Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A Phase Ib, Randomized, Double-Blind, Placebo Controlled, Sequential Study of Single Oral Doses of M5717 to Explore the Chemoprophylactic Activity of M5717 in a Controlled *Plasmodium falciparum* Sporozoite Challenge Model in Healthy Participants
Study Number:	MS201618_0003
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Study Phase:	Ib
Short Title:	Chemoprophylactic Activity of M5717 in PfSPZ Challenge Model
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Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	30-Sep-2019
2.0	Amendment	05-Feb-2020
3.0	Amendment	20-Jul-2020
4.0	Amendment	03-Dec-2020

Protocol Version 4.0 (03 December 2020)

This amendment is substantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The original protocol of this malaria challenge study excluded women of childbearing potential. Since designing the protocol, the following toxicological data have become available that allow inclusion of this population:

a. Absence of fetal abnormalities and no adverse effects on embryo-fetal survival with M5717 in the embryo fetal development (EFD) studies in rats (treatment from gestation day 6 to 16) up to the no-observed-adverse-effect level (NOAEL) of 80 mg/kg. Cmax and AUC at the NOAEL were respectively 12 and 21 times higher than Cmax and AUC observed in humans at the anticipated therapeutic dose for cure of 800 mg (blood stage).

b. There was no effect on embryo-fetal survival or morphological development up to the NOAEL of 40 mg/kg in EFD studies in rabbits (treatment from gestation day 6 to 18). Cmax and AUC at the NOAEL were both 5 times higher than Cmax and AUC observed in humans at the anticipated therapeutic dose for cure of 800 mg.

Although the maximum dose in this study was set at 1200 mg initially, the efficacy is expected to be reached at markedly lower doses. Therefore, from an (embryo) toxicological point of view, there is no reason to exclude women of childbearing potential in view of the results of dedicated EFD in animals and the doses that will be administered in the study. The inclusion of women will add to the value of the study as information on the compound when administered to (non pregnant) women will contribute to assessment of potential benefit for women from the experimental treatment under investigation. This will inform early on how the compound behaves in women and will allow inclusion of women in the next developmental clinical patient studies.

As a preventive measure, women will need to use effective contraception in this study according to Merck standards.

In this context it is important to note that there is no untoward drug-drug interaction anticipated between M5717 and the oral contraceptive pill to diminish the efficacy of the oral contraceptive or increase the exposure of the oral contraceptive (see below). Likewise, oral hormonal contraceptives (i.e. combined estrogen- and progestogen-containing hormonal contraceptives to inhibit ovulation) do not act as perpetrators, hence no effect by oral contraceptive pill on M5717 pharmacokinetics (PK) and pharmacodynamics (PD) is anticipated.

So far in human hepatocytes, M5717 did not induce any CYP enzymes (1A2, 2B6, 2C9, 2C19, and 3A4) at the maximum concentration (margin of above 600 of in vitro versus Cmax at 800 mg) refer to Investigator's Brochure [IB]). For contraceptives, PXR-mediated induction of drug-metabolizing enzymes (e.g., 3A4) leading to increased metabolism of ethinylestradiol and progesterones is the main concern for decreased efficacy (Lee, 2009). As M5717 did not induce 3A4 in vitro, drug-drug interactions via induction of the metabolism of contraceptive steroids by M5717 are not expected.

In contrast, M5717 is a weak 2D6 and 3A4 inhibitor, but preliminary physiological based pharmacokinetic modeling suggested that this level of inhibition was insufficient to increase midazolam concentrations. An interaction of decreased metabolism by 3A4 (leading to increased exposure of contraceptives) and possible safety concerns related to contraceptive use is therefore not likely.

In summary, from a toxicological point of view, as well as interaction regarding efficacy of contraception and safety considerations, there seems to be no objection to include women of childbearing potential on adequate contraceptives in the study.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis (Study Intervention Groups and Duration)	Corrected Study Intervention Day 4 to Day 5 for 'Late liver stage'.	Incorrect translation of 'after 4 days' in the Schedule of Activities.
1.3 Schedule of Activities (Tables 1 and 3)	Added clarification that BP and PR can be measured within 24 hours before malaria inoculum.	Clarification purposes
1.3 Schedule of Activities (Tables 1 and 3)	Clarified pregnancy and FSH testing.	All women can now be included; requirement for negative serum pregnancy test at the Screening Visit, Day -1, Day 4, and End of Study visits applies to all female participants. FSH testing is applicable to women of non-childbearing potential only.
1.3 Schedule of Activities (Tables 2 and 4)	Added urine pregnancy test at End of Study Visit.	Omitted in original protocol.
1.3 Schedule of Activities (Tables 3 and 4)	Corrected Study Intervention Day 4 to Day 5 in table titles for 'Late liver stage' participants and cross checked mark in Table 3.	Incorrect translation of 'after 4 days' in the Schedule of Activities.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (Tables 3 and 4)	Study Day 32 added.	Omitted in original protocol due to incorrect translation of 'after 4 days' in the Schedule of Activities.
1.3 Schedule of Activities (Table 1 through Table 4)	Removed vital signs and clinical laboratory assessments at 168, 264 and 408 hours after Study Intervention Administration.	Blinded data from the first cohort (200 mg M5717 or placebo) in the current study indicate a lower dose range (probably below 200 mg) to be tested in subsequent cohorts to characterize the exposure-response relationship. No safety concerns at these low doses that would necessitate the initially implemented frequent scheduled assessments are anticipated on the basis of safety data from the first-in-human (FIH) study and accumulated safety data from the current study. Deleting 3 safety assessments will decrease the burden, as well as the number of ambulatory visits and blood samples for the participants in the study. The proposed change will not affect the unscheduled safety laboratory assessments when parasitemia develops, since when qPCR level reaches ≥ 100 aPf/mL, an additional clinical laboratory sample should be taken within 24 hours (unless already scheduled).
1.3 Schedule of Activities (Table 1 through Table 4)	Updates and/or corrections were made to several timepoints in the tables as follows: Ambulatory visit was removed and added as a phone call visit at study Day 18 in Table 2. Hospitalization, ambulatory visits, and ambulatory phone call visits in Table 3 and 4 timepoints were updated. Timepoints of physical examination, urine drugs of abuse, alcohol breath test, diary cards, and PK sampling timepoints were also updated in Table 3.	Updates and/or corrections to tables.
4.3.2 Selection of Further Doses	Corrected Study Intervention Day 4 to Day 5 for 'Late liver stage' participants.	Incorrect translation of after 4 days in the Schedule of Activities.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Added that women of childbearing potential can be included.	In order to expand the study to the female study population which allows to gain more representative data.
8.2.2 Vital Signs	Added that oral temperature may be used if in opinion of Investigator the reading is more reliable than the tympanic measurement.	Increase reliability of measurement.
8.2.4 Clinical Safety Laboratory Assessments	Added further clarification on fasting times.	Clarify fasting times for all cohorts.
8.2.4 Clinical Safety Laboratory Assessments	Added mandatory text for additional serum or highly sensitive urine pregnancy tests that may be needed.	Mandatory text.
10 References	Reference added.	To add a reference used in this amendment.
Appendix 1 Abbreviations	Abbreviations added.	To define abbreviations used in this amendment.
Appendix 3 Contraception	Removed text that female participants must not be women of childbearing potential.	Not relevant anymore.

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1 Protocol Summary

1.1 Synopsis

Protocol Title:

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

Short Title:

Chemoprophylactic Activity of M5717 in *Plasmodium falciparum* Sporozoite (PfSPZ) Challenge Model

Rationale:

CCI

Objectives and Endpoints:

Primary Objectives	Endpoints
To assess chemoprophylactic activity of single oral doses of M5717 administered after DVI of *Plasmodium falciparum* sporozoites (PfSPZ) challenge in healthy participants.	Response endpoints: • Number of participants over time with positive parasitemia defined as first positive qPCR outcome equal or greater than 100 asexual parasites per mL of blood within 28 days of PfSPZ challenge • Time to parasitemia, defined as time from PfSPZ DVI to the first qPCR outcome equal or greater than 100 asexual parasites per mL of blood (time frame: number of days from PfSPZ DVI challenge to positive parasitemia, or 28 days) • Number of participants with documented blood stage parasite growth, defined as an increase of qPCR measured asexual parasites per mL compared to the first parasitemia measurement, within 28 days of PfSPZ DVI • Clinical symptoms of malaria using the Malaria Clinical Score.
To explore the dose-exposure-response relationship of a single oral dose of M5717 administered after DVI of PfSPZ challenge in healthy participants.	Dose-exposure-response relationship: • Selected pharmacokinetic (PK) endpoints/ concentrations (e.g. AUC_{0-24}, AUC_{0-168}, C_{24}, C_{168}) and pharmacodynamic (PD) endpoints (cured/not-cured) will be used for PK/PD modeling approaches.
Secondary Objectives	**Endpoints**
To evaluate the safety and tolerability of single, oral doses of M5717 in healthy participants following infection with PfSPZ challenge	• Nature, incidence, frequency, severity of (treatment emergent) adverse events (AEs)/ serious adverse events (SAEs), and relationship to the study intervention • Incidence of clinically significant changes and abnormalities in safety laboratory parameters (hematology, coagulation, biochemistry [specifically alanine aminotransferase (ALT) and aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin (total)], and urinalysis) • Incidence of clinically significant changes and abnormalities in vital signs and 12-lead electrocardiogram (ECG).
To investigate the PK of M5717 after administration of single, oral doses in healthy participants following infection with PfSPZ	Exposure endpoints: • Concentration-time curve for M5717 after single-dose administration • Pharmacokinetic parameters of M5717 such as $AUC_{0-\infty}$, AUC_{0-t}, AUC_{0-24}, AUC_{0-168}, C_{max}, C_{24}, C_{168}, t_{max}, $t_{1/2}$, λ_Z, CL/f and Vz/f to be specified in the Integrated Analysis Plan.

DVI=direct venous inoculation, PD=pharmacodynamics, PfSPZ=Plasmodium Falciparum Sporozoites, PK=pharmacokinetics, qPCR=quantitative polymerase chain reaction.

Overall Design:

This is a Phase Ib, single center, sequential, double-blind, randomized, placebo-controlled study to investigate the chemoprophylactic activity and dose/exposure-response relationship of single doses of M5717 administered after DVI of *P. falciparum* sporozoites (PfSPZ challenge) to healthy malaria-naïve male and female participants, 18 to 45 years of age.

Number of Participants:

The study will involve up to a maximum of 50 healthy adult men and women (between 4 and 12 healthy participants per dose group, with up to 5 cohorts).

Given the exploratory nature of this study, the sample size will not be based on power calculations. Historically, 8 to 12 participants in a dose cohort have provided sufficient data to characterize the chemoprophylactic activity of a drug on malaria parasite load following induction in healthy participants using DVI with PfSPZ. This number is comparable with previously published experiences (Sulyok 2017).

As the exact number of participants who might show recrudescence is unknown, 4 to 5 cohorts are planned to be able to evaluate adapted doses of the study intervention to collect sufficient data on participants who are cured and participants with recrudescence, to explore the dose-exposure-response relationship.

The number of participants in the current study will be 4 to 12 participants per cohort with an active to placebo ratio of 3:1 and a block size of 4 (e.g. 4 [3 active:1 placebo], 8 [6 active:2 placebo] or 12 [9 active:3 placebo]). The number of participants for a subsequent dose group will be based on available PD (cured/not-cured) and PK data from the actual/preceding dose groups. Once the efficacious dose level for the early liver stage has been identified, a cohort of 12 participants will be evaluated whether this dose is also efficacious on the late liver stage (administration of M5717 at Day 5 after PfSPZ challenge).

A screening failure rate of 30% is expected and therefore about 70 participants should be screened.

With 3 actively treated participants, the probability that the protection rate is 50% or greater was calculated using the Bayesian method. The assumption is that the protection status follows a binomial distribution with parameter θ (true protection rate) which follows a non-informative prior distribution beta (0.5, 0.5). The posterior probability that the true protection rate is ≥ 50% given various situations to be observed from Cohort 1, are tabulated below:

Number of actively treated participants	Number of protected participants observed	Posterior probability (true protection rate ≥ 50%)
3	3	97%
3	2	71%
3	1	29%
3	0	3%

If ≥ 2 protected participants out of 3 actively treated participants are observed in the first cohort, it is likely (probability ≥ 71%) that the true protection rate is greater than 50%, so in the next cohort the cohort will be expanded in order to identify the dose for a 50% protection rate.

Study Intervention Groups and Duration:

A maximum 28-day screening period is foreseen for each participant.

Dose-finding 'early liver stage': Participants that will be dosed on Study Day 1 will be admitted at the site on Study Day -1. For COVID-19 risk assessment measures upon admission, see Appendix 11. Randomization will occur either on Study Day -1 or Day 1; PfSPZ IV inoculation and study intervention administration will occur on Study Day 1 after randomization. Participants will be hospitalized for 2 nights from Study Day -1 to Day 2, which includes 24 hours post study intervention administration. Thereafter they will enter an ambulatory visit period from Study Day 3 to Day 28. During this period, they will return as outpatients for serial PK samplings, qPCR tests and evaluation of the malaria clinical score, as scheduled. In case blood-stage parasite growth is noted, the participant will be given rescue medication immediately. Participants will be contacted daily either during a visit to the unit or via phone calls from the site while being outpatient, from Study Day 3 to Day 33, for a safety check and for compliance with the rescue medication use. On Study Days 3, 4, 5, 12, 18, 21, 23, 25 and 27 ambulatory visits by phone call only are planned. Once participants are discharged from the clinic, they need to keep a diary about their health status that will be checked every time they report back to the clinic. The End of Study visit will be performed on Study Day 33 (+ 3). In case rescue medication is given before Study Day 28, an adapted visit schedule might apply.

'Late liver stage': Following randomization either on Study Day -1 or Day 1 and PfSPZ IV inoculation on Study Day 1, participants will be admitted at the site on Study Day 4 and will be dosed on Study Day 5 (equal to study intervention administration Day 1). For COVID-19 risk assessment measures upon admission, see Appendix 11. They will also be hospitalized for 2 nights from Study Day 4 to 6 (equal to study intervention administration Day -1 to 2), which includes 24 hours post study intervention administration. Thereafter, participants will enter an ambulatory visit period similar to that of participants dosed on Study Day 1, as described above. In case blood-stage parasite growth is noted, the participant will be given rescue medication immediately, otherwise rescue medication will be administered on Study Day 32 (which represents study intervention administration Day 28). The End of Study visit for this cohort will be on Study Day 36 (+ 3).

Involvement of Special Committee(s):

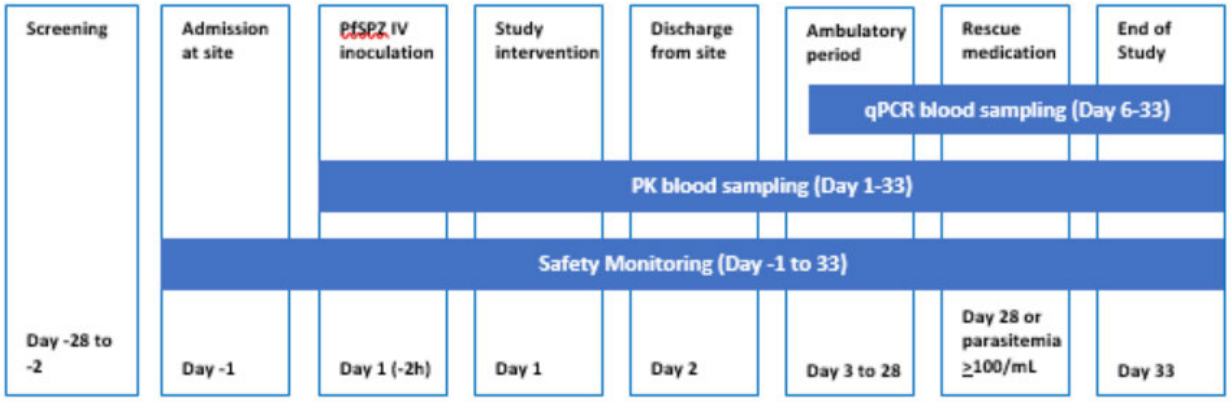
A Safety Monitoring Committee (SMC) will be established before enrolment of the first participant to review the data after each cohort is completed, and to decide on the dose, dose regimen, and number of participants for the next cohort as per protocol. The SMC will include the Chairperson (Global Patient Safety Product Responsible), core sponsor members (Medical Responsible, Clinical Pharmacology Representative, and Biostatistician). The following external members will be included: Principal Investigator (and Sub-Investigator(s)), CRO representative, and an independent external expert (if applicable). Only Merck members and the investigators will be voting members, and, as applicable, the independent external expert. Further persons may be represented on the team if their input is required. Details regarding SMC roles, responsibilities, activities, procedures to reduce potential bias, and possible SMC recommendations will be provided in a separate SMC charter.

1.2 Schema

The overall design of the study per cohort for dose finding, from Screening, direct intravenous inoculation (DVI, i.e. bolus) with malaria sporozoites, study intervention administration, medical, quantitative polymerase chain reaction (qPCR) and pharmacokinetic monitoring, to discharge and rescue treatment, is summarized in Figure 1.

After discharge participants will visit the study site on a daily basis for serial qPCR, pharmacokinetics (PK) and safety assessments as scheduled, until study intervention administration Day 28 when rescue medication will be administered. When indicated and deemed safe by the Investigator, participants may also visit on a less regular basis from study intervention administration Day 20 until Day 28. However, on the days that the participants do not visit the study site, the participant will be contacted by telephone, SMS or email by site staff. Once they are discharged from the clinic, the participants need to keep a diary about their health status that will be checked every time they report back to the clinic. The End of Study visit (including safety examinations, PK and qPCR) will be done at study intervention Day 33 (+ 3). In case blood-stage parasite growth is noted and confirmed; the participant will have a blood sample taken for *P. falciparum* genotyping and be given rescue medication immediately. Blood-stage parasite growth is defined as an increase of parasite load compared to the load measured at first parasitaemia. If no blood-stage growth develops before study intervention administration Day 28, participants will receive rescue treatment on study intervention administration Day 28. In the first 3 or 4 cohorts enrolled, the study intervention will be administered 2 hours after PfSPZ challenge so that the sporozoites can be deposited in the liver without any interference by M5717, and the effect of the study intervention on the (pre-erythrocytic) intracellular liver stages can be evaluated. Based on (PK)/pharmacodynamics (PD) and safety analysis of the previous cohorts, subsequent cohorts (up to 5 cohorts in total) will be initiated with the same and/or an adaptive study design (i.e. changes in either doses or time interval between DVI and M5717 administration; see Section 4.3.2).

