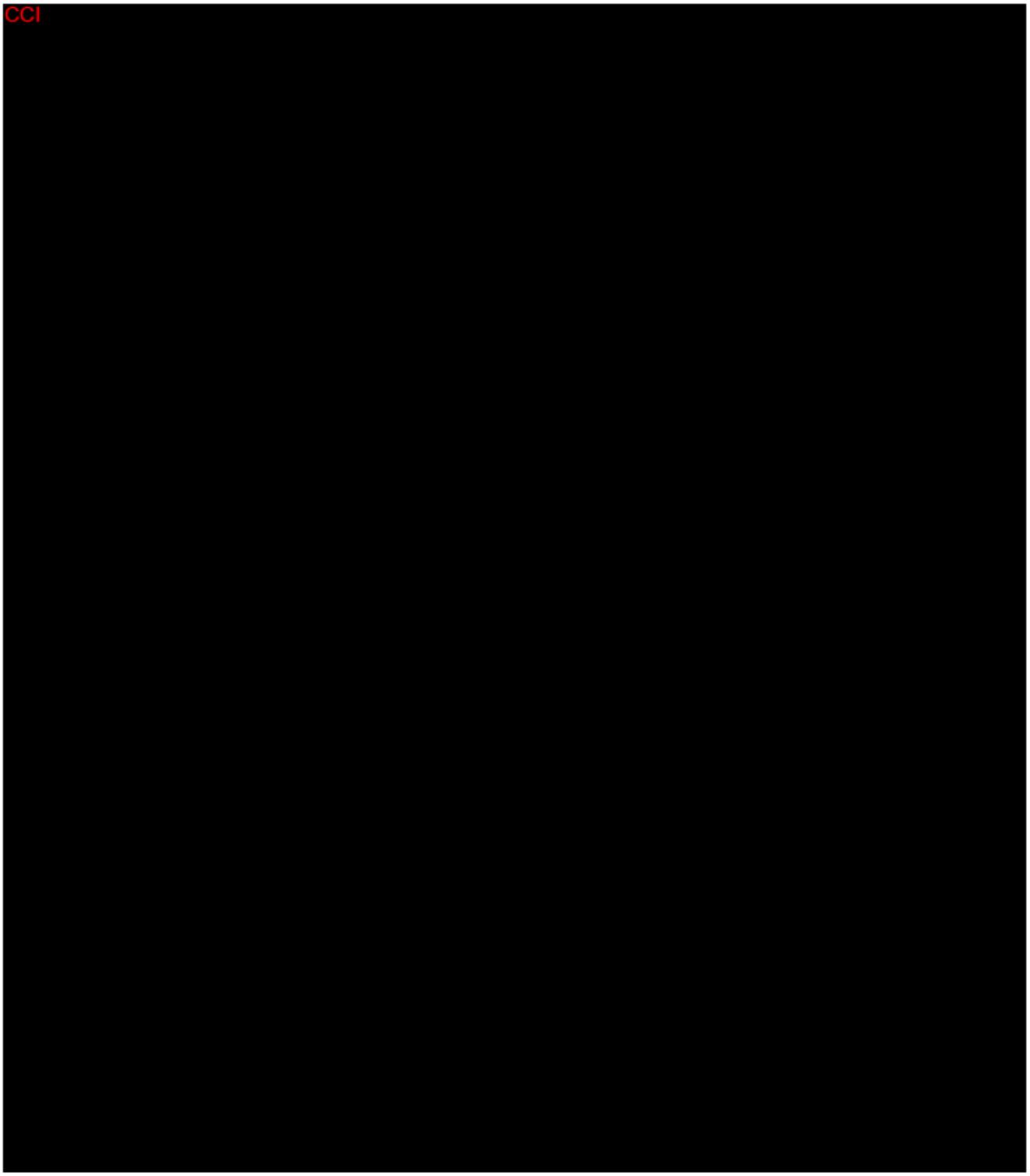

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