Figure 1 Overall Study Design per Cohort for Dose Finding



IV = intravenous; PfSPZ = *Plasmodium falciparum* sporozoite; PK = pharmacokinetic; qPCR = quantitative polymerase chain reaction.

1.3 Schedule of Activities

Table 1 Schedule of Activities (for DVI and Study Intervention Administration on Day 1; Screening to Week 2)

Activity	Screening	Admission to Site	Hospitalization and DVI/Study Intervention Administration										Ambulatory Visits							Comments
Study Week			1										2							
Study Day	-28 to -2	-1	1			2	3	4	5	6	7	8	9	10	11	12	13	14		
Hours After Study Intervention Administration			-2	pre	0 to <24	24	48	72	96	120	144	168	192	216	240	264	288	312		
Informed Consent	X																			
CCI	X																			CCI
Hospitalization		X	X	X	X	X														For COVID-19 risk assessment measures on Day -1, see Appendix 11.
Ambulatory Visit										X	X	X	X	X	X		X	X		
Ambulatory visits via Phone Call or Visit							X	X	X							X				Participants will be contacted daily either during a visit to the unit or via phone calls while being outpatients, from Day 3 to Day 33, for a safety check and for compliance with the rescue medication use.
Inclusion and Exclusion Criteria Check/Recheck	X	X																		
Demographic and Medical History	X																			

Activity	Screening	Admission to Site	Hospitalization and DVI/Study Intervention Administration										Ambulatory Visits							Comments
Study Week			1										2							
Study Day	-28 to -2	-1	1			2	3	4	5	6	7		8	9	10	11	12	13	14	
Hours After Study Intervention Administration			-2	pre	0 to <24	24	48	72	96	120	144		168	192	216	240	264	288	312	
Physical examination	X	X																		A complete physical examination, including examination of all body systems, will be performed at Screening and the End of Study visit (Day 33 + 3 days) - see Section 8.2.1. An abbreviated physical examination will be performed at admission. At other time point(s) an abbreviated physical examination can be performed at the discretion of the study investigator.
Vital Signs (BP, PR, Respiratory Rate, Body Temperature)[a]	X		X			X				X					X					a Vital signs assessment prior to administration of malaria inoculum as well as 30-minutes post-DVI. BP and PR can be measured within 24 hours before malaria inoculum.
Safety 12-lead ECG	X	X				X														
Clinical Laboratory (Hematology, Biochemistry, Urinalysis)	X	X				X				X					X					When qPCR level reaches ≥ 100 aPf/mL, an additional Clinical Laboratory sample should be taken within 24 hours (unless already scheduled).
Serology	X																			
Pregnancy testing	X	X																		All women must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at Day -1 and at End of Study visit. For more details see Section 5.1.
FSH	X																			Women of non-childbearing potential only

Activity	Screening	Admission to Site	Hospitalization and DVI/Study Intervention Administration										Ambulatory Visits							Comments
Study Week			1										2							
Study Day	-28 to -2	-1	1			2	3	4	5	6	7		8	9	10	11	12	13	14	
Hours After Study Intervention Administration			-2	pre	0 to <24	24	48	72	96	120	144		168	192	216	240	264	288	312	
Urine Drugs of Abuse	X	X																		Additional timepoints at the discretion of the investigator
Alcohol Breath Test	X	X																		Additional timepoints at the discretion of the investigator.
Randomization		X[b]	X[b]																	b Randomization can either be done on Day -1 or Day 1 (prior to DVI PfSPZ).
DVI PfSPZ			X																	
Study Intervention Administration					X															Study intervention administration will occur after baseline PK blood sampling.
Prior and Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
Diary Cards							X	X	X	X	X		X	X	X	X	X	X	X	Diary cards will be provided to participants for more details on data collection and process see Section 6.4.
Parasitemia by qPCR[c]			X[d]							X[e]	X[e]		X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	c At all time points at which the participant returns as an outpatient for a qPCR test, the malaria clinical score will be evaluated. Malaria clinical score will also be evaluated at any timepoint when malaria-related symptoms occur. d First qPCR will be done before DVI administration. e Once daily from Day 6 onwards, until rescue medication is administered, and then daily until the qPCR is negative for 48 hours, then 3 times per week, at the Investigator's discretion, until Day 28.

Activity	Screening	Admission to Site	Hospitalization and DVI/Study Intervention Administration										Ambulatory Visits							Comments
Study Week			1										2							
Study Day	-28 to -2	-1	1			2	3	4	5	6	7		8	9	10	11	12	13	14	
Hours After Study Intervention Administration			-2	pre	0 to <24	24	48	72	96	120	144		168	192	216	240	264	288	312	
PK Sampling[f]				X	X[g]	X				X[h]			X[h]	X[h]						f At visits where assessment time points coincide with each other, the following procedure should be followed: (i) perform vital sign assessments, (ii) perform ECG assessments on time, and (iii) do PK blood sampling at specific time points. Use of the agreed upon time windows (specified in Table 5). g PK sampling timepoints 0 to < 24 h: 0 (= pre-dose), 0.5, 1, 2, 3, 6, 12 hours. h When qPCR level reaches ≥ 100 aPf/mL, an additional PK sample should be taken on the subsequent day. As long as the qPCR value stays < 100 aPf/mL, PK sampling is to be done per scheduled time points as indicated in this table.
Blood sampling for P. falciparum genotyping										X										Blood sample for *P. falciparum* genotyping for possible mutations has to be taken when parasitemia develops (i.e. confirmed qPCR showing ≥ 100 aPf/mL) after administration of the IMP, and before initiation of rescue medication.
CCI																				

aPF=asexual *Plasmodium falciparum*, BP=blood pressure, DVI=direct venous inoculation, ECG=electrocardiogram, FSH=follicle-stimulating hormone, LLOQ=lower limit of quantification, qPCR=quantitative polymerase chain reaction, CCI PK=pharmacokinetic(s), Pre=predose, PR=pulse rate, SMC=Safety Monitoring Committee.

Grey shaded boxes: no activity; white shaded boxes: activities.

Table 2 Schedule of Activities (for DVI and Study Intervention on Day 1; Week 3 to End of Study)

Activity	Ambulatory & Follow up Visits														End of Study Visit	Comments
Study Week	3							4							5	
Study Day	15	16	17	18	19	20	21	22	23	24	25	26	27	28	33 (+ 3)	
Hour After Study Intervention Administration	336	360	384	408	432	456	480	504	528	552	576	600	624	648	768	
Ambulatory Visit	X	X	X		X	X		X		X		X		X	X	
Ambulatory visits via Phone Call or Visit				X			X		X		X		X			Participants will be contacted daily either during a visit to the unit or via phone calls as depicted in this row while being outpatient, from Day 3 to Day 33, for a safety check and for compliance with the rescue medication use.
Physical examination															X	A complete physical examination, including examination of all body systems, will be performed at Screening, and the End of Study visit (Day 33 + 3 days) - see Section 8.2.1. At other time point(s) an abbreviated physical examination can be performed at the discretion of the study investigator.
Vital Signs (BP, PR, Body Temperature)	X							X						X	X	
Safety 12-lead ECG															X	
Clinical Laboratory (Hematology, Biochemistry, Urinalysis)	X							X						X	X	When qPCR level reaches ≥ 100 aPf/mL, an additional Clinical Laboratory sample should be taken within 24 hours (unless already scheduled)
Pregnancy test (urine)															X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Activity	Ambulatory & Follow up Visits														End of Study Visit	Comments
Study Week	3							4							5	
Study Day	15	16	17	18	19	20	21	22	23	24	25	26	27	28	33 (+ 3)	
Hour After Study Intervention Administration	336	360	384	408	432	456	480	504	528	552	576	600	624	648	768	
Diary Cards	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Diary cards will be provided to participants for more details on data collection and process see Section 6.4.
Parasitemia by qPCR	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]		X[a]		X[a]		X[a]		X[a]	X	a Once daily from Day 6 onwards, until rescue medication is administered, and then daily until the qPCR is negative for 48 hours, then 3 times per week, at the Investigator's discretion, until Day 28.
PK Sampling[b]												X[c]			X[c]	b At visits where assessment time points coincide with each other, the following procedure should be followed: (i) perform vital sign assessments, (ii) perform ECG assessments on time, and (iii) do PK blood sampling at specific time points. Use of the agreed upon time windows (specified in Table 5). c When qPCR level reaches ≥ 100 aPf/mL, an additional PK sample should be taken on the subsequent day. As long as the qPCR value stays < 100 aPf/mL, PK sampling is to be done per scheduled time points as indicated in this table.
Blood sampling for P. falciparum genotyping	X[d]															d Blood sample for *P. falciparum* genotyping for possible mutations has to be taken when parasitemia develops (i.e. confirmed qPCR showing ≥ 100 aPf/mL) after administration of the IMP, and before initiation of rescue medication.
Rescue Medication														X		Rescue medication will be given • after confirmation that the first qPCR outcome is equal or greater than 100 aPf/mL of blood, and provided that a subsequent qPCR shows higher parasitemia than the first positive qPCR,

Activity	Ambulatory & Follow up Visits														End of Study Visit	Comments
Study Week	3							4							5	
Study Day	15	16	17	18	19	20	21	22	23	24	25	26	27	28	33 (+ 3)	
Hour After Study Intervention Administration	336	360	384	408	432	456	480	504	528	552	576	600	624	648	768	
																• or on Day 28 if qPCR outcome remains below this threshold (Section 6.5.1). Safety assessments (Section 8.2) must be performed before administration of rescue medication. Administration of rescue medications prior to Day 28 will be determined at the Investigators discretion.

aPF=asexual *Plasmodium falciparum*, BP=blood pressure, DVI=direct venous inoculation, ECG=electrocardiogram, FSH=follicle-stimulating hormone, LLOQ=lower limit of quantification, qPCR=quantitative polymerase chain reaction, CCI [redacted], PK=pharmacokinetic(s), Pre=predose, PR=pulse rate, SMC=Safety Monitoring Committee.
Grey shaded boxes: no activity; white shaded boxes: activities.

Table 3 Schedule of Activities (for DVI on Day 1 and Study Intervention on Day 5; Screening to Week 2)

Activity	Screening		DVI administration		Admission to site	Hospitalization and Study Intervention Administration			Ambulatory Visits												Comments
Study Week			1								2										
Study Day	-28 to -2	-1	1	2	3	4	5		6	7	8	9	10	11	12	13	14	15	16	17	
Study Intervention Administration Day			-4	-3	-2	-1	1		2	3	4	5	6	7	8	9	10	11	12	13	
Hours After Study Intervention Administration			-96	-72	-48	-24	pre	0 to <24	24	48	72	96	120	144	168	192	216	240	264	288	
Informed Consent	X																				
CCI	X																				CCI
Hospitalization						X	X	X	X												For COVID-19 risk assessment measures on Study Day 4, see Appendix 11.
Ambulatory Visit		X	X										X	X	X	X	X	X		X	
Ambulatory Visits via Phone Call or Visit				X	X					X	X	X							X		Participants will be contacted daily either during a visit to the unit or via phone calls while being outpatients, from Study Day 7 to Study Day 32, for a safety check and for compliance with the rescue medication use.
Inclusion and Exclusion Criteria Check/Recheck	X	X			X	X															
Demographic and Medical History	X																				

Activity	Screening		DVI administration		Admission to site	Hospitalization and Study Intervention Administration			Ambulatory Visits													Comments
Study Week			1								2											
Study Day	-28 to -2	-1	1	2	3	4	5		6	7	8	9	10	11	12	13	14	15	16	17		
Study Intervention Administration Day			-4	-3	-2	-1	1		2	3	4	5	6	7	8	9	10	11	12	13		
Hours After Study Intervention Administration			-96	-72	-48	-24	pre	0 to <24	24	48	72	96	120	144	168	192	216	240	264	288		
Physical examination	X	X				X																A complete physical examination, including examination of all body systems, will be performed at Screening and the End of Study visit (Study Day 36 + 3 days) - see Section 8.2.1. An abbreviated physical examination will be performed at admission. At other time point(s) an abbreviated physical examination can be performed at the discretion of the study investigator.
Vital Signs (BP, PR, Respiratory Rate, Body Temperature)[a]	X		X						X				X				X					a Vital signs assessment prior to administration of malaria inoculum as well as 30-minutes post-DVI. BP and PR can be measured within 24 hours before malaria inoculum.
Safety 12-lead ECG	X	X							X													
Clinical Laboratory (Hematology, Biochemistry, Urinalysis)	X	X				X			X				X				X					When qPCR level reaches ≥ 100 aPf/mL, an additional Clinical Laboratory sample should be taken within 24 hours (unless already scheduled).
Serology	X																					
Pregnancy testing	X	X				X																All women must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at Study Day -1 and Study Day 4 and at End of Study visit. For more details see Section 5.1.
FSH	X																					Women of non-childbearing potential only.

Activity	Screening		DVI administration		Admission to site	Hospitalization and Study Intervention Administration			Ambulatory Visits												Comments
Study Week			1								2										
Study Day	-28 to -2	-1	1	2	3	4	5		6	7	8	9	10	11	12	13	14	15	16	17	
Study Intervention Administration Day			-4	-3	-2	-1	1		2	3	4	5	6	7	8	9	10	11	12	13	
Hours After Study Intervention Administration			-96	-72	-48	-24	pre	0 to <24	24	48	72	96	120	144	168	192	216	240	264	288	
Urine Drugs of Abuse	X					X															
Alcohol Breath Test	X		X			X															
Randomization		X[b]	X[b]																		b Randomization can either be done on Study Day -1 or Study Day 1 (prior to DVI PfSPZ).
DVI PfSPZ			X																		
Study Intervention Administration								X													Study intervention administration will occur after baseline PK blood sampling.
Prior and Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Diary Cards			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Diary cards will be provided to participants for more details on data collection and process see Section 6.4.

Activity	Screening		DVI administration		Admission to site	Hospitalization and Study Intervention Administration		Ambulatory Visits												Comments
Study Week			1							2										
Study Day	-28 to -2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
Study Intervention Administration Day			-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	
Hours After Study Intervention Administration			-96	-72	-48	-24	pre / 0 to <24	24	48	72	96	120	144	168	192	216	240	264	288	
Parasitemia by qPCR[c]			X[d]					X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	c At all time points at which the participant returns as an outpatient for a qPCR test, the malaria clinical score will be evaluated. Malaria clinical score will also be evaluated at any timepoint when malaria-related symptoms occur. d First qPCR will be done before DVI administration. e Once daily from Study Day 6 onwards, until rescue medication is administered, and then daily until the qPCR is negative for 48 hours, then 3 times per week, at the Investigator's discretion, until Study Day 32.

Activity	Screening		DVI administration		Admission to site	Hospitalization and Study Intervention Administration			Ambulatory Visits												Comments
Study Week			1								2										
Study Day	-28 to -2	-1	1	2	3	4	5		6	7	8	9	10	11	12	13	14	15	16	17	
Study Intervention Administration Day			-4	-3	-2	-1	1		2	3	4	5	6	7	8	9	10	11	12	13	
Hours After Study Intervention Administration			-96	-72	-48	-24	pre	0 to <24	24	48	72	96	120	144	168	192	216	240	264	288	
PK Sampling[f]							X	X[g]	X				X[h]		X[h]	X[h]					f At visits where assessment time points coincide with each other, the following procedure should be followed: (i) perform vital sign assessments, perform ECG assessments on time, do PK blood sampling at specific time points. Use of the agreed upon time windows (specified in Table 5). g PK sampling timepoints 0 to < 24 h: 0 (= pre-dose, 0.5, 1, 2, 3, 6, 12 hours. h When qPCR level reaches ≥ 100 aPf/mL, an additional PK sample should be taken on the subsequent day. As long as the qPCR value stays < 100 aPf/mL, PK sampling is to be done per scheduled time points as indicated in this table.
Blood sampling for *P. falciparum* genotyping									X												Blood sample for *P. falciparum* genotyping for possible mutations has to be taken when parasitemia develops (i.e. confirmed qPCR showing ≥ 100 aPf/mL) after administration of the IMP, and before initiation of rescue medication.
CCI																					

aPF=asexual *Plasmodium falciparum*, BP=blood pressure, DVI=direct venous inoculation, ECG=electrocardiogram, FSH=follicle-stimulating hormone, LLOQ=lower limit of quantification, qPCR=quantitative polymerase chain reaction, CCI PK=pharmacokinetic(s), Pre=predose, PR=pulse rate, SMC=Safety Monitoring Committee.
Grey shaded boxes: no activity; white shaded boxes: activities.

Table 4 Schedule of Activities (for DVI on Day 1 and Study Intervention on Day 5; Week 3 to End of Study)

Activity	Ambulatory & Follow up Visits															End of Study Visit	Comments
Study Week	3							4								5	
Study Day	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	36 (+ 3)	
Study Intervention Administration Day	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	33	
Hours After Study Intervention Administration	312	336	360	384	408	432	456	480	504	528	552	576	600	624	648	768	
Ambulatory Visit	X	X	X	X		X	X		X		X		X		X	X	
Ambulatory visits via Phone Call or Visit					X			X		X		X		X			Participants will be contacted daily either during a visit to the unit or via phone calls as depicted in this row while being outpatient, from Study Intervention Day 3 to Day 28 (Study Day 7 to Study Day 32), for a safety check and for compliance with the rescue medication use.
Physical examination																X	A complete physical examination, including examination of all body systems, will be performed at Screening and the End of Study visit (Study Day 36 + 3 days) - see Section 8.2.1. At other time point(s) an abbreviated physical examination can be performed at the discretion of the study investigator.
Vital Signs (BP, PR, Body Temperature)		X							X						X	X	
Safety 12-lead ECG																X	
Clinical Laboratory (Hematology, Biochemistry, Urinalysis)		X							X						X	X	When qPCR level reaches ≥ 100 aPf/mL, an additional Clinical Laboratory sample should be taken within 24 hours (unless already scheduled).

Activity	Ambulatory & Follow up Visits																End of Study Visit	Comments
Study Week	3							4								5		
Study Day	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	36 (+ 3)		
Study Intervention Administration Day	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	32		
Hours After Study Intervention Administration	312	336	360	384	408	432	456	480	504	528	552	576	600	624	648	744		
Pregnancy test (urine)																X	Women only	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Diary Cards	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Diary cards will be provided to participants for more details on data collection and process see Section 6.4.	
Parasitemia by qPCR	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]		X[a]		X[a]		X[a]		X[a]	X	a Once daily from Day 6 onwards, until rescue medication is administered, and then daily until the qPCR is negative for 48 hours, then 3 times per week, at the Investigator's discretion, until Study Intervention Day 28 (Study Day 32).	
PK Sampling[b]													X[c]			X[c]	b At visits where assessment time points coincide with each other, the following procedure should be followed: (i) perform vital sign assessments, perform ECG assessments on time, do PK blood sampling at specific time points. Use of the agreed upon time windows (specified in Table 5). c When qPCR level reaches ≥ 100 aPf/mL, an additional PK sample should be taken on the subsequent day. As long as the qPCR value stays < 100 aPf/mL, PK sampling is to be done per scheduled time points as indicated in this table.	

Activity	Ambulatory & Follow up Visits															End of Study Visit	Comments
Study Week	3							4								5	
Study Day	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	36 (+ 3)	
Study Intervention Administration Day	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	32	
Hours After Study Intervention Administration	312	336	360	384	408	432	456	480	504	528	552	576	600	624	648	744	
Blood sampling for *P. falciparum* genotyping	X																Blood sample for *P. falciparum* genotyping for possible mutations has to be taken when parasitemia develops (i.e. confirmed qPCR showing ≥ 100 aPf/mL) after administration of the IMP, and before initiation of rescue medication.
Rescue Medication															X		Rescue medication will be given • after confirmation that the first qPCR outcome is equal or greater than 100 aPf/mL of blood, and provided that the subsequent qPCR shows higher parasitemia than the first positive qPCR, • or on Study Intervention Administration Day 28 (= Study Day 32) if qPCR outcome remains below this threshold (Section 6.5.1). • Safety assessments (Section 8.2) must be performed before administration of rescue medication. Administration of rescue medications prior to Study Intervention Administration Day 28 will be determined at the Investigators discretion.

aPF=asexual *Plasmodium falciparum*, BP=blood pressure, DVI=direct venous inoculation, ECG=electrocardiogram, FSH=follicle-stimulating hormone, LLOQ=lower limit of quantification, qPCR=quantitative polymerase chain reaction, CCI PK=pharmacokinetic(s), Pre=predose, PR=pulse rate, SMC=Safety Monitoring Committee.
Grey shaded boxes: no activity; white shaded boxes: activities.

Table 5 Allowed Time Windows for Scheduled Time Points

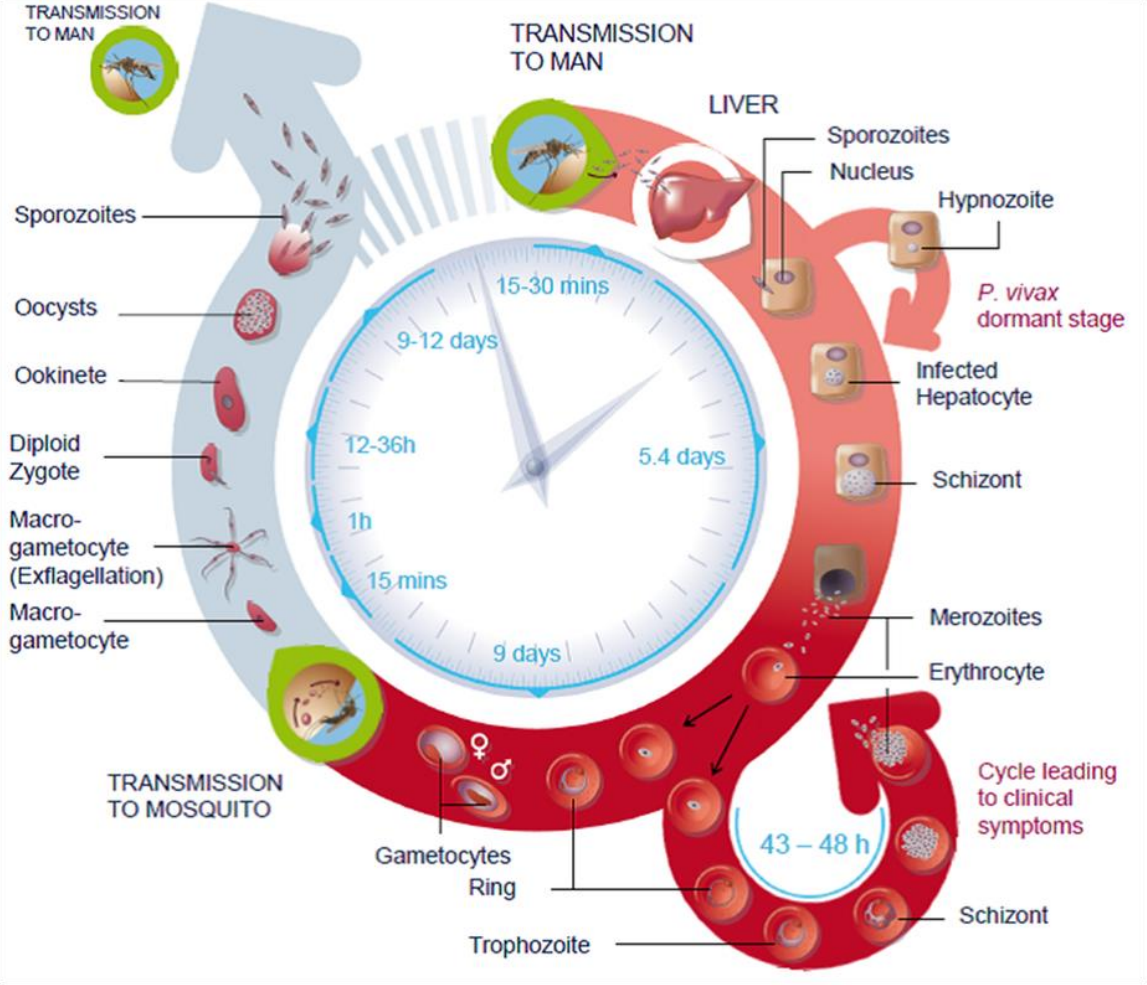
Time Point	Tolerance Window
Pharmacokinetic/Pharmacodynamic (blood samples)	
Predose	- 60 min to 0 h
0.5 h to 1.0 h post	± 3 min
2 h to 3 h post	± 3 min
6 h to 24 h post	± 10 min
120 h to 192 h post	± 6 h
600 h and 768 h post	± 72 h
12-Lead Electrocardiogram/Vital Signs/Respiratory Rate/Temperature/Safety Laboratory Samples	
Predose	- 150 min to 0 h
24 h post	± 10 min
120 h to 408 h post	± 6 h
504 h post	± 24 h
648 h and 768 h post	± 72 h

2 Introduction

M5717 is a first-in-class New Chemical Entity (NCE) targeting the *Plasmodium* cytosolic protein synthesis "elongation factor 2". This target is involved in the guanosine triphosphate-dependent translocation of the ribosome and is essential for protein synthesis. From preclinical and human data, M5717 seems to be highly selective for the *Plasmodium* species and no effects on protein synthesis in humans are to be expected.

The molecule is intended to be developed in combination with a partner molecule as a single dose for the treatment of uncomplicated malaria and/or the prevention of malaria in endemic populations and travelers. M5717 is highly efficacious against multiple life-cycle stages of the *P. falciparum* and *P. vivax* malaria parasites, including the erythrocytic, the liver schizont, and the gametocyte stages of the parasite (Figure 2).

Figure 2 ***Plasmodium*** **Life Cycle: Sporogony in Mosquito (Sexual Cycle) and Human Stages (Asexual Cycle)**



Potent prophylactic activity of M5717 has been demonstrated in preclinical models. The safety and tolerability of M5717 has been monitored closely in preclinical studies, and in completed and

ongoing clinical studies (Single Ascending Dose [SAD] and Controlled Human Malaria Infection [CHMI] studies).

Since M5717 has been confirmed to have in vitro and in vivo activity on the liver stage, the aim of the current protocol is to investigate the effect of M5717 on the development of the parasite in the human liver using the injected *P. falciparum* sporozoite (NF54 strain) CHMI model, in support of a potential preventive chemotherapy indication.

Complete information on the chemistry, pharmacology, efficacy, and safety of M5717 is in the Investigator's Brochure [IB]).

CCI

2.2 Background

Human malaria is an acute febrile illness caused by five *Plasmodium* parasite species (*P. falciparum, P. vivax, P. malariae, P. ovale and P. knowlesi*). According to the latest estimates, released on 19 November 2018 by the World Health Organization (WHO), there were about 219 million cases of malaria and an estimated 435,000 deaths due to malaria worldwide in 2017 (WHO Malaria report , 2018). Most deaths (60%) occur among children below 5 years of age, most of whom live in Africa. In a non-immune individual, symptoms appear about 7 days after the infective mosquito bite and the subsequent asymptomatic liver stages. Although atovaquone-proguanil

(Malarone®) and recently tafenoquine (Arakoda™, 60 Degrees Pharmaceuticals, Washington, DC, USA) have been registered for chemoprophylaxis in the traveler population, there are limited preventive chemotherapy options available for extended use by the populations in endemic areas and migrants. Chemoprophylactic agents are mainly based on the repurposing of drugs used for treatment and all of these agents are facing emerging or established resistance.

The development of new treatments in malaria targeting prophylaxis and transmission is becoming increasingly important. Target Product Profiles have been defined in the malaria drug development field to address future cure and chemoprophylaxis compound profiles, consistent with the strong recommendation from WHO to develop only combination therapies, to minimize the risk of emerging resistance (Burrows 2013).

M5717 is a first-in-class compound with a new mode of action (i.e., inhibition of plasmodial protein synthesis by targeting the Plasmodium eukaryotic translation Elongation Factor 2 [PeEF2]) and shows excellent activity against malaria blood-stages (including clinical isolates and drug-resistant strains), liver-stages, and in transmission blocking assays in preclinical investigations. M5717 displayed a long half-life and an effective exposure with high potency against all forms of the parasite. This allows for administration of a single oral dose and maintaining protection over an extended period of time.

In the view of accelerating the development of new antimalarial medications, CHMI studies have been established, involving infection of participants with low numbers of malaria parasites, either through injection of sporozoites and allowing the development of pre-erythrocytic stages, or injection of malaria-infected erythrocytes (blood stage). These models are well-accepted, their safety profile is well understood, and their overall benefit was demonstrated in terms of reduction of development times and limiting the number of participants in Phase II dose-finding studies.

The DVI of *P. falciparum* sporozoites (PfSPZ) is a validated and standardized model for 100% induction of malaria infection in healthy participants (Mordmüller 2015). DVI of 3200 PfSPZ has been implemented for testing efficacy of malaria vaccines (Jongo 2018, Mordmüller 2017) and more recently for evaluating efficacy of antimalarial drugs (Murphy 2018, Sulyok 2017).

The aim of this study is to assess the chemoprophylactic activity and to explore the dose-exposure-response relationship of single oral doses of M5717 administered immediately (early liver stage) or few days after (late liver stage) DVI of PfSPZ Challenge in malaria-naïve, healthy participants in the CHMI model.

2.3 Benefit/Risk Assessment

Benefits are mainly to society for the potential availability of a more convenient product for chemoprophylaxis of malaria in travelers and populations in endemic settings.

Potential risks to participants in the PfSPZ Challenge model include development of mild/moderate symptoms associated with PfSPZ inoculation and the subsequent infection with malaria parasites, as well as the adverse effects of M5717 and the approved malaria rescue medications atovaquone/proguanil (Malarone 250 mg/100 mg, Glaxo Wellcome S.A.) and artemether/lumefantrine (Riamet® 20 mg/120 mg, Novartis). The risk to develop malaria symptoms is minimized, as the rescue treatment will be started at a low parasitemia level.

There have been three cardiac adverse events in previous controlled human infection studies of which two were published as case reports (Nieman 2009, Van Meer 2014). A third case happened in the BMGF1 study (NL48301.91.14). All cases were reported to the regulatory authorities concerned. Although the relation with the malaria infection was not resolved, the temporal relationship makes an association with CHMI likely.

No such events are expected in the present study however as treatment will be initiated at very low levels of parasitemia. Rescue treatment in the present study is initiated when blood-stage growth is detected after a first parasitemia of just $\geq$ 100 asexual parasites/mL as measured by qPCR and provided that the subsequent qPCR shows higher parasitemia than the first positive qPCR, or on Day 28 if qPCR outcome remains below this threshold (see Section 6.5.1). To compare, the 23-year-old male in the TIP5 study had 13,293 parasites/ml on the day of treatment, measured by qPCR retrospectively after a positive thick blood smear triggered rescue treatment. Thick blood smears become positive at much higher levels of parasite load compared to qPCR. 13,293 is not an unusual level for a first positive thick blood smear. In fact, the detection threshold of a thick blood smear is estimated to be at 4-20 parasites/ul (= 4000 – 20 000 p/ml). All three cardiac cases occurred in studies where a positive thick blood smear was the trigger for rescue treatment. Moreover, these previous studies were done with bites of *P. falciparum* infected mosquitoes of which the load of initial parasite exposure is less reliably estimated when compared to DVI of PfSPZ parasites.

Currently, for controlled human malaria infection studies, the use of qPCR with a treatment threshold of 100 parasites/ml is highly sensitive and specific and improves safety (Walk 2016). Moreover, frequent Hs-Troponin T testing (a marker for cardiac necrosis) is incorporated as part of the safety labs in the present study.

The risk to participants in this study will be minimized by an adequate selection of eligibility criteria, a dense schedule of medical monitoring of admitted participants, including ambulatory follow up, and administration of standard of care (SoC) medication to participants. Since infection with malaria parasites may lead to transiently increased levels of liver enzymes in some participants (Woodford 2018), close monitoring of liver function and other relevant clinical laboratory parameters will be assessed regularly as part of the safety monitoring in this study. Of note, no additional effects on liver enzymes were observed by administration of M5717 to participants challenged with infected erythrocytes in the CHMI part of the Phase I study (refer to the IB).

In repeat-dose toxicity studies in dogs and rats, the main target organs of toxicity of M5717 were the liver, the lymphatic system, and the epithelia of the gastrointestinal tract. Thus, the following potential risks of the investigational product were identified as:

- Change in hematology (test abnormal) and biochemistry parameters (e.g., decrease in reticulocytes, platelet increase, liver enzymes [alanine aminotransferase (ALT)/ aspartate aminotransferase (AST)/ Bilirubin] increases),
- Leukocyte vacuolization,
- Gastrointestinal symptoms (nausea, vomiting, diarrhea),
- Photosensitivity/light sensitivity (cutaneous reactions),
- Drug-drug interactions.

In vitro safety pharmacology studies included off-target receptor profiling (employing 145 radioligand binding and enzyme assays), activity testing on cardiac ion channels, and measuring of refractory period in isolated guinea pig papillary muscle. Results showed that M5717 did not induce relevant off-target effects at 10 μM (= 4630 ng/mL) a concentration that is higher than the concentrations reached in the FIH study. At a dose of 800 mg, where 8/8 participants achieved full cure in an induced human blood stage model (IBSM), the highest concentration observed was 615 ng/mL. Based on these data, the probability for off-target effects at the expected pharmacologically relevant concentration is considered to be low.

As of 08 May 2019, single ascending doses of M5717 up to 2100 mg (as succinate) have been administered. Overall, across all cohorts, M5717 showed a favorable safety profile, with no treatment emergent adverse events (TEAEs) leading to death, discontinuation or withdrawal. Drug-related TEAEs were mostly mild, transient in nature, and resolved without sequelae. High doses of 1800 and 2100 mg M5717 succinate showed mild to moderate neurological effects (headache, blurred vision, dizziness) in a few participants, but these adverse events (AEs) resolved spontaneously and without sequelae. The doses intended to be used in this study will be lower or within the dose range (200 to 800 mg M5717) showing different grades of efficacy in the IBSM model in the FIH study and will not exceed 1250 mg.

Periodic blood draws will be needed to monitor the participants' safety, to perform qPCR for early detection of *P. falciparum* parasitemia, and for PK analysis. Throughout the whole study, the amount of blood collected over the course of 2 months will be less than 450 mL.

Furthermore, the participants will be prescribed curative therapy for malaria: atovaquone/proguanil or artemether/lumefantrine for final clearance of the parasite at the end of the study. A full discussion of the potential risks from atovaquone/proguanil and artemether/lumefantrine may be found in the respective approved manufacturer's prescribing information (see Appendix 8 for package inserts of Malarone and Riamet).

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of M5717 may be found in Section 4.2 and the IB.

Based on the available nonclinical and clinical data to date, the conduct of the study, as specified in this protocol, is considered justifiable.

Due to the currently ongoing threat of the SARS-CoV-2 pandemic, additional COVID-19 related risk assessment measures were implemented. See Appendix 11.

3 Objectives and Endpoints

The study objectives and endpoints are listed in Table 6 below. See Section 9.4 (Statistical Analysis) for the statistical aspects of the endpoints.

Table 6 Objectives and Endpoints

Primary Objectives	Endpoints
To assess chemoprophylactic activity of single oral doses of M5717 administered after DVI of *Plasmodium falciparum* sporozoites (PfSPZ) challenge in healthy participants.	• Response endpoints: • Number of participants over time with positive parasitemia defined as first positive qPCR outcome equal or greater than 100 asexual parasites per mL of blood within 28 days of PfSPZ challenge • Time to parasitemia, defined as time from PfSPZ DVI to the first qPCR outcome equal or greater than 100 asexual parasites per mL of blood (time frame: number of days from PfSPZ DVI challenge to positive parasitemia, or 28 days) • Number of participants with documented blood stage parasite growth, defined as an increase of qPCR measured asexual parasites per mL compared to the first parasitemia measurement, within 28 days of PfSPZ DVI • Clinical symptoms of malaria using the Malaria Clinical Score.
To explore the dose-exposure-response relationship of a single oral dose of M5717 administered after DVI of PfSPZ challenge in healthy participants.	Dose-exposure-response relationship: • Selected pharmacokinetic (PK) endpoints/ concentrations (e.g. AUC_{0-24}, AUC_{0-168}, C_{24}, C_{168}) and pharmacodynamic (PD) endpoints (cured/not-cured) will be used for PK/PD modeling approaches.
Secondary Objectives	**Endpoints**
To evaluate the safety and tolerability of single, oral doses of M5717 in healthy participants following infection with PfSPZ challenge	• Nature, incidence, frequency, severity of (treatment emergent) adverse events (AEs)/ serious adverse events (SAEs), and relationship to the study intervention • Incidence of clinically significant changes and abnormalities in safety laboratory parameters (hematology, coagulation, biochemistry [specifically alanine aminotransferase (ALT) and aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin (total)], and urinalysis) • Incidence of clinically significant changes and abnormalities in vital signs and 12 lead electrocardiogram (ECG).
To investigate the PK of M5717 after administration of single, oral doses in healthy participants following infection with PfSPZ	Exposure endpoints: • Concentration-time curve for M5717 after single-dose administration • Pharmacokinetic parameters of M5717 such as $AUC_{0-\infty}$, AUC_{0-t}, AUC_{0-24}, AUC_{0-168}, C_{max}, C_{24}, C_{168}, t_{max}, $t_{1/2}$, λ_z, CL/f and Vz/f to be specified in the Integrated Analysis Plan.
CCI [redacted]	

DVI=direct venous inoculation, PD=pharmacodynamics, PfSPZ= *P. falciparum* sporozoites, PK=pharmacokinetics, qPCR=quantitative polymerase chain reaction.