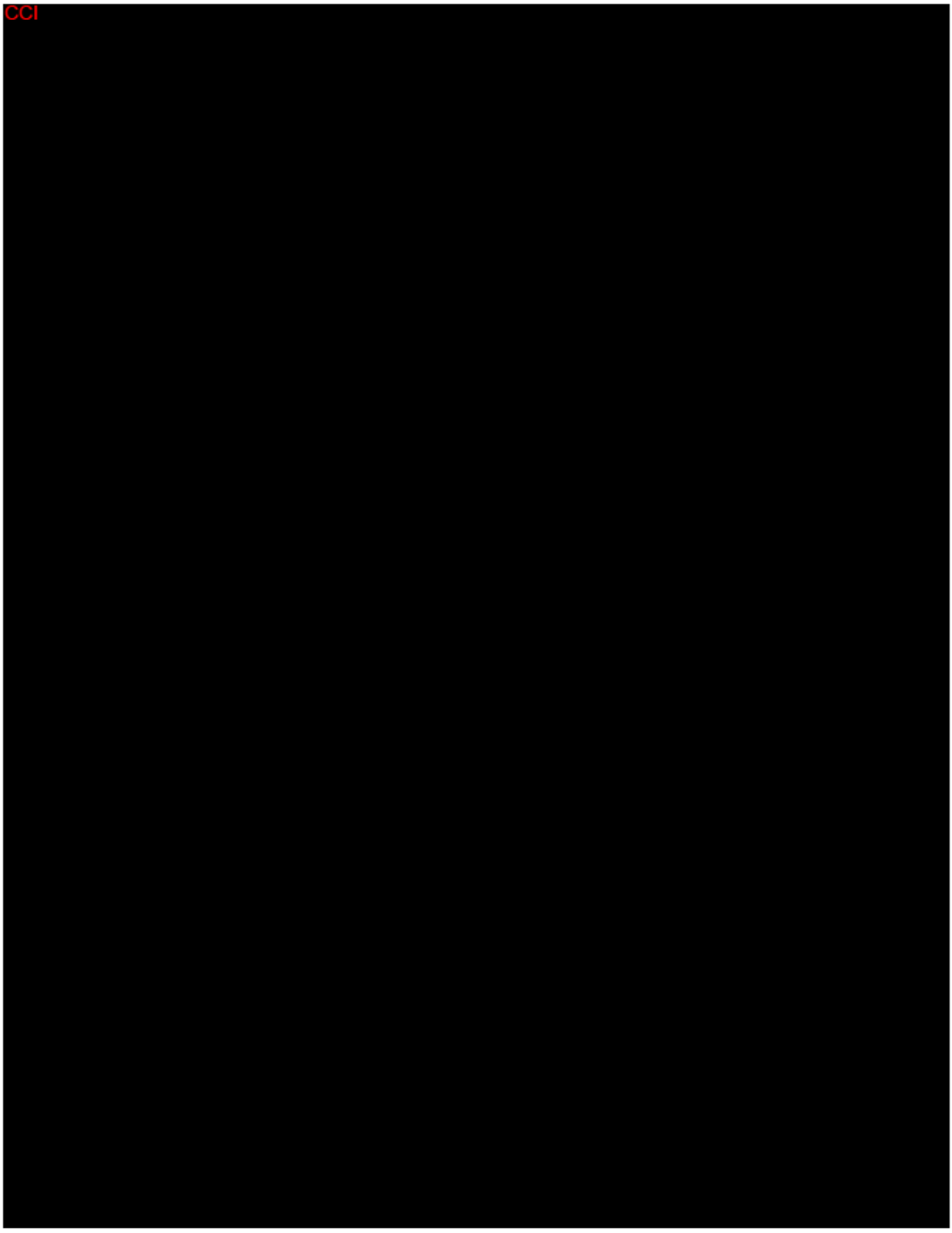