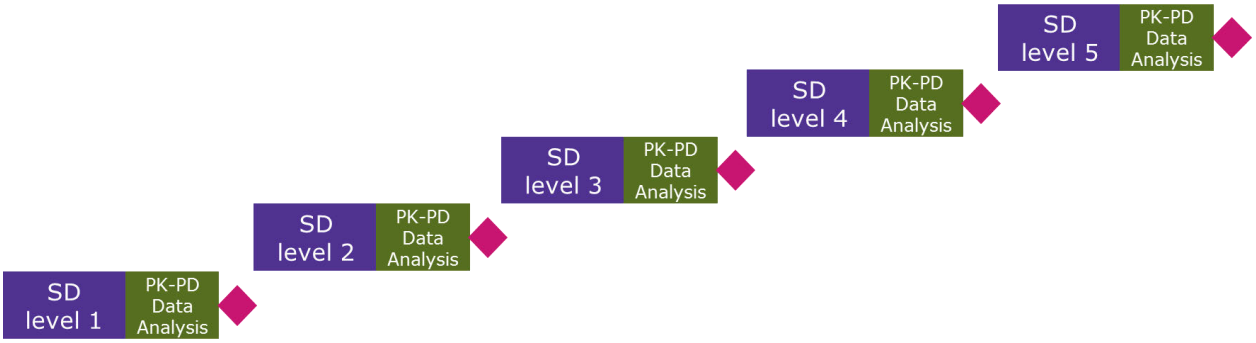
4 Study Design

4.1 Overall Design

This is a Phase Ib, single center, sequential, double-blind, randomized, placebo controlled study to investigate the chemoprophylactic activity and dose-exposure-response relationship of single doses of M5717 administered after DVI of *P. falciparum* sporozoites (PfSPZ challenge) to healthy malaria-naïve male and female participants (see Section 2 for more details).

The study will involve up to a maximum of 50 healthy adult men and women (between 4 and 12 healthy participants per dose group, with up to 5 cohorts), 18 to 45 years of age and all receiving PfSPZ challenge. The sequence of cohorts (dose escalation or de-escalation and time interval between DVI with PfSPZ and M5717 administration) will depend on Safety Monitoring Committee (SMC) review for safety and PK/PD (Figure 3).

Figure 3 Overall Study Design Assuming 5 Cohorts for Dose-Finding



SD=study dose, PD=pharmacodynamics, PK=pharmacokinetics.
PK-PD data analysis will be performed as needed on the basis of the PD results of the respective cohort(s) and according to the algorithm for adaptive dose selection as shown in Figure 4.

For each cohort, between 4 and 12 participants will be randomly assigned to receive a single dose of M5717 or placebo at a pre-defined ratio of 3:1 and a block size of 4. Number of participants may be adapted (e.g., 4 [3 active:1 placebo], 8 [6 active:2 placebo], or 12 [9 active:3 placebo]) for the subsequent dose group based on available PD (cured/not-cured) and PK data from the actual/preceding dose groups. This approach allows for a data-driven assessment of the chemoprophylactic activity of M5717 and the PK/PD relationship. As such, subsequent dose level (up to a total of 5) and/or time interval will be suggested based on the available PK/PD and safety data, and decided by the SMC, with the goal to identify the dose (exposure) level achieving full prophylaxis on Day 1. Once the efficacious dose level for the early liver stage has been identified, a cohort with 12 participants will be evaluated whether this dose is also efficacious on the late liver stage (administration of M5717 at Day 5 after PfSPZ challenge).

The placebo control will facilitate the identification of effects related to administration of M5717 in the active group rather than to the study procedures or situation, i.e. to minimize bias. The placebo treatment will also allow confirmation of biological activity of the DVI PfSPZ challenge and the determination of shortest time to first qPCR positivity as part of the primary endpoints.

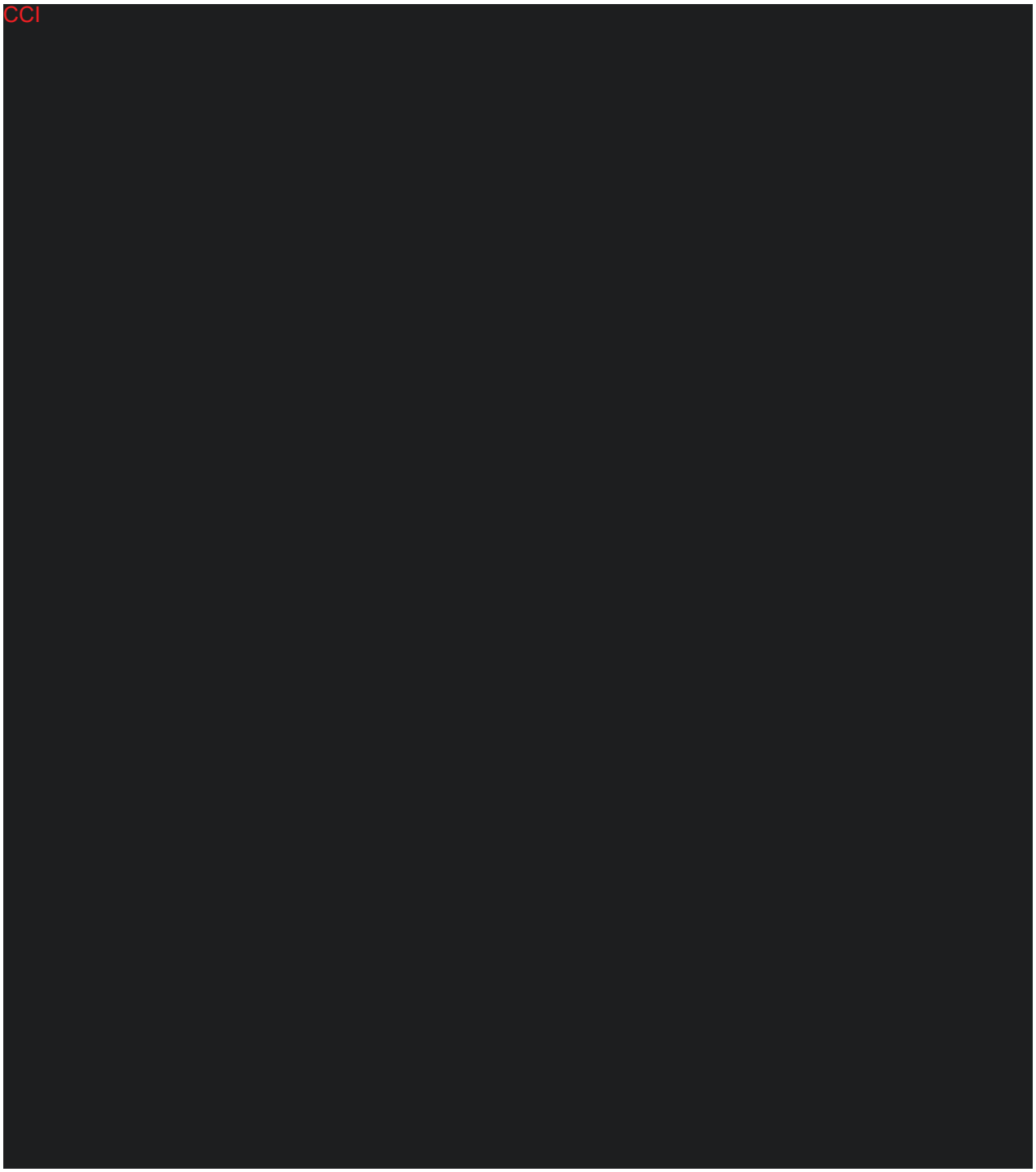
No participant will be enrolled in more than 1 cohort in the study.

Serial blood samples will be collected throughout the inpatient and outpatient period for laboratory safety, PD and PK assessments.

The timing of the end of study will depend on the number of cohorts (up to 5 cohorts planned). An Early Termination visit will be conducted for participants who withdraw prematurely. The same assessments as for the End of Study visit will be conducted at the Early Termination visit.

A detailed SoA (Schedule of Activities) is provided in Section 1.3.

CCI



CCI

4.3 Justification for Dose

4.3.1 Justification for First Dose

Currently, limited data exist for the translation of efficacious exposure data from animal models to the human sporozoite challenge model. Only a few study interventions have so far been explored in the PfSPZ Challenge model.

Exploratory internal preclinical data suggested that an average concentration (Cav) of ~30 nM needs to be maintained for 24 hours in plasma to prevent liver-stage infection in mice, whereas a Cav of 5 nM did not lead to any prevention. Assuming the following: i) full translatability of mouse to human, ii) similar susceptibility of *P. berghei* and *P. falciparum* to M5717, iii) Cav as a relevant parameter, as well as iv) a blood-to-plasma ratio in humans of 1.6, and since 1 nM corresponds to 0.46 ng/mL, the corresponding area under the curve (AUC_{blood}) over 24 hours was calculated to be 30 x 1.6 x 0.46 x 24 or 530 ng/mL*h to prevent liver-stage infection. Using the draft population PK model from the FIH SAD study, this AUC corresponds to a dose of approximately 183 mg free

base (rounded to 200 mg), at which 50 % of the participants are expected to have an exposure above 530 ng/mL*h.

It is recognized that there are many assumptions regarding this first dose level and therefore the study follows a sequential adaptive design to be able to escalate or de-escalate the dose in the subsequent cohorts, to find a dose that leads to protection in the majority of the participants. By exploring the dose-exposure-response relationship via population PK/PD modeling approaches, it is envisaged that effective Phase II doses and dosing regimen can be extrapolated. For dosing considerations, see Section 6.6.

The proposed starting dose of 200 mg in this study was shown to be safe in the FIH study (MS201618-0013) and is well below the highest dose that was assessed in the FIH SAD study (2100 mg).

4.3.2 Selection of Further Doses

The decision to proceed to the next cohort (either an increase or a decrease of M5717 single, oral dose or change in time interval between DVI with PfSPZ and M5717 administration) will be made by the SMC based on all available safety, tolerability and PD data. PK data will be included if appropriate. Due to a high uncertainty in the dose setting for the human situation, the single, oral dose will be adjusted for subsequent cohorts. Considering preclinical data from animal models it is expected that the dose for prophylaxis is lower than the dose for cure. The effective dose range in the IBSM model for cure in the FIH study was about 200 mg – 800 mg M5717. Therefore, the highest dose in this protocol is deemed not to exceed 1250 mg M5717. SMC guidance on dose selection and modification will follow the algorithm for adapted dose selection as shown in Figure 4 and taking into account the available safety data. Details will be described in the SMC charter (see Appendix 2 Study Governance).

The number of participants per dose group will be flexible and depend on the uncertainty of the prediction. The first dose group(s) will contain few participants (3 active:1 placebo). When there is more certainty on efficacious AUC exposures, the number of participants per group can be increased to 8 (6 active:2 placebo) or 12 (9 active:3 placebo).

Once an efficacious dose and AUC is identified and sufficient data are available for evaluating the exposure-dose response relationship, another cohort will be initiated and dosed with M5717 at a later time-point, i.e., 4 days after DVI, to assess the effect of M5717 on late liver stages.

The decision to proceed to the next cohort will be made by the SMC. See Figure 4 for a summary of possible adaptive designs after evaluation of the first and/or second cohort. Decisions for the next cohorts will follow a comparable algorithm. If 100% cure is observed in 3/3 active participants (assuming the placebo will not be cured), the dose will be halved, and another 4 participants will be treated with a lower dose. If again 100% cure is observed at this lower dose it is at the discretion of the SMC to propose a lower dose for the next cohort. For example, the following scenario could be possible: 200 mg – 100 mg – 60 mg – 30 mg, taking into account available dose strengths of the study intervention.

If 1 or 2 active participants show cure, the cohort will be expanded at that dose with another 8 participants (6 actives). Subsequently, the PK data of all 12 participants (9 actives) will be analyzed. The goal is to see whether a PK parameter can be identified that predicts cure and to propose a subsequent dose that will lead to around 50% cured participants in the next cohort.

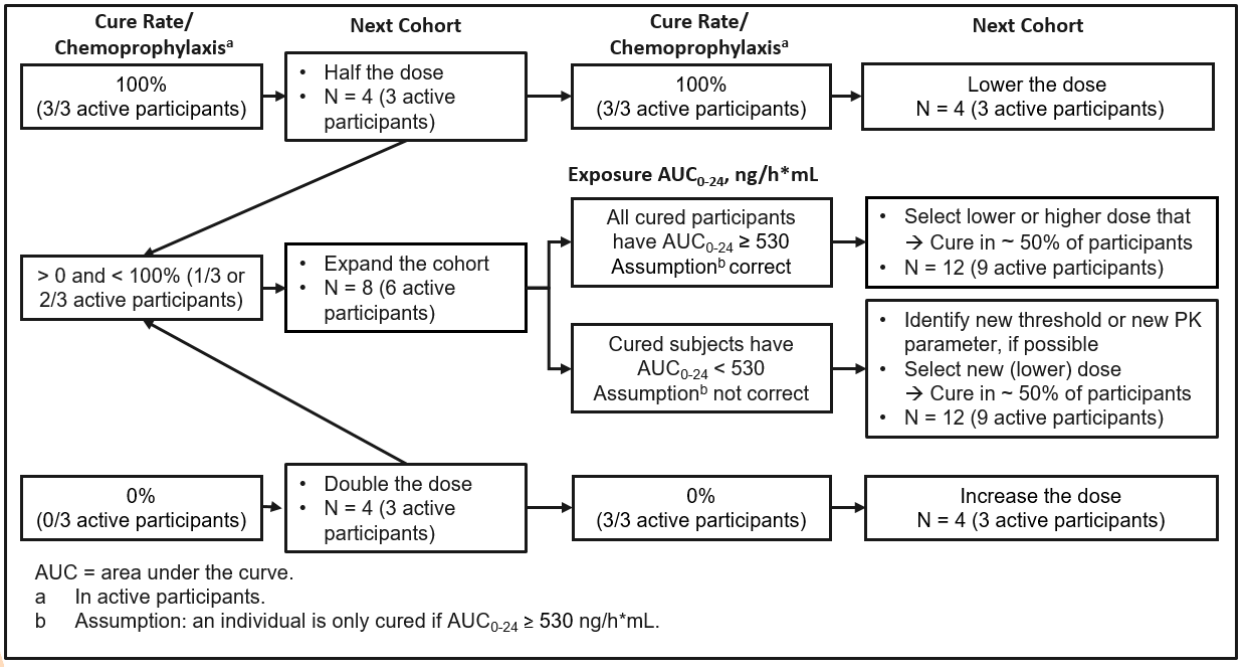
For example, if the assumption $AUC_{0-24} \geq 530$ ng/h*mL, in all cured participants is confirmed, another cohort of 12 participants can be added with a lower or higher dose assumed to reach about 50% of cured participants to provide sufficient data for determination of the dose-exposure-response relationship. Once this has been accomplished the SMC can decide to evaluate administration of M5717 on Day 5 after PfSPZ inoculation.

In case of uncertainty in the goal of reaching 50% of cured participants, the SMC might propose to evaluate less than 12 participants (4 or 8) or propose to explore 2 doses in the next cohort.

In case there are cured participants that have an $AUC_{0-24} < 530$ ng/h*mL it means that the initial assumption is not valid, or it could also mean that AUC_{0-24} is not the correct parameter. In this case modeling and simulation should evaluate whether another threshold can be identified, or whether another PK parameter can be defined and inform the SMC accordingly on possible doses.

Similarly, if no participants are cured at the first dose, the dose will be doubled if safety allows. If after the second dose again none of the participants is cured the SMC can propose another increase of the dose taking into consideration the observed safety signals. This can be repeated until 1 or 2 active participants show cure, then that dose will be expanded, or until a dose of 1250 mg is reached.

Figure 4 Summary of Adaptive Design Steps after Evaluation of First and Second Cohort



The available formulations for the study intervention are 30 mg and 100 mg M5717 free base capsules. The participants will receive the content of capsules of 30 and/or 100 mg or placebo.

4.4 End of Study Definition

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

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

5 Study Population

The criteria in Sections 5.1 and 5.2 are designed to enroll only participants, who are appropriate for the study; thereby, ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a participant is suitable for this study.

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Before performing any study assessments that are not part of the participant's routine medical care, the Investigator will confirm that the participant or the participant's legal representative has provided written informed consent, as indicated in Appendix 2 Study Governance.

The study population comprises healthy, malaria-naïve, male and female, adult participants. Following approval by the accredited institutional review board (IRB)/IEC, potential participants will be contacted by email and telephone from the site's database of healthy participants and through study-specific advertisement including print-, social-, and online media, including websites such as proefpersoon.nl, controlledhumaninfection.nl or the site's website. In addition, short presentations may be given to students before lectures. Only persons meeting all inclusion criteria and none of the exclusion criteria may be enrolled into the study as participants. The criteria have to be checked at Screening, and on the day of DVI of PfSPZ.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Age

1. Are between 18 and 45 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Are overtly healthy as determined by medical evaluation, including 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 participant safety or interfere with the study evaluation, procedures or completion.

Weight

3. Have a body weight within 50 to 100 kg and body mass index within the range 19.0 to 29.9 kg/m^2 (inclusive).

Sex

4. Are male or female

Contraceptive use by males or females will be consistent with local regulations on contraception methods for those participating in clinical studies.

- **Male Participants**:

  Agree to the following during the study intervention period and for at least 120 days after the day of the study intervention dose (covering a full sperm cycle of 90 days starting after 5 half-lives of last dose of study intervention:

  - Refrain from donating sperm

  PLUS, either:

  - Abstain from intercourse with a woman of childbearing potential

  OR

  - Use a male condom:
    - When having sexual intercourse with a woman of childbearing potential, who is **not** currently pregnant, **and** advise her to use a highly effective contraceptive method with a failure rate of < 1% per year, as described in Appendix 3 Contraception, since a condom may break or leak.

- **Female Participants:**
  - Have a negative serum test at Screening and a highly sensitive urine pregnancy test within 24 hours before the first study intervention (DVI) and within 24 hours before the second study intervention (M5717) administration, as required by local regulations. [If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive].
  - Are not pregnant or breastfeeding, and at least one of the following conditions applies:
    - Not a woman of childbearing potential
      - At least 1 year post-menopausal (amenorrhea ≥ 12 months and follicle-stimulating hormone (FSH) ≥ 40 mIU/mL) at Screening;
      - Surgically sterile (bilateral oophorectomy, hysterectomy or bilateral salpingectomy; tubal ligation alone is not sufficient).

    OR

    - If a woman of childbearing potential, use a highly effective contraceptive method (i.e., with a failure rate of < 1% per year), preferably with low user dependency, as described in Appendix 3 for the following time periods:
      - Before the first dose of the study intervention(s), if using hormonal contraception:
        - Has completed at least one 4-week cycle of an oral contraception pill and either had or has begun her menses

OR

- Has used a depot contraceptive or extended-cycle oral contraceptive for at least 28 days and has a documented negative pregnancy test using a highly sensitive assay.

- During the intervention period
- After the study intervention period (i.e., after the last dose of study intervention is administered) for at least 62 days, corresponding to the time needed to eliminate any study intervention(s) (5 times terminal half-live of 155 hours) plus 30 days (a menstrual cycle) after the last dose of study intervention (and agree not to donate eggs (ova, oocytes) for reproduction during this period).

- Additional requirements for pregnancy testing during and after study intervention are in Section 8.2.4.
- The investigator reviews the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy.

Informed Consent

5. Capable of giving signed informed consent, as indicated in Appendix 2 Study Governance, which includes compliance with the requirements (including mandatory intake of rescue medication to participants who have been administered the investigational *P. falciparum* sporozoite challenge) and restrictions listed in the informed consent form (ICF) and this protocol.

Other Inclusions

6. A non-smoker or ex-smoker for more than 90 days prior to Screening, or a smoker of no more than 5 cigarettes per day or nicotine products (spray, patch, e-cigarette, etc.) equivalent of no more than 5 cigarettes per day. Participants must agree to abstain from smoking while in the study.
7. Willing to adhere to the prohibitions and restrictions (see Section 6.5.3) specified in this protocol, including willingness to stay confined to the inpatient unit for the required duration and willingness to avoid extensive travelling during the study period.
8. Different ways of being reachable 24 hours per day, 7 days per week (e.g., by mobile phone, regular phone or electronic mail) during the whole study period.
9. Does not live alone (from start of DVI with malaria sporozoites until at least the end of the antimalarial drug treatment), willing to provide contact details of a person living with him/her who is contactable and available for the duration of the study.

See Appendix 11 for COVID-19 related Inclusion Criteria.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. 12-Lead electrocardiogram (ECG) outside normal range (QTcF > 450 ms, PR interval > 215 ms, or QRS > 120 ms) and deemed clinically relevant by the Investigator.
2. Supine systolic blood pressure > 140 or < 90 mmHg, diastolic blood pressure > 90 or < 50 mmHg, and pulse rate > 90 or < 50 beats per minute (min) at Screening and at Admission on Day -1 (Any abnormal blood pressure or pulse rate results may be repeated once and if the repeat result is within the normal range, it is not considered to have met the exclusion criterion).
3. Seropositive for human immunodeficiency virus (HIV) I and II antibody or antigen), hepatitis B virus (HBV; hepatitis B surface antigen [HBsAg]), or hepatitis C virus (HCV; antibody) tests.
4. Liver function tests (see Appendix 5 Liver Safety: Suggested Actions and Follow-up Assessments) above the upper limit of normal (ULN) (> 3xULN) (as specified in the Laboratory Manual) the day before DVI / study intervention administration (Day -1).
5. History or presence of diagnosed food or known drug allergies (including but not limited to allergy to any of the antimalarial rescue medications to be used in the study), or history of anaphylaxis or other severe allergic reactions.

   Note: Participants with seasonal allergies/hay fever, house dust mite allergy, or allergy to animals that are untreated and asymptomatic at the time of dosing can be enrolled in the study.
6. History of a serious psychiatric condition that may affect participation in the study or preclude compliance with the protocol.
7. Any surgical or medical condition possibly affecting drug absorption (e.g. cholecystectomy, gastrectomy, bowel disease), distribution, metabolism or excretion.
8. Any history of gallbladder disease, including cholecystitis and/or cholelithiasis.
9. Any condition that in the opinion of the investigator would jeopardize the safety or rights of a person participating in the study or would render the person unable to comply with the protocol.
10. Frequent headaches of clinical relevance and/or migraine, recurrent nausea, and/or vomiting (> 2 times per month).
11. Ingestion of any poppy seeds within 24 hours prior to each Drug Abuse Screening.
12. Personal history of malaria or medical history of possible exposure to malaria.
13. Presence of acute infectious disease or fever (i.e., sublingual temperature ≥ 38.0°C) within the 5 days prior to DVI with malaria sporozoites.

Prior/Concomitant Therapy

14. Use of medications known to interact with atovaquone-proguanil (Malarone) or artemether-lumefantrine (Riamet) such as cimetidine, metoclopramide or antacids, or an anticipated requirement for the use of these at any point during the study period (see also Section 5.1).

15. Use of systemic antibiotics with known antimalarial activity within 30 days (or 5 half-lives whichever is longer) of first study intervention administration (e.g. trimethoprim-sulfamethoxazole, doxycycline, tetracycline, clindamycin, erythromycin, fluoroquinolones or azithromycin) or an anticipated requirement for the use of these during the study period.
16. Use of any prescription drugs, herbal supplements (e.g., St John's Wort) or over-the-counter medication within 7 days or five half-lives (whichever is longer) prior to the first study intervention administration, or an anticipated requirement for the use of these during the course of the study.

    Note: If necessary, the incidental use of non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol (2 g/day, 10 g/week), vitamins and topical treatments may be acceptable after approval by the Investigator and will be documented in the eSource system. The use of nutritional supplements during this time that are not believed to have the potential to affect participant safety or the overall results of the study, may be permitted on a case-by-case basis, following approval by the Sponsor in consultation with the Investigator.

Prior/Concurrent Clinical Study Experience

17. Participation in an investigational drug or device study within 3 months prior to first dosing or more than 4 times a year or plans to participate in other investigational drug or vaccine research during the study period.

Diagnostic Assessments

None.

Other Exclusions

18. Personnel (e.g. investigator, sub-investigator, research assistant, pharmacist, study coordinator or anyone mentioned in the delegation log) directly involved in the conduct of the study or students of the departments involved.
19. Intake of grapefruit, Seville oranges, cranberries, star fruit or juices of these fruits, as well as quinine-containing food/beverages (e.g., tonic water, bitter lemon), within 14 days prior to study intervention administration until the end of the ambulatory period.
20. Participant has travelled to or lived in a malaria-endemic area for more than 4 weeks during the 12 months prior to first study intervention administration or spent any time in an endemic area during the 4 weeks prior to first study intervention administration.
21. Plans to travel to a malaria-endemic region during the study period up to last Follow-Up (FU) visit.
22. Previous participation in any malaria vaccine or CHMI study.
23. Participant with a whole blood donation or loss of > 450 mL within 60 days before administration of study drug or unwilling to defer blood donations for 6 months.

See Appendix 11 for temporary exclusion criteria for participants with a risk factor for a COVID-19 infection.

5.3 Lifestyle Considerations

Participants will be required to adhere to the COVID-19 measures and procedures outlined in the CCI site-specific COVID-19 SOP. See Appendix 11.

5.3.1 Meals and Dietary Restrictions

Refrain from consumption of Seville oranges, grapefruit or grapefruit juice, cranberries, star fruit or juices of these fruits, as well as quinine-containing food/beverages (e.g., tonic water, bitter lemon) from 14 days before the start of study intervention until after the end of the ambulatory period. See Section 5.2 (Exclusion Criteria).

Participants will fast from 8 hours prior until 4 hours after study intervention dose. Water will be allowed up to 2 hours predose and again after 2 hours postdose.

5.3.2 Caffeine, Alcohol, Tobacco, and Cannabinoid

Participants must refrain from alcohol use for 1 week prior to study treatment. After release of confinement from the study site, participants will be requested not to consume more than 1drink (2 units) of alcohol per day until the End of Study visit.

Use of tobacco products will not be allowed for the duration of participation in the study until the End of Study visit.

See Section 6.8 (Special Precautions).

5.3.3 Activity

Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities (e.g., watching television or reading).

Participants will refrain from taking up any new unaccustomed exercise from Screening until the End of Study visit. See Section 6.8 (Special Precautions).

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. A potential rescreening will occur at the discretion of the Investigator. Rescreened participants will be assigned a new participant number. Results of any retest must be available prior to DVI. The result of the retest will be considered for participant eligibility at the Investigator's discretion.

6 Study Intervention(s)

Study intervention is any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant per the study protocol.

6.1 Study Intervention(s) Administration

Study Intervention	
Study Intervention Name:	M5717
Dose Formulation:	M5717: Capsules containing 30 or 100 mg of M5717 powder. Placebo: Capsules containing 100 mg of placebo matched to a similar number of capsules with M5717.
Unit Dose Strength(s)/ Dosage Level(s):	First dose 200 mg (2 x 100 mg); other doses to be decided based on SMC recommendation
Route of Administration:	Oral
Dosing Instructions:	The number of capsules will be dependent on the dose to be administered and will be calculated by the pharmacist. For the first cohort, the participants will receive 2 capsules (100 mg each) in total. The appropriate number of M5717 or placebo capsules will be opened, the content will be transferred into 20 mL water (if the dose is between 30-90 mg) or 50 mL water (if the dose is above 90 mg) and the suspension will be swallowed by the participant. The beaker will be rinsed with another 10 or 50 mL of water that is also to be swallowed by the participant. If a low dose is given, participants need to drink an additional 70 mL thereafter in order to have a comparative total volume intake of 100 mL. For further details, refer to Pharmacy Manual.
Other study interventions: PfSPZ Challenge	
1. Malaria inoculum	
Study Intervention Name:	Purified, aseptic, cryopreserved *P. falciparum* sporozoites, strain NF54 (PfSPZ Challenge; Sanaria Inc, Rockville, MD, USA)
Dose Formulation:	Cryopreserved sporozoites 15,000/20µL/vial
Unit Dose Strength(s)/ Dosage Level(s):	3200 sporozoites per injection
Route of Administration:	Intravenous/Bolus
Dosing Instructions:	According to the instructions supplied by Sanaria Inc. For further details see pharmacy manual.
2. Rescue medications	
Each participant will receive rescue treatment as specified in Section 6.5.1: - Atovaquone/proguanil (Malarone) as first line rescue treatment in case of any intolerance. - Artemether/lumefantrine (Riamet) as back-up rescue medication. - Intravenous artesunate will be used in case of suspicion of severe malaria.	

PfSPZ=Plasmodium Falciparum Sporozoites, SMC=Safety Monitoring Committee.

6.2 Study Intervention(s) Preparation, Handling, Storage, and Accountability

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- Upon receipt of the study intervention(s), the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery. Further

guidance and information for study intervention accountability are provided in the Pharmacy Manual.

- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply it. All study intervention(s) must be stored in a secure, environmentally-controlled, and monitored (manual or automated) area, in accordance with the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study intervention(s) accountability records at the study site will include the following:
    - Confirmation of receipt, in good condition and in the defined temperature range.
    - The inventory provided for the clinical study and prepared at the site.
    - The dose(s) each participant used during the study.
    - The disposition (including return, if applicable) of any unused study intervention(s).
    - Dates, quantities, batch numbers, container numbers, expiry dates, and the participant numbers.
- The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) must not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be re-dispensed to a different participant.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.

Further guidance and information for the final disposition of unused study intervention(s) are provided in the Pharmacy and Monitoring Manuals.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

After confirmation of participant's eligibility and at the last practical moment prior to study intervention administration, participants will be centrally allocated to either M5717 or placebo in a 3:1 ratio using an Interactive Web Response System (IWRS), which forms part of the built-in functionality of the clinical data management system, and per a computer-generated randomization list.

The IWRS will be used to assign unique participant numbers, allocate participants to study intervention group at the randomization visit, and study intervention to participants at each study intervention visit.

Before the study is initiated, the log in information and directions for the IWRS will be provided to the site. The site will randomize any eligible participant in the database on Study Day -1 or Study Day 1, prior to DVI PfSPZ and to starting study intervention administration for each participant.

Participants will be assigned at a randomization ratio of 3:1 to M5717:placebo treatment. Cohorts will be expanded in multitudes of 4, i.e. a cohort will start off with 4 participants (assigned 3:1) and may then be expanded to include either 8 or 12 participants (with the randomization ratio kept fixed at 3:1). The randomization code will be generated using SAS 9.4 for Windows or newer (SAS Institute Inc., Cary, NC, USA) by a study-independent statistician.

Code-break envelopes will be provided to the site in case an emergency unblinding of an individual participant's study intervention is required.

Participants who are withdrawn from the study by the Investigator due to AEs after the start of administration of the study intervention will not be replaced. Participants who withdraw for any other reason may be replaced after discussion with the Sponsor. Replacement participants, if utilized, will receive the same treatment as the participants they are replacing, using randomization replacement numbers.

6.3.2 Blinding

Blinding Method

The study will be double-blind. Blinding will be maintained throughout the duration of the study for the participants and for the investigator, i.e., until final database lock. After initiating the rescue medication of all participants in each cohort, the SMC will perform a blinded data review. The SMC will remain blinded throughout the study. Only the unblinded PK/PD scientist and Pharmacometrician of the Sponsor and the responsible analyst from the Contract Research Organization (CRO) performing the PK/PD evaluation will analyze the unblinded PK/PD data, and will provide the PK/PD results in a blinded manner only to the SMC in order to decide on the dose and number of participants, as well as the timing of the study intervention in relation to the DVI challenge for the next. Only when the study is completed, database locked, data file verified, and protocol deviations determined, will the drug codes be broken and made available for final data analysis.

Details including but not limited to SMC membership, meeting frequencies, and responsibilities will be provided in the SMC charter.

Assignment Method Retention

The randomization list is to be kept strictly confidential, accessible only to authorized persons (e.g., randomization statistician, pharmacists, and the bioanalytical laboratories that prepare and analyze relevant samples), until the time of unblinding. The study blind may be broken for an individual participant only if knowledge of the study intervention is essential for clinical management of the participant. The Investigator or designee will unblind the participant using the individual code-break envelope provided by the randomization statistician. The Investigator must promptly explain the reason for any unblinding of an study intervention to the Sponsor without revealing the result to any Sponsor employee except the designated Drug Safety representative (using the Emergency Unblinding Notification Form, see Section 6.3.3).

Unblinding Clinical Studies for Sample Analysis of Special Data

For the purposes of the SMC, safety data listings will use the participant identification numbers as entered in the electronic Case Report Form (eCRF). The unblinded PK/PD scientist and Pharmacometrician of the Sponsor and the responsible analyst from the CRO performing the PK/PD evaluation will analyze the unblinded PK/PD data and will provide the PK/PD results in a blinded manner to the SMC for decision making. A process for SMC data review will be established to describe the process of data flow for SMC meetings and the requirements for SMC presentation.

The bioanalytical laboratory for measurement of M5717 concentrations will be unblinded since obtaining the concentration data reveals the study intervention arm for the participant. This is acceptable, as this function is not involved in the SMC decision making process. M5717 concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

6.3.3 Emergency Unblinding

In an emergency, the Investigator is solely responsible for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in this decision. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to the unblinding, unless this could delay emergency treatment. The Sponsor must be notified within 24 hours after unblinding. The Investigator must provide the Sponsor the reason for unblinding without revealing the study intervention, except to the designated drug safety representative via the Emergency Unblinding Notification Form. The date of and reason for unblinding must be recorded in the source documents and eCRF. Contact information for unblinding in an emergency is given on the participant emergency card provided to each participant, as noted in Appendix 2 Study Governance.

The Sponsor's drug safety department will submit any Suspected Unexpected Serious Adverse Reactions (SUSAR) reports to regulatory authorities and ethics committees with unblinded information, per applicable regulations. Only blinded information will be provided to the study team.

6.4 Study Intervention Compliance

The study intervention will be administered by the study site personnel within the confines of the study site. A mouth and hand check will be performed after study intervention dose administration to ensure that it has been swallowed.

Diary cards will be provided to participants for collection of data related to their daily physical activity, daily alcohol consumption and their oral (sublingual) temperature. Participants will bring their completed diary cards to the study site for all Ambulant and the End of Study visits.

6.5 Concomitant Therapy

Record in the eCRF all concomitant therapies (e.g., medicines or nondrug interventions) used from the time the participant signs the informed consent until completion of the study, including any changes. Changes in concomitant procedures and concomitant medication or other interventions

need to be recorded. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information.

Contact the Medical Monitor for any questions on concomitant or prior therapy.

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

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the End of Study visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

Ibuprofen, at doses of ≤ 1 g/24 hours, is permitted for use at any time during the study; other concomitant medication may be considered on a case-by-case basis by the Investigator. If necessary, the incidental use of NSAIDs, paracetamol (2 g/day, 10 g/week), vitamins and topical treatments may be acceptable after approval by the study Sponsor and will be documented in the eSource system.

6.5.1 Rescue Medicine

Rescue medication(s) will be administered mandatorily to participants who have been administered the *P. falciparum* sporozoite challenge to ensure participants' safety and complete cure from the investigational malaria challenge. Rescue medication will be given either (i) after confirmation that the first qPCR outcome is equal or greater than 100 asexual parasites per mL of blood and provided that the subsequent qPCR shows higher parasitemia than the first positive qPCR, or (ii) on study intervention administration Day 28 after study intervention administration if qPCR outcome remains below this threshold. An additional blood sample will be drawn for the analysis of emerging genetic mutations for resistance in the parasites. In any case, safety assessments must be performed prior to starting rescue medication, as indicated in the SoA (Table 1 through

Table **4**). With the start of rescue medication, daily qPCR is to be performed until the qPCR is negative and remains negative for 48 hours.