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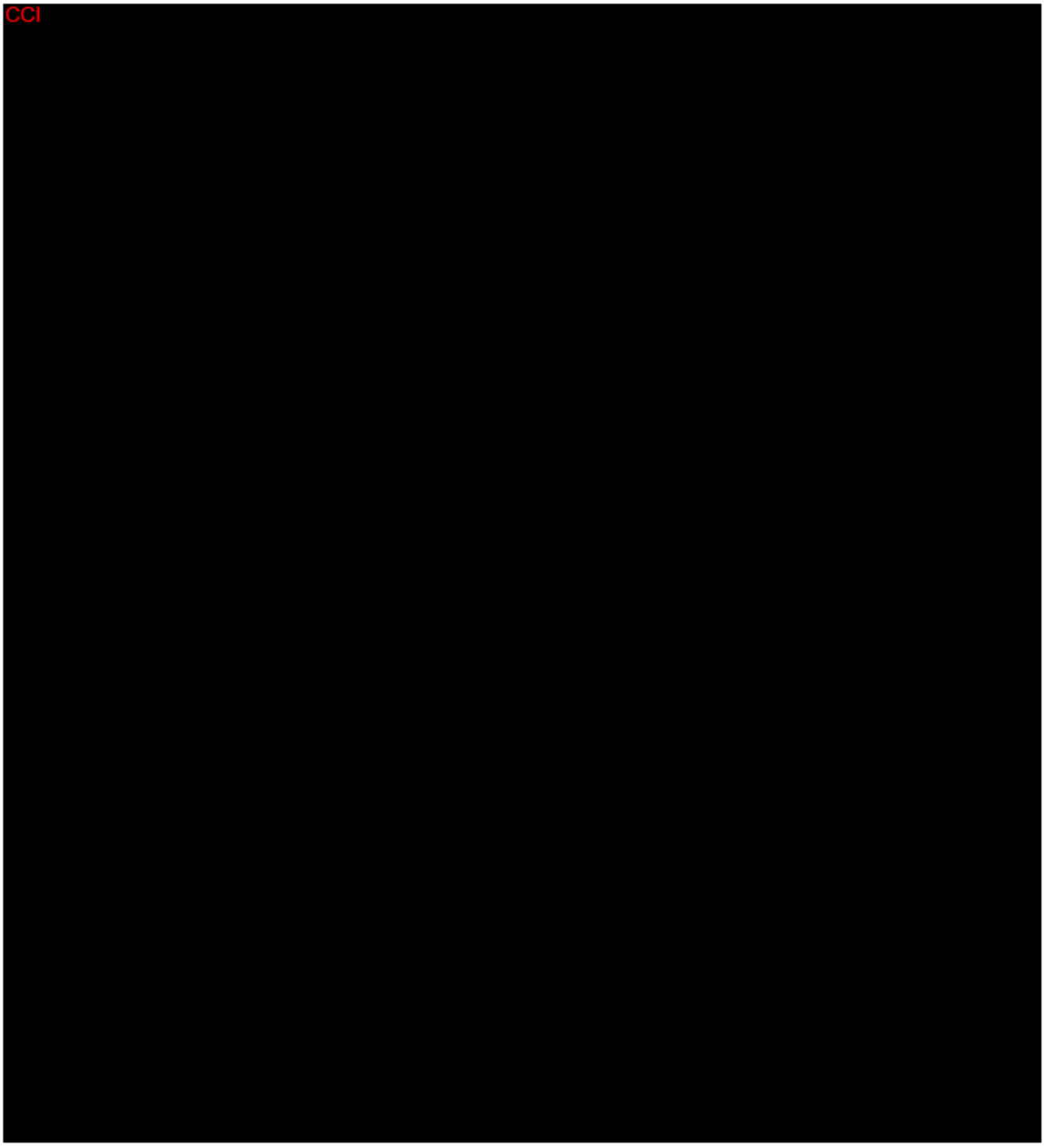