See Appendix 11 for the COVID-19 contingency plan if any participant presents with COVID-19 related symptoms and/or has a positive SARS-CoV-2 PCR test.

The study site will supply all rescue medication. The investigator or a qualified designee will ensure that the received drugs are of the specified formulation. The site pharmacist or a qualified designee is responsible for maintaining an accurate inventory and accountability record of drug supplies for this study. Participants will be prescribed an approved regimen for curative therapy for malaria, to assure final parasite clearance, at recrudescence or at the end of the study on study intervention administration Day 28. All participants will receive the following rescue medication as first choice, atovaquone-proguanil (Malarone):

1. Malarone (250 mg atovaquone/100 mg proguanil hydrochloride) oral tablets, film coated. Atovaquone-proguanil has two uses: (i) to prevent malaria, and (ii) to treat malaria.
2. Riamet (20 mg artemether/120 mg lumefantrine) oral tablets. Artemether-lumefantrine is used for the treatment of acute uncomplicated malaria infections caused by *P. falciparum*.

Rescue treatment will be administered according to standard protocols for treatment of CHMI malaria at the clinical site. In case of a known allergy or intolerance to artemether and/or lumefantrine or any of the ingredients of Riamet, another artemisinin-derivative combination therapy will be administered in accordance with the WHO Guidelines for the Treatment of Malaria.

Treatments mentioned are in accordance with Stichting Werkgroep Antibiotica Beleid guidelines for non-severe *P. falciparum* malaria.

In case of suspicion of severe malaria: intravenous/intramuscular artesunate for at least 24 hours. Once a patient has received at least 24 hours of parenteral therapy and can tolerate oral therapy, complete treatment with 3 days of artemisinin-based combined therapy (ACT).

6.5.2 Permitted Medicines

The only permitted medications are the following:

1. Ibuprofen is the preferred symptomatic treatment for pain relieve or fever, if needed during the study.
2. Paracetamol, which may facilitate liver enzyme elevations in the context of PfSPZ DVI in nonimmune participants, should be avoided. Doses of paracetamol up to ≤ 2 g/24 hours, at the discretion of the Investigator, may be allowed but only if ibuprofen is contraindicated or considered insufficient to treat the symptoms.
3. 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 participant welfare and will not interfere with the study intervention may be given at the Investigator's discretion.

Any medicines that are considered necessary to protect the participant's welfare in emergencies may be given at the Investigator's discretion, regardless if it results in a protocol deviation.

6.5.3 Prohibited Medicines

The participants are prohibited from using prescription medications within 2 weeks or 5 half-lives, whichever is longer, prior to the first study intervention administration, during the study, and until after the End of Study visit (this includes vitamins, and minerals). Participants 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 2 weeks prior to the first study intervention administration until the end of study, and enzyme inhibitors during the study. Use of any investigational agent is not permitted within 8 weeks before dosing. After consultation with the Sponsor, study participants will be discontinued if they use any prohibited medicine.

6.5.4 Other Interventions

Additional restrictions that study participants should adhere to until the End of Study/Early Termination Assessment visit are detailed in Section 5.2.

6.6 Dose Selection and Modification

See Section 4.3.2 (Selection of Further Doses). No dose changes for single participants are permitted.

6.7 Study Intervention after the End of the Study

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

6.8 Special Precautions

The study will be performed in a university hospital and in a Phase I unit (study site) with direct access to a Hospital Emergency Unit. Equipment and other agents (epinephrine, prednisolone equivalents, etc.) will be available at the study site in case of severe allergic reactions. The participants will remain at the study site at the early phase Clinical Research Unit (CRU) of the CCI from Day -1 to Day 2 *('early liver stage')* and from Day 3 to Day 5 *('late liver stage')*. The participants' health and wellbeing will be continuously monitored during this time. Participants will receive DVI at the Leiden University Medical Centre (LUMC) and will afterwards be transferred back to the CCI.

Study participants should adhere to the following restrictions:

- Male participants must agree to use and have their female partners (if women of childbearing potential) use highly effective medically acceptable methods of contraception (according to ICH Guidance M3[R2] – Nonclinical safety studies for the conduct of human clinical studies and marketing authorization for pharmaceuticals) during the period of participation in the study and for at least 120 days after the study intervention administration (Inclusion 4)
- Be stable nonsmokers for the duration of participation in the study until the End of Study visit

- Refrain from alcohol use for 1 week prior to study treatment. After release of confinement from the study site, participants will be requested not to consume more than 1 drink (2 units) of alcohol per day until the End of Study visit
- Refrain from taking up any new unaccustomed exercise from Screening until the End of Study visit.

Compliance checks will be performed and documented at each visit following discharge from the study site. Additional checks for drug and/or alcohol abuse can be done at the discretion of the investigator.

6.9 Management of Adverse Events of Interest

No adverse events of special interest are defined for this study.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

As only a single dose of M5717 will be given, study intervention cannot be discontinued, but participants can be withdrawn from the study (see Section 7.2).

In any case, rescue medication(s) (see Section 6.5.1) will be administered mandatorily to participants who have been administered the investigational *P. falciparum* sporozoite challenge, independent of whether the scheduled M5717 administration took place or not, to ensure participants' safety and proof of complete cure (i.e. absence of parasitemia) from the investigational malaria challenge.

The SoA (Section 1.3) specifies the data to collect at study intervention discontinuation and follow-up, and any additional evaluations that need to be completed.

7.1.1 Temporary Discontinuation

Not applicable.

7.1.2 Rechallenge

Not applicable.

7.2 Participant Discontinuation/Withdrawal from the Study

A participant must be withdrawn if any of the following occur during the study:

- A participant may withdraw from the study at any time, at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- The participant may be withdrawn by the Investigator due to participation in another clinical study.
- Use of a nonpermitted concomitant medication. However, any medications that are considered necessary for the participant's wellbeing may be given at the discretion of the Investigator.
- Protocol noncompliance judged as significant by the Investigator, including noncompliance to the required study considerations (e.g., caffeine intake/food/diet requirements/alcohol and/or drug abuse).
- Participant lost to follow-up.
- Any events that unacceptably endanger the safety of the participant (e.g., occurrence of a SAE).
- At the time of discontinuing from the study, if possible, a discontinuation visit will be conducted, as listed in the SoA. The SoA specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed.

- Withdrawal from the study for any reasons after having received the PfSPZ challenge must be followed mandatorily by rescue medication and proof of absence of parasitemia.
- If the participant withdraws consent for future involvement in the study, any data collected up to that point may still be used, but no future data can be generated, and any biological samples collected will be destroyed.
- A participant has the right at any time to request destruction of any biological samples taken. The investigator must document this in the site study records.

Please see Appendix 11 for participant withdrawal/discontinuation procedures for participants who test positive for a SARS-CoV-2 infection.

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

If a participant has failed to attend scheduled study 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 participant will remain under the supervision of the Investigator until satisfactory health has returned or care has been transferred to the participant's general practitioner or to a hospital consultant. In case a participant has to be withdrawn from the study, the Study Monitor and Clinical Study Leader at the Local and Funding Sponsors will be informed immediately.

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wants to or should continue in the study.
- Before a participant is deemed "lost to follow-up", the Investigator or designee must make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant's last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant's general practitioner for information. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the SoA (see Section 1.3).

- **No** protocol waivers or exemptions are allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a Screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for Screening failure.
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 2 Study Governance).
- Procedures conducted as part of the participant's routine medical care (e.g., blood count) and obtained before signing of the ICF may be used for Screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy Assessments and Procedures

The primary efficacy assessment will be of the chemoprophylactic effect of M5717, defined as number of participants with absence of parasitemia by qPCR from PfSPZ Challenge up to Day 28.

The time from DVI PfSPZ Challenge to the first positive qPCR outcome, defined as equal or greater than 100 asexual parasites per mL of blood (time frame: number of days from PfSPZ DVI challenge to positive parasitemia, or 28 days) is also going to be measured.

The malaria clinical score is defined in Appendix 6 Malaria Clinical Score for Treatment Initiation and needs to be assessed in case any malaria-related symptoms emerge.

Efficacy examinations will be scheduled according to the applicable SoA (Table 1 through

Table **4**).

8.2 Safety Assessments and Procedures

The safety profile of the study intervention will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings, vital signs, electrocardiograms, and laboratory tests.

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.1.

8.2.1 Physical Examinations

A complete physical examination, including examination of all body systems, will be performed at Screening and the End of Study visit (Day 33 + 3 days). At other time points an abbreviated physical examination can be performed. Additional physical examinations may be performed as deemed necessary, per the Investigator's discretion.

A complete physical examination will include, at a minimum, assessments of all body systems (including general appearance, skin, head, neck [including thyroid], eyes, ears, nose, throat, cardiovascular and pulmonary system, abdomen, neurological, peripheral vascular, and musculoskeletal system).

A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

Measurement of Vital Signs will be done at the time points as indicated in the SoA, Table 1 through

Table **4**. On Day 1 Vital signs assessment will be done prior to administration of malaria inoculum as well as 1-hour post-DVI.

- Height and weight will be measured and recorded at Screening, and weight at the End of Study visit.
- Tympanic temperature, pulse rate, respiratory rate, and blood pressure will be assessed. Oral temperature may be used if in the opinion of the investigator the reading is more reliable than the tympanic measurement. For SARS-CoV-2 symptoms screening, see Appendix 11.
- Blood pressure and pulse measurements will be assessed with the participant in the supine position, with a completely automated device. Manual techniques will be used only if an automated device is not available. Blood pressure will be assessed once again after 5 minutes with the participant in the supine position.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the eCRF.

8.2.3 Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT intervals. The ECG done during Screening will be used to determine eligibility and during study conduct as part of the safety assessments. At visits where multiple assessments and procedures are to be done at the same time point the ECG should be done after vital sign assessment and before blood sampling.

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.

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

8.2.4 Clinical Safety Laboratory Assessments

Blood (fasting state mandatory during Screening, Day 1 Predose and Study Intervention Administration Day 2 visits for Cohorts 1 to 4, and mandatory during Screening, Day 1 Predose and Study Intervention Administration Day 5 visits for Cohort 5; fasting will be optional from Days 6 to 33) and urine samples will be collected for the clinical laboratory tests listed in Appendix 7 Clinical Laboratory tests at the time points listed in the SoA. All samples should be clearly identified.

Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations. Cholesterol, Triglycerides, HDL cholesterol and glucose tested during Screening must be collected in a fasted state. The participant must be fasted for at least 8 hours prior to sample collection.

Additional serum or highly sensitive urine pregnancy tests may be conducted, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the study.

The tests will be performed by a local laboratory. Details on process for collection and shipment of these samples are in the Laboratory Manual.

The Sponsor must receive a list of the local laboratory normal ranges before shipment of study intervention(s). Any changes to the ranges during the study must be forwarded to the Sponsor.

The Investigator must review each laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

8.2.5 Suicidal Risk Monitoring

Not applicable.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE and a SAE are in Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

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

Any SAE assessed as related to study intervention must be recorded and reported, as indicated in Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting, whenever it occurs, irrespective of the time elapsed since the last administration of study intervention.

The method of recording, evaluating, and assessing causality of AEs (including SAEs) and the procedures for completing and transmitting SAE reports are in Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit, the participant will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the participant's condition will be recorded as AEs, regardless if reported by the participant 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. All SAEs must be additionally documented and reported using the appropriate Report Form as specified in Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

AEs are recorded and assessed continuously throughout the study, as specified in Section 8.3.1 and are assessed for their outcome at the End of Study Visit. All SAEs ongoing at the End of Study Visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the participant 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. Further information on follow-up procedures is given in Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

The Sponsor will send appropriate safety notifications to Health Authorities 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 study participants to the IEC/IRB that approved the study.

In accordance with ICH GCP, the Sponsor/designee will inform the Investigator of findings that could adversely affect the safety of participants, impact the conduct of the study or alter the IEC's/IRB's approval/favorable opinion to continue the study. In line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations regarding Safety Report notifications to Investigators will be considered.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB 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 IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For studies covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

8.3.5 Pregnancy

Only pregnancies the Investigator considers to be related to the study intervention (e.g., resulting from a drug interaction with a contraceptive method) are AEs. However, all pregnancies with an estimated conception date during the period defined in Section 8.3.1 must be recorded in the AE page/section of the eCRF for both pregnancies in female participants and pregnancies in female partners of male participants. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted by the same process specified for SAE reporting in Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting, section on Reporting Serious Adverse Events.

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

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the participant sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event. Any abnormal outcome (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported in an expedited manner, as specified in Section 8.3.1, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a participant occurring during the study, the participant must be discontinued from study intervention. The Sponsor/designee must be notified without delay and the participant must be followed as indicated above.

8.4 Treatment of Overdose

For this study, any dose greater than the highest daily dose included in a clinical study protocol or planned for an individual participant enrolled in the study is considered an overdose.

Even if it is not associated with an AE or a SAE, any overdose is recorded in the eCRF and reported to drug safety in an expedited manner. Overdoses are reported on a SAE Report Form, following the procedure in Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting, section on Reporting of Serious Adverse Events.

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.

See package inserts of the rescue medication in Appendix 8 for details regarding the effects and management of an overdose.

8.5 Pharmacokinetics

8.5.1 Pharmacokinetic Samples

Blood samples for measurement of M5717 concentrations in whole blood will be collected at the time points indicated in the SoA (Table 1 through Table 4). Metabolite concentrations, as

applicable, may also be measured in blood samples. Remaining samples collected for measurement of M5717 may also be used for testing of bioanalytical standards.

Actual date and time of the PK sampling, as well as date/time of drug administration, will be recorded in the eCRF. Samples and assessments obtained outside the allowed time window (see Table 5) from dosing will be captured as a minor protocol deviation, if the exact time of the assessment/sample collection is noted on the source document and data collection tool (e.g., eCRF).

Volume of blood taken per treatment timepoint and the 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 participants randomized to placebo treatment, no PK samples will be analyzed unless deemed necessary by the Investigator and/or Sponsor. Details on blood sample collection, preparation for processing, and shipment will be specified in a separate Laboratory Manual.

8.5.2 Pharmacokinetic Calculations

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

- The following PK parameters will be calculated, when appropriate:

Table 7 Definition of Individual PK Parameters

Symbol	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 (i.e., 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. $AUC_{0-\infty}=AUC_{0-t}+C_{last\ pred}/\ \lambda z$
AUC_{0-24}	The AUC from time zero (= dosing time) to 24 hours post dose. Calculated using the mixed log linear trapezoidal rule (linear up, log down) using the nominal dosing interval. The actual dosing interval calculated from CRF time data should not be used.
AUC_{0-168}	The AUC from time zero (= dosing time) to 168 hours post dose. Calculated using the mixed log linear trapezoidal rule (linear up, log down) using the nominal dosing interval. The actual dosing interval calculated from CRF time data should not be used.
C_{max}	Maximum blood concentration observed
C_{24}	Blood concentration at 24 hours
C_{168}	Blood concentration at 168 hours
t_{max}	Time to reach the maximum blood concentration (1st occurrence in case of multiple/identical C_{max} values)
$t_{1/2}$	Apparent terminal half-life, calculated as ln2/λz
λz	Terminal first order (elimination) rate constant. Determined from the terminal slope of the log-transformed concentration curve using linear regression on terminal data points of the curve
CL/f	Total body clearance of drug from blood following oral administration, calculated as Dose/$AUC_{0-\infty}$. The predicted $AUC_{0-\infty}$ should be used.
Vz/f	Apparent volume of distribution during the terminal phase following extravascular administration. The predicted $AUC_{0-\infty}$ should be used.
$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0-\infty}$.
AUC_{0-t}/ Dose	The Dose normalized AUC from time zero to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Normalized using the actual dose, using the formula AUC_{0-t} /Dose.
$AUC_{0-\infty}$/Dose	The Dose normalized AUC from time zero extrapolated to infinity. Normalized using actual dose and $AUC_{0-\infty}$, using the formula $AUC_{0-\infty}$ /Dose.
C_{max}/Dose	Dose-normalized C_{max}

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

Additional PK parameters might be added based on emerging data and detailed in the Integrated Analysis Plan.

- For measurement of whole blood concentrations of M5717, as specified in the SoA. The actual date and time (24-hour clock time) of each sample will be recorded to calculate actual time elapsed since the prior dose administration.
- The quantification of M5717 in whole blood will be performed using a validated assay method. Concentrations will be used to evaluate the PK of M5717.
- Remaining samples collected for analyses of M5717 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

- Details on processes for collection and shipment of these samples are provided in the Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

8.6 Pharmacodynamics

Blood samples will be collected for measurement of malaria clinical scores (parasitemia) every time a participant returns as an outpatient for a polymerase chain reaction (qPCR) test; see Table 1 through Table 4. qPCR is performed at the LUMC according to standard procedures described in Adegnika 2006 and Hermsen 2001. qPCR is performed on the multicopy 18S ribosomal RNA gene on an automated system with PhHV spiking as a control for extraction efficacy.

Details on processes for collection and shipment of these samples are in the Laboratory Manual. The Sponsor will store the samples in a secure storage space with adequate measures to protect confidentiality. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

The malaria clinical score will also be evaluated at any timepoint when malaria-related symptoms occur. Participants with first positive qPCR outcome equal or greater than 100 asexual parasites per mL of blood within 28 days of PfSPZ Challenge will be considered positive. For the analysis purposes participants will only be considered negative if they remain negative by qPCR throughout the study period (see Section 9.4.3 for details on the statistical analyses).

CCI

[redacted]

8.9 Health Economics

Not applicable.

8.10 Immunogenicity Assessments

Not applicable.

9 Statistical Considerations

Details of the statistical analyses will be defined in the Integrated Analysis Plan.

9.1 Statistical Hypotheses

No formal statistical hypothesis will be tested, as the study is designed to be exploratory.

CCI

[redacted]

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9.3 Populations for Analyses

The analysis populations are specified in Table 9 below. The final decision to exclude participants from any analysis population will be made during a blinded data review meeting prior to database lock and unblinding.