Major Scientific Changes

Comparison with Clinical Trial Protocol Version 1.0, 14 June 2017

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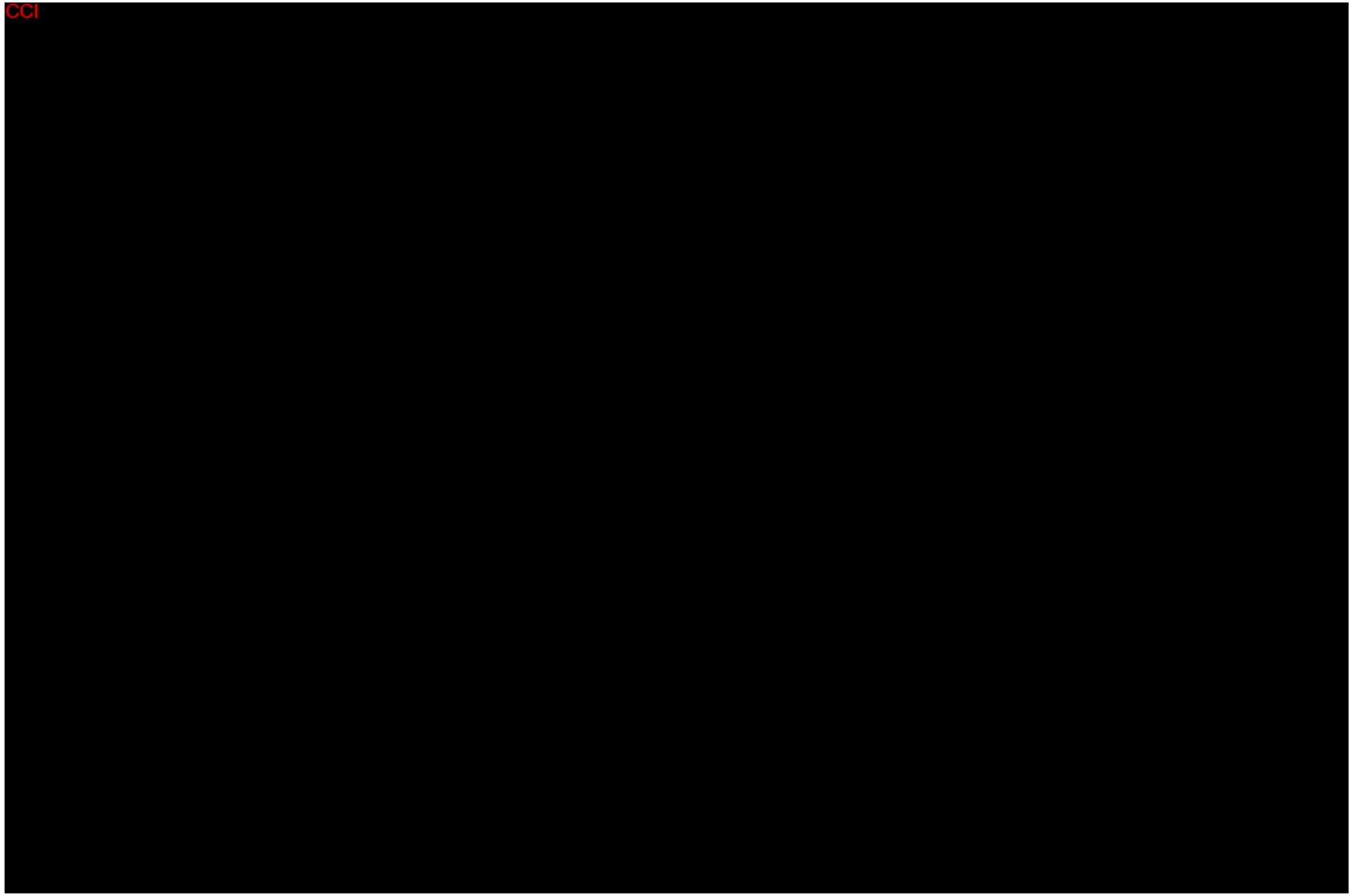
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Change	Section	Previous Wording[a]	New Wording[b]
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CCI [redacted]

Signature Page –Protocol Co-Lead (Medical Responsible)

Trial 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
Clinical Trial Protocol Number:	MS201618-0013
PPI	PPI
IND Number:	Not Applicable
EudraCT Number:	Not Applicable
Clinical Trial Protocol Date / Version:	17 December 2018 / Version 5.0 including Amendment 4

Protocol Co-Lead (Medical Responsible):

I approve the design of the clinical trial:

_____ _____

Signature Date of Signature

Name, academic degree:	PPI
Function / Title:	Medical Responsible/ Senior Medical Lead
Institution:	Merck KGaA
Address:	Frankfurter Strasse 250, Postcode: F130/005, 64293 Darmstadt, Germany
Telephone number:	PPD
Fax number:	PPD
E-mail address:	PPD

Signature Page – Protocol Co-Lead

Trial 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
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Clinical Trial Protocol Date / Version:	17 December 2018 / Version 5.0 including Amendment 4

Protocol Co-Lead:

I approve the design of the clinical trial:

_____ _____

Signature Date of Signature

Name, academic degree: PPD

Function / Title: PPD

Institution: PPD

Address: PPD

Telephone number: PPD

Fax number: -

E-mail address: PPD

Signature Page – Principal Investigator

Trial 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
Clinical Trial Protocol Number:	MS201618-0013
[redacted]	[redacted]
IND Number:	Not Applicable
EudraCT Number:	Not Applicable
Clinical Trial Protocol Date / Version:	17 December 2018 / Version 5.0 including Amendment 4
Center Number:	01
Principal Investigator:	[redacted]

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Council for Harmonization Good Clinical Practice (Topic E6), The National Statement, and all applicable Health Authority requirements and national laws.

I agree to inform all participants that the trial drug is being used for investigational purposes and I will ensure that the requirements related to obtaining informed consent are in accordance with ICH Guidelines for GCP Section 4.8 and local requirements.

I agree to report adverse events that occur in the course of the trial to the Sponsor in accordance with ICH Guidelines for GCP Section 4.11 and local requirements.

I have read and understand the information in the Investigator's Brochure, including the potential risks and side effects of the trial drug.

I agree to promptly report to the HREC all changes in the research activity and all unanticipated problems involving risk to participants. I will not make any changes to the conduct of the trial without HREC and Sponsor approval, except when necessary to eliminate apparent immediate harm to participants.

I agree to maintain adequate and accurate records and make those records available in accordance with ICH Guidelines for GCP Section 4.11 and local requirements.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the trial are informed about their obligations in meeting the above commitments.

I understand that the trial may be terminated or enrolment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the best interest of the participants.

_____ _____

Signature Date of Signature

Name, academic degree:	PPD
Function / Title:	PPD
Institution:	PPD PPD
Address:	PPD
Telephone number:	PPD
Mobile number:	PPD
E-mail address:	PPD
Institution:	PPD
Address:	PPD
Telephone number:	PPD or PPD
Mobile number:	PPD
E-mail address:	PPD

Sponsor Responsible Persons not Named on the Cover Page

Name, academic degree:	PPD
Function / Title:	PPD
Institution:	EMD Serono, Inc.
Address:	45A Middlesex Turnpike - C105G, Billerica, Massachusetts, United States of America
Telephone number:	PPD
Fax number:	-
E-mail address:	PPD

Name, academic degree:	PPD
Function / Title:	PPD
Institution:	PPD
Address:	PPD
Telephone number:	PPD
Fax number:	PPD
E-mail address:	PPD