Table 9 Analysis Populations

Analysis Set	Description
Screening (SCR)	All participants who provided informed consent, regardless of the participant's randomization and study intervention status in the study.
Intention-to-Treat (ITT)	All participants, who were randomized to study intervention. Analyses performed on the ITT population will consider participants' allocation to study intervention groups as randomized.
Safety (SAF)	All ITT participants, who have been inoculated using a DVI of PfSPZ and who were administered one dose of study intervention (M5717 or placebo). All Safety analyses will be based on this analysis set. Analyses will consider participants as treated.
Per-Protocol (PP)	All SAF participants who comply with the protocol and meet no criteria that could impact the proper evaluation of key objectives of the study (as will be defined in the Integrated Analysis Plan and approved at the Data Review Meeting). Participants who meet one of the following criteria will be excluded from the PP: • Incorrect study intervention group allocation, different to assignment at randomization. All Efficacy analyses will be based on this analysis set.
Pharmacokinetic (PK)	All participants, who receive one dose of M5717, have no clinically important protocol deviations or important events affecting PK, and provide at least one measurable post-dose concentration. Participants will be analyzed per the actual study intervention they received. All PK analyses will be based on the PK analysis set.

DVI=direct intravenous inoculation, ITT=intention-to-treat, PfSPZ=Plasmodium Falciparum Sporozoites, PK=pharmacokinetic, PP=per-protocol, SCR=screening, SAF=safety.

9.4 Statistical Analyses

The following descriptive statistics will be used as applicable to summarize study data by actual dose or study intervention, unless otherwise specified:

- Continuous variables: number of non-missing observations, mean, standard deviation, median, first and third quartiles, minimum, and maximum
- Categorical variables: frequencies and percentages.

No formal statistical hypothesis testing will be performed. Missing data will not be imputed. A participant who withdraws prior to the last planned observation in a study period will be included in the analyses up to the time of discontinuation.

All participants will be included in individual participant data listings. All derived data will also be listed.

The Baseline measurement is defined as the pre-dose value reported on Day 1 or the Screening value as relevant in accordance with the SoA.

Data will be presented by dose cohort and data of participants who received placebo may be pooled across dosing cohorts.

Further details on all statistical analyses will be presented in the Integrated Analysis Plan that will be finalized before database lock.

Changes in the conduct of the study or planned analyses will be reported in the corresponding section of the Integrated Analysis Plan, if applicable, and in the clinical study report.

A separate statistical analysis plan for SMC purposes will be established to document technical and detailed specifications for the analyses to be provided to the SMC members as defined in the SMC charter and will be finalized before the first SMC meeting.

9.4.1 Efficacy Analyses

All efficacy analyses will be performed on the Per-Protocol Analysis population. Efficacy endpoints will be compared between participants who received M5717 and placebo within the same cohorts and overall (pooling all participants receiving placebo across cohorts). Protection rate, defined as 1 minus the proportion of participants with positive parasitemia qPCR outcome equal or greater than 100 asexual parasites per mL of blood within 28 days of PfSPZ Challenge will be summarized. Clopper-Pearson confidence interval (CI) (nominal 95%) for the protection rate will be provided.

Kaplan-Meier curves and median estimates (with 95% CI) of the time from DVI PfSPZ to positive parasitemia will be generated. Efficacy endpoints are the presence or absence of clinical signs and symptoms of malaria until Day 28 (Table 10).

Table 10 Statistical Analysis Methods Used for Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	
• Number of participants over time with positive parasitemia defined as first positive qPCR outcome equal or greater than 100 asexual parasites per mL of blood within 28 days of PfSPZ challenge • Time to parasitemia, defined as time from PfSPZ DVI to the first qPCR outcome equal or greater than 100 asexual parasites per mL of blood (time frame: number of days from PfSPZ DVI challenge to positive parasitemia, or 28 days) • Number of participants with documented blood stage parasite growth, defined as an increase of qPCR measured asexual parasites per mL compared to the first parasitemia measurement, within 28 days of PfSPZ DVI • To explore the dose/exposure-response relationship of M5717 and liver stage or blood stage breakthrough	• Descriptive statistics of the protection rate. Clopper-Pearson confidence interval will be provided. • Kaplan-Meier curves and median estimates (with nominal 95% CI) of the time from DVI PfSPZ to positive parasitemia will be generated.
• Clinical signs and symptoms of malaria	• The malaria clinical score for treatment initiation will be listed and summarized by cohort and treatment group.

CI=confidence interval, DVI=direct intravenous inoculation, qPCR=quantitative polymerase chain reaction, PfSPZ=Plasmodium Falciparum Sporozoites.

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis population (Table 11).

Table 11 Statistical Analysis Methods Used for Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	No primary Safety endpoints
Secondary	
Nature, occurrence, and severity of treatment-emergent adverse events (TEAEs)	The number and percentage of participants experiencing at least 1 TEAE will be summarized by treatment and the number of events. Tables by relationship to study drug and by severity will be generated. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology.
Change from Baseline in safety laboratory parameters	All laboratory data will be reported with SI units. Laboratory parameters will be summarized using descriptive statistics for absolute values and change from baseline over time, by postdose shifts relative to baseline, and data listings of abnormalities.
Absolute values and change from Baseline in vital signs	Vital signs data will be summarized by changes-from-baseline values by treatment using descriptive statistics.
Absolute and change from Baseline in 12-lead safety ECGs	ECG data will be summarized by changes-from-baseline values by treatment using descriptive statistics. Clinical noteworthy ECG findings for individual participants will be listed and summarized as appropriate.

AE=adverse event(s), ECG=electrocardiogram, MedDRA=Medical Dictionary for Regulatory Activities, TEAE=treatment-emergent adverse event(s).

9.4.3 Other Analyses

PK analyses will be specified in the Integrated Analysis Plan.

M5717 concentrations in blood, along with the prespecified PK and PD parameters, will be presented in tables and descriptively summarized by dose level and/or nominal time point, as appropriate, using count (n), arithmetic mean, standard deviation, median, minimum, maximum, and coefficient of variation. Values below the lower level of quantification will be taken as zero for descriptive statistics of PK concentrations. Descriptive statistics of PK parameters will additionally show the geometric mean, geometric coefficient of variation, and the 95% confidence interval for the geometric mean. Graphical displays will be provided, where appropriate.

Estimation of Individual PK Parameter

Pharmacokinetic parameters will be calculated by the CRO and overseen by the Clinical PK/PD Group of Quantitative Pharmacology, Merck Healthcare KGaA, Darmstadt, Germany, using standard non-compartmental methods and the actual administered dose. PK parameters will be calculated using the actual elapsed time since dosing, given with a precision of 14 significant digits or the SAS format Best12. When the actual sampling time is missing, calculations will be performed using the scheduled time. Otherwise, there will be no further imputation of missing data.

- Non-compartmental computation of PK parameters will be performed using the computer program Phoenix® WinNonlin® version 6.4, or higher (Certara, L.P., 1699 S Hanley Road, St Louis, MO 63144, USA).
- The statistical software to be used is SAS® (Statistical Analysis System, SAS-Institute, Cary, NC, USA, windows version 9.1 or higher).

CCI

PK, PD, CCI [redacted] will be specified in the Integrated Analysis Plan, which will be finalized before database lock.

PK/PD modeling

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

$$logit(P) = log\left(\frac{P}{1-P}\right) = \beta_0 + \beta_1 \cdot PK\ exposure + \beta_2 \cdot X_2 + \beta_3 \cdot X_3 + \cdots + \beta_n \cdot X_n$$

Here, P is the probability of response, β0 is the intercept, β1…βn are the regression coefficients for the n covariates (Xn), PK exposure refers to different exposure metrics that will be assessed. The exposure metrics may also be parametrized as emax model, if allowed by the data. The response here is binary, i.e., 0 (not-cured) or 1 (cured). Participants with first positive qPCR outcome equal or greater than 100 asexual parasites per mL of blood within 28 days of PfSPZ challenge are referred to as not-cured and cured if they remain negative by qPCR throughout the study period. The modeling details will be specified in a separate Integrated Analysis Plan. Integrated analyses across studies, such as the population PK analysis and PD analyses, will be presented separately from the main clinical study report (CSR).

9.4.4 Sequence of Analyses

The SMC will be established before enrollment of the first participant, will review the data after each cohort is completed, and decide on the dose, dose regimen, and number of participants for the next cohort as per protocol. Details will be provided in the SMC charter.

All final, planned analyses identified in the Clinical Study Protocol will be performed only after the last participant has completed the last visit, i.e. FU/End of Study visit, with all study data in-house, all data queries resolved, and the database locked.

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11 Appendices

Appendix 1 Abbreviations

ACT	Artemisinin-based Combined Therapy
ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under Blood Concentration-Time Curve
BP	Blood Pressure
Cav	Average Concentration
CCMO	Central Committee on Research Involving Human Subjects (Dutch Competent Authority)
CCI	[redacted]
CHMI	Controlled Human Malaria Infection
CI	Confidence Interval
COVID-19	Coronavirus disease 2019, the disease caused by the SARS-CoV-2 virus
CRF	Case Report Form
CRO	Contract Research Organization
CRU	Clinical Research Unit
CSR	Clinical Study Report
CTFG	Clinical Trial Facilitation Group
DNA	Deoxyribonucleic Acid
DVI	Direct Intravenous Inoculation
ECG	Electrocardiogram
EFD	Embryo Fetal Development
eCRF	Electronic Case Report Form
FIH	First-in-Human
FU	Follow-Up
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High-density Lipoprotein
HIV	Human Immunodeficiency Virus

HRT	Hormonal Replacement Therapy
IB	Investigator's Brochure
IBSM	Induced Human Blood Stage Model
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention-to-Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-releasing System
IV	Intravenous
IWRS	Interactive Web Response System
LAM	Lactational Amenorrhoea Method
LLOQ	Lower Limit of Quantification
LUMC	Leiden University Medical Centre
MedDRA	Medical Dictionary for Regulatory Activities
NCE	New Chemical Entity
NOAEL	No-Observed-Adverse-Effect Level
NSAIDs	Non-steroidal Anti-inflammatory Drugs
PCR	Polymerase chain reaction, a test used to detect the presence of RNA or DNA
PD	Pharmacodynamics
PeEF2	Plasmodium eukaryotic translation Elongation Factor 2
PfSPZ	Plasmodium Falciparum Sporozoites
PK	Pharmacokinetics
PP	Per-Protocol
PR	Pulse Rate
Pre	Predose
qPCR	Quantitative Polymerase Chain Reaction
RIVM	Rijksinstituut voor Volksgezondheid en Milieu (Dutch National Institute for Public Health and the Environment)
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAF	Safety
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2, the virus causing COVID-19

SCR	Screening
SD	Study Dose
SMC	Safety Monitoring Committee
SoA	Schedule of Activities
SoC	Standard of Care
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
PPD	
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential
WONCBP	Women of Non-Childbearing Potential

Appendix 2 Study Governance

Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions on the study.
- Participants must be informed that their participation is voluntary.
- Participants or their legally-authorized representative will be required to sign a statement of informed consent that meets the requirements of local regulations; ICH guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- If the ICF is updated during their participation in the study, participants must be re-consented to the most current, approved version.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- The original signed and dated consent will remain at the Investigator's site and must be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within the Screening period of 28 days from the previous ICF signature date. If rescreening falls outside this time period, a new ICF has to be signed. In these cases, the new study number would be noted together with the previous number.

Data Protection

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. All participant records or datasets transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor must inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate

IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

Study Administrative

The study will be conducted in one center:

- Leiden University Medical Centre, The Netherlands, with study participants being recruited, screened and hospitalized at the Clinical Research Unit CCI [redacted]

The Principal Investigator listed on the title page, PPD , Leiden University Medical Centre, represents all Investigators for decisions and discussions on this study, per ICH GCP. The Principal Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the clinical study report.

The study will appear in the following clinical studies registry: EudraCT 2019-003414-14.

This clinical study will be sponsored by:

Merck Healthcare KgaA, Darmstadt, Germany, an affiliate of Merck KgaA, Darmstadt, Germany
Frankfurter Str. 250
Darmstadt, Germany.

The Sponsor will enlist the support of the following CRO for full services:

PPD

PPD will enlist the support of the following CRO for in-country Clinical Project Management, Regulatory Services, Clinical Monitoring and Site Management:

PPD

The sponsor will enlist the following laboratory for PK analyses:

PPD

Details of structures and associated procedures will be defined in separate manuals: Safety Management Plan, Integrated Analysis Plan, Laboratory Manual, Pharmacy Manual, CRF Completion Guidelines and Monitoring Plan.

The study interventions administered in this study will be supplied and distributed by the Sponsor or designee.

A Safety Monitoring Committee (SMC) will be established before enrolment of the first participant, will review the data after each cohort is completed, and decide on the dose, dose regimen, and number of participants for the next cohort as per protocol. The SMC will include the Chairperson (Global Patient Safety Product Responsible), core sponsor members (Medical Responsible, Clinical Pharmacology Representative, and Biostatistician). The following external members will be included: Principal Investigator (and Sub-Investigator(s)), CRO representative, and an independent external expert (if applicable). Only Merck members and the investigators will be voting members, and, as applicable, the independent external expert. Further persons may be represented on the team if their input is required. Details regarding SMC roles, responsibilities, activities, procedures to reduce potential bias, and possible SMC recommendations will be provided in a separate SMC charter.

All details about the country specific reporting requirements for Individual Case Safety Reports (ICSRs) and periodic safety reports to Health Authorities will be described in the Safety Management Plan.

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
    - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The Investigator must submit the protocol, protocol amendments (if applicable), ICFs, Investigator Brochure(s), and other relevant documents (e.g., advertisements) to an IRB/IEC and the IRB/IEC must review and approve them before the study is initiated.
- Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The Investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures.
    - Notifying the IRB/IEC of SAEs or other significant safety findings, as required by IRB/IEC procedures.
    - Providing oversight of the study conduct at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant. The information 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 study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.

When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor (or designee) physician. This includes provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor (or designee) physician to assist with the medical emergency "and to provide support for the potential unblinding of the participant concerned".

When 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 participant concerned.

Clinical Study Insurance and Compensation to Participants

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

Clinical Study Report

After study completion, the Sponsor will write a clinical study report in consultation with the Principal Investigator.

Publication

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows Merck to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by agreement. For this single center study, please refer to Section 11 of the Clinical Trial Agreement.

- Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

The study results will be disseminated according to Merck's policy and SOPs. The procedures for publication planning will also follow the most recent recommendations from the International Committee of Medical Journal Editors.

The specific study information and data will also be disclosed by the Sponsor publicly by registering clinical studies on publicly accessible web platforms such as www.clinicaltrials.gov prior to, during and after the completion of the clinical study in manners consistent with applicable laws and rules governing protection of patient privacy and intellectual property. In addition, the study results will be made publicly available by means of a Clinical Study Report synopsis in accordance with privacy legislation and rules. Other researchers can, by following the appropriate Merck KGaA processes, gain access to the data for additional analysis or information as part of EFPIA/PhRMA commitment to Responsible Data Sharing. Merck KGaA observes stringent data protection rules and as such has implemented a strict process whereby external researchers may apply for access to the data. All details concerning obtaining access to the clinical study data are available on a dedicated web page on the Merck KGaA website: http://biopharma.merckgroup.com/en/research_development/clinical_trials/commitment_to_responsible_clinical_trial_data_sharing/commitment_to_responsible_clinical_trial_data_sharing.html.

Healthy participants might be provided with the results of the medical examinations at request. After finalization of the study, healthy participants might be provided with the information published on ClinicalTrials.gov and/or the European Clinical Trial database at request.

Data Quality Assurance

- All participant study data will be recorded on printed or electronic CRFs or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the CRF. Details for managing CRFs are in the CRF Completion Guidelines
- The Investigator must maintain accurate documentation (source data) that supports the information in the CRF.
- The Investigator must permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the Monitoring Plan.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality

control and quality assurance procedures have been completed. PDF files of the CRFs will be provided to the Investigators at study completion.

- Study monitors will perform ongoing source data verification to confirm that data in the CRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- The Investigator must keep a paper or electronic file (medical file and original medical records) at the site for each study participant. The file must identify each participant, contain the following demographic and medical information for the participant, and should be as complete as possible:
    - Participant's full name, date of birth, sex, height, and weight
    - Medical history and concomitant diseases
    - Prior and concomitant therapies (including changes during the study)
    - Study identifier (i.e., the Sponsor's study number) and participant's study number.
    - Dates of entry into the study (i.e., signature date on the informed consent) and each visit to the site
    - Any medical examinations and clinical findings predefined in the protocol
    - All AEs
    - Date that the participant left the study, including any reason for early withdrawal from the study or study intervention, if applicable.
- All source data must be filed (e.g., CT or MRI scan images, ECG recordings, and laboratory results). Each document must have the participant number and the procedure date; ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records should be performed, documented, signed and dated by the Investigator.
- Data recorded on printed or electronic CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- The study monitors will use printouts of electronic files (e.g., laboratory reports) for source data verification. These printouts must be signed and dated by the Investigator and kept in the study file.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval.
- Definition of what constitutes source data is found in ICH GCP Guideline E6 Chapter 1.51.

Study and Site Closure

- The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been completed.
- The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
- Reasons for the early closure of a study site by the Sponsor or Investigator may include:
    - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
    - Inadequate recruitment of participants by the Investigator
    - Discontinuation of further development of the Sponsor's compound.

Appendix 3 Contraception

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile, as specified below.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, consider additional evaluation.

A WOCBP is **not**:

1. Premenarchal
2. A premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

    Documentation can come from the site personnel's review of the female's medical records, medical examination, or medical history interview.

    For a female with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion applies to determine study entry.
3. A postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, more than 1 FSH measurement is required in the postmenopausal range.
    - A female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

A male will be considered eligible for enrolment if he agrees to the following during the study intervention period and for at least 120 days after the day of the study intervention dose (covering a full sperm cycle of 90 days starting after 5 half-lives of last dose of study intervention):

- Refrain from donating sperm

PLUS, either:

- Abstain from intercourse with a WOCBP

OR

- Use a male condom:

- When having sexual intercourse with a WOCBP, who is **not** currently pregnant, **and** advise her to use a highly effective contraceptive method with a failure rate of < 1% per year, since a condom may break or leak.

Contraceptive Guidance

Highly Effective Methods That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner: a highly effective contraceptive method provided that the partner is the sole sexual partner of a WOCBP, and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - Oral
  - Intravaginal
  - Transdermal
  - Injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation
  - Oral
  - Injectable
- Sexual abstinence: a highly effective method only if defined as refraining from intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study.

Notes:

Contraceptive use by men or women is consistent with local regulations on the use of contraceptive methods for clinical study participants.

Highly effective methods are those with a failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

Hormonal contraception may be susceptible to interaction with the study intervention(s), which may reduce the efficacy of the contraceptive method. As such, male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are **not** acceptable methods of contraception for this study. Male condom and female condom cannot be used together (due to risk of failure with friction).

Highly Effective Contraceptive Methods That Are User Dependent
Failure rate of <1% per year when used consistently and correctly.

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]
  • oral
  • intravaginal
  • transdermal

• Progestogen-only hormonal contraception associated with inhibition of ovulation[b]
  • oral
  • injectable

Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device • Intrauterine hormone-releasing system • bilateral tubal occlusion
• Vasectomized partner (A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)
• Sexual abstinence (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case 2 highly effective methods of contraception should be utilized during the treatment period and for at least 20 weeks after the last dose of study treatment.

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions

Adverse Event

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product, regardless of causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, regardless if it is 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 is required to grade the severity or toxicity of each AE.

Investigators must assess the severity of AEs per the Qualitative Toxicity Scale, as follows:

Mild: The participant is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate: The participant experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe: Significant impairment of functioning: the participant is unable to carry out his or her usual activities.

Investigators must also systematically assess the causal relationship of AEs to study intervention (including any other non-study interventions, radiation therapy, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the M5717, DVI or rescue medication include, but may not be limited to, temporal relationship between the AE and the product, known side effects of the product, medical history, concomitant medication, course of the underlying disease, and study procedures.

Unrelated: Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g., on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to study intervention discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (e.g., anemia or increased ALT) 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. Life-threatening refers to an event in which the participant 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. 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 participant 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 a study intervention is also considered an SAE, as specified below for reporting SAEs.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study intervention or procedures (e.g., an overnight stay to facilitate intravenous therapy) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (i.e., 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 study visit that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions and are not to be considered AEs.

Recording and Follow-Up of AE and/or SAE

It is important that each AE report include a description of the event, its duration (onset and resolution dates and also onset and resolution times, when it is important to assess the time of AE onset relative to the recorded study intervention administration time), its severity, its causal relationship with the study intervention, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the study intervention, and its outcome. In addition, serious cases should be identified, and the appropriate seriousness criteria documented.

Specific guidance is in the CRF Completion and Monitoring Guidelines.

Reporting Serious Adverse Events

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 Sponsor or its designee in writing. All written reports should be transmitted using the SAE Report Form, which must be completed by the Investigator following specific completion instructions.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, a written report must be sent immediately thereafter by fax or e-mail. Names, addresses, and telephone and fax numbers for SAE reporting will be included in the study specific SAE Report Form.

Relevant pages from the CRF may be provided in parallel (e.g., medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (e.g., laboratory results, hospital report, autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the CRF.

The Investigator must respond to any request for follow-up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee 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 Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the study monitor, although in exceptional circumstances the drug safety department may contact the Investigator directly to obtain further information or to discuss the event in case of limited provided information.

Appendix 5 Liver Safety: Suggested Actions and Follow-up Assessments

The drug induced liver injury will be defined as following:

- an elevated ALT or AST by > 3xULN. Often with ATs much greater: 5-10xULN.
- an elevated ALT or AST by > 3xULN plus serum total bilirubin (TBL) of > 2xULN, without findings of cholestasis (defined as serum alkaline phosphatase activity < 2ULN).
- no other reason can be found to explain the combination of increased AT and serum TBL, such as viral hepatitis, alcohol abuse, ischemia, preexisting liver disease, or another drug capable of causing the observed injury.

An increase of serum ALT to > 3xULN should be followed by repeat testing within 48 to 72 hours of all four of the usual serum measures (ALT, AST, ALP, and TBL) to confirm the abnormalities and to determine if they are increasing or decreasing. The need for prompt repeat testing is especially great if AT is much > 3xULN and/or TBL is > 2xULN.

If symptoms persist or repeat testing shows AT > 3xULN for participants with normal baseline measures, it is appropriate to initiate close observation to determine whether the abnormalities are improving or worsening.

Close observation includes:

- Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize and the participant is asymptomatic,
- Obtaining a more detailed history of symptoms and prior or concurrent diseases,
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets,
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease,
- Obtaining a history of exposure to environmental chemical agents,
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., international normalized ratio [INR], direct bilirubin),
- Considering gastroenterology or hepatology consultations.

All study participants showing possible drug induced liver injury should be followed until all abnormalities return to normal or to the baseline state.

Appendix 6 Malaria Clinical Score for Treatment Initiation

Symptoms	Clinical Score			
	Absent	Mild (1)	Moderate (2)	Severe (3)
Headache				
Myalgia (muscle ache)				
Arthralgia (joint ache)				
Fatigue/lethargy				
Malaise (general discomfort/uneasiness)				
Chills/Shivering/Rigors				
Sweating/hot spells				
Anorexia				
Nausea				
Vomiting				
Abdominal discomfort				
Fever				
Tachycardia				
Hypotension				
Total Score	**XX**			

Maximum Score: 3 x 14 = 42.

Appendix 7 Clinical Laboratory Tests

Table 12 Protocol-Required Clinical Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Hemoglobin Hematocrit Red blood cell count Reticulocytes Platelet count	MCV MCH MCHC	White Blood Cell Count with Differential[a]: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Biochemistry	Aspartate aminotransferase Alanine aminotransferase Alkaline phosphatase Gamma-glutamyl-transferase Lactate dehydrogenase Creatine phosphokinase[a] Total Protein Albumin Bilirubin (total) [a] hs Troponin T	Cholesterol[b] Triglycerides[b] HDL cholesterol[b] Amylase Lipase Uric acid Blood Urea Nitrogen Creatinine Glucose (fasting, fasting optional for Days 6 to 33)	Electrolytes: • Sodium • Potassium • Chloride • Calcium • Magnesium • Bicarbonate • Phosphate
Coagulation[b]	INR Activated partial thromboplastin time		
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 Details of liver chemistry stopping criteria and required actions and Follow-up assessments after liver stopping or monitoring event are given in Section 7.1 (Discontinuation of Study Intervention) and Appendix 9.			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (only if blood, protein, leucocyte esterase, or nitrite is positive) (only if dipstick is clinically significant as deemed by the investigator).		
Urine drug screen	Cocaine Amphetamines Methamphetamines Opiates	Barbiturates MDMA (ecstasy) Benzodiazepine Methadone	THC (cannabinoids) Phencyclidine Tricyclic antidepressants
Serology	Hepatitis B surface antigen Hepatitis B core antibody Hepatitis C antibody Human immunodeficiency virus (HIV) I and II antibodies		
Pregnancy	Serum hCG pregnancy test (at Screening) Urine pregnancy test (on Day -1)		
Other Screening Tests	• Urine cotinine • Alcohol breath test		

Laboratory Assessments	Parameters
	• Follicle-stimulating hormone (for postmenopausal women) All study-required clinical laboratory assessments will be performed by the LUMC laboratory, except for urine drug screen, urine cotinine, routine urinalysis, and alcohol breath test which will be performed at CCI

CCI hCG=human chorionic gonadotropin, HDL=high-density lipoprotein, INR=prothrombin time, LUMC=Leiden University Medical Centre, MCV=mean corpuscular volume, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration.

Appendix 8 Package Inserts of Malarone and Riamet

Package leaflet: Information for the patient

Malarone 250 mg/100 mg film-coated tablets
atovaquone/proguanil hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Malarone is and what it is used for

Malarone belongs to a group of medicines called *antimalarials*. It contains two active ingredients, atovaquone and proguanil hydrochloride.

What Malarone is used for

Malarone has two uses:

- **to prevent malaria**
- **to treat malaria**

Dosage instructions for each use are in Section 3, *How to take Malarone.*

Malaria is spread by the bite of an infected mosquito, which passes the malaria parasite *(Plasmodium falciparum)* into the bloodstream. Malarone prevents malaria by killing this parasite. For people who are already infected with malaria, Malarone also kills these parasites.

Protect yourself from catching malaria

People of any age can get malaria. It is a serious disease, but is preventable.

As well as taking Malarone, it is very important that you also take steps to avoid being bitten by mosquitoes.

- **Use insect repellent on exposed areas of the skin**
- **Wear light coloured clothing that covers most of the body**, especially after sunset as this is the time when mosquitoes are most active
- **Sleep in a screened room** or under a mosquito net impregnated with insecticide
- **Close windows and doors at sunset**, if they are not screened

- **Consider using an insecticide** (mats, spray, plug-ins) to clear a room of insects or to deter mosquitoes from entering the room.

→ **If you need further advice**, talk to your doctor or pharmacist.

It is still possible to get malaria after taking the necessary precautions. Some types of malaria infection take a long time to cause symptoms, so the illness may not start until several days, weeks or even months after returning from abroad.

→ **See a doctor immediately if you get symptoms** such as high temperature, headache, shivering and tiredness after returning home.

2. What you need to know before you take Malarone

Do not take Malarone:

- **if you are allergic** to atovaquone, proguanil hydrochloride or any of the ingredients of this medicine listed in section 6.

- **for preventing malaria, if you have severe kidney disease.**

→ **Tell your doctor if either of these apply to you.**

Take special care with Malarone
Talk to your doctor or pharmacist before taking Malarone if:
- you have severe kidney disease
- your child is being treated for Malaria and weighs less than 11 kg. There is another tablet strength to treat children who weigh less than 11 kg (see section 3).

→ **Tell your doctor or pharmacist** if any of these applies to you.

Other medicines and Malarone
Tell your doctor or pharmacist if you are taking, have recently taken, or might take **any** other medicines, including medicines you've bought without a prescription.

Some medicines can affect the way Malarone works, or Malarone itself can strengthen or weaken the effectiveness of other medicines taken at the same time. These include:
- **metoclopramide**, used to treat nausea and vomiting
- the antibiotics, **tetracycline, rifampicin** and **rifabutin**
- **efavirenz** or **certain highly active protease-inhibitors** used to treat HIV
- **warfarin** and other medicines that stop blood clotting
- **etoposide** used to treat cancer.

→ **Tell your doctor** if you are taking any of these. Your doctor may decide that Malarone isn't suitable for you, or that you need extra check ups while you're taking it.

→ **Remember to tell your doctor** if you start taking any other medicines while you're taking Malarone.

Malarone with food and drink

Take Malarone with food or a milky drink, where possible. This will increase the amount of Malarone your body can absorb, and make your treatment more effective.

Pregnancy and breast-feeding

If you are pregnant, do not take Malarone unless your doctor recommends it.

→ Ask your doctor or pharmacist for advice before taking Malarone

Do not breast-feed while taking Malarone, as the ingredients of Malarone may pass into breast milk and may harm your baby.

Driving and using machines

If you feel dizzy, do not drive.
Malarone makes some people feel dizzy. If this happens to you, do not drive, use machines or take part in activities where you may put yourself or others at risk.

3. How to take Malarone

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Take Malarone with food or a milky drink, where possible.

It is best to take Malarone at the same time each day.

If you are sick (*vomit*)

For preventing malaria:
- **if you are sick** *(vomit)* **within 1 hour of taking your Malarone tablet,** take another dose straight away
- **it is important to take the full course of Malarone**. If you have to take extra tablets due to sickness, you may need another prescription.
- **if you have been vomiting,** it is especially important to use extra protection, such as repellents and bednets. Malarone may not be as effective, as the amount absorbed will be reduced.

For treating malaria:
- **if you have vomiting and diarrhoea** tell your doctor, you will need regular blood tests. Malarone will not be as effective, as the amount absorbed will be reduced. The tests will check whether the malaria parasite is being cleared from your blood.

To prevent malaria

The recommended usual dose for adults is 1 tablet once a day, taken as below.

Not recommended for preventing malaria in children, or in adults who weigh less than 40 kgs. Malarone paediatric tablets are recommended for preventing malaria in adults and children who weigh less than 40 kgs.

To prevent malaria in adults:
- start taking Malarone 1 to 2 days before travelling to an area which has malaria
- continue taking it every day during your stay
- continue taking it for another 7 days after your return to a malaria-free area.

To treat malaria

The recommended dose for adults is 4 tablets once a day for 3 days.

For children the dose depends on their bodyweight:
- 11-20 kg – 1 tablet once a day for 3 days
- 21-30 kg – 2 tablets once a day for 3 days

- 31-40 kg – 3 tablets once a day for 3 days
- over 40 kg – dose as for adults.

Not recommended for treating malaria in children who weigh less than 11 kgs.

For children who weigh less than 11 kgs talk to your doctor. There may be a different type of Malarone tablet available in your country.

If you take more Malarone than you should

Contact a doctor or pharmacist for advice. If possible show them the Malarone pack.

If you forget to take Malarone

It is very important that you take the full course of Malarone.
If you forget to take a dose, don't worry. Just take your next dose as soon as you remember. Then continue your treatment as before.
Don't take extra tablets to make up for a missed dose. Just take your next dose at the usual time.

Don't stop taking Malarone without advice

Keep taking Malarone for 7 days after you return to a malaria-free area. Take the full course of Malarone for maximum protection. Stopping early puts you at risk of getting malaria, as it takes 7 days to ensure that any parasites that may be in your blood following a bite from an infected mosquito are killed.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Look out for the following severe reactions. They have occurred in a small number of people, but their exact frequency is unknown.
Severe allergic reactions - signs include:
- rash and itching
- sudden wheezing, tightness of the chest or throat, or difficulty breathing
- swollen eyelids, face, lips, tongue or other part of the body.

→ **Contact a doctor immediately** if you get any of these symptoms. **Stop taking Malarone.**

Severe skin reactions
- skin rash, which may blister and looks like small targets (central dark spots, surrounded by paler area with a dark ring around the edge) (*erythema multiforme*)
- severe widespread rash with blisters and peeling skin, particularly occurring around the mouth, nose, eyes and genitals (*Stevens-Johnson syndrome*).

→ **If you notice any of these symptoms contact a doctor urgently.**

Most of the other side effects reported have been mild and have not lasted very long.

Very common side effects

These may affect **more than 1 in 10 people:**
- headache
- feeling sick and being sick (*nausea* and *vomiting*)
- stomach pain

- diarrhoea.

Common side effects

These may affect **up to 1 in 10 people:**

- dizziness
- sleeping problems *(insomnia)*
- strange dreams
- depression
- loss of appetite
- fever
- rash which may be itchy
- cough

Common side effects, which may show up in your blood tests are:

- reduced numbers of red blood cells *(anaemia)* which can cause tiredness, headaches and shortness of breath
- reduced numbers of white blood cells *(neutropenia)* which may make you more likely to catch infections
- low levels of sodium in the blood *(hyponatraemia)*
- an increase in liver enzymes.

Uncommon side effects

These may affect **up to 1 in 100 people:**

- anxiety
- an unusual awareness of abnormal beating of the heart *(palpitations)*
- swelling and redness of the mouth
- hair loss
- itchy, bumpy rash (hives).

Uncommon side effects that may show up in your blood tests:

- an increase in amylase *(an enzyme produced in the pancreas).*

Rare side effects

These may affect **up to 1 in 1,000 people:**

- seeing or hearing things that are not there (*hallucinations*)

Other side effects

Other side effects have occurred in a small number of people but their exact frequency is unknown.

- Inflammation of the liver(*hepatitis*)
- blockage of the bile ducts (*cholestatis*)
- increase in heart rate (*tachycardia*)
- inflammation of the blood vessels (*vasculitis*) which may be visible as red or purple raised spots on the skin but can affect other parts of the body
- fits (*seizures*)
- panic attacks, crying
- nightmares
- severe mental health problem in which the person loses contact with reality and is unable to think and judge clearly
- indigestion

- mouth ulcers
- blisters
- peeling skin
- increased sensitivity of the skin to sunlight.

Other side effects that may show up in your blood tests:

- A decrease in all types of blood cells (*pancytopenia*).

Reporting of side effects
If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Malarone

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Malarone does not require any special storage conditions.

Do not throw away any medicines via waste water or household waste. Ask your pharmacist how to throw away medicines you no longer use. This will help protect the environment.

6. Contents of the pack and other information

What Malarone contains

The active ingredients are: 250 mg of atovaquone and 100 mg of proguanil hydrochloride in each tablet.
The other ingredients are:
tablet core: poloxamer 188, microcrystalline cellulose, hydroxypropyl cellulose, povidone K30, sodium starch glycollate (Type A), magnesium stearate
tablet coating: hypromellose, titanium dioxide (E171), iron oxide red (E172), macrogol 400 and polyethylene glycol 8000 (see section 2).

→ **Tell your doctor, without taking Malarone** if you might be allergic to any of these ingredients.

What Malarone looks like and contents of the pack

Malarone tablets are round, pink film-coated tablets engraved 'GX CM3' on one side. They are supplied in blister packs containing 12 tablets.

The marketing authorisation holder is Glaxo Wellcome UK Ltd, Stockley Park West, Uxbridge, UK

The manufacturer is
Aspen Bad Oldesloe GmbH, Industriestrasse 32-36, 23843 Bad Oldesloe, Germany

Or

Glaxo Wellcome S.A., Avenida de Extremadura, 3, 09400 Aranda de Duero, Burgos, Spain

Other formats:

To listen to or request a copy of this leaflet in Braille, large print or audio, please call, free of charge:

0800 198 5000 (UK Only)

Please be ready to give the following information:

Product name	Malarone 250 mg/100 mg film-coated tablets
Reference number	10949/0258

This is a service provided by the Royal National Institute of Blind People.

This leaflet was last revised in June 2017.

Riamet®

Artemether and lumefantrine

Consumer Medicine Information

What is in this leaflet?

This leaflet answers some common questions about Riamet. It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

The information in this leaflet was last updated on the date listed on the final page. Some more recent information on the medicine may be available.

Speak to your pharmacist or doctor to obtain the most up to date information on the medicine. You can also download the most up to date leaflet from www.novartis.com.au.
Those updates may contain important information about the medicine and its use of which you should be aware.

All medicines have risks and benefits. Your doctor has weighed the risks of you taking this medicine against the benefits they expect it will provide.

If you have any concerns about this medicine, ask your doctor or pharmacist.

Keep this leaflet with the medicine.
You may need to read it again.

What Riamet is used for

Riamet contains two antimalarial medicines, artemether and lumefantrine. These ingredients work together to kill the Plasmodium falciparum parasite in uncomplicated or mixed infections of malaria.

Malaria commonly occurs in sub-tropical and tropical areas.

Riamet is used to treat malaria acquired in areas where the parasite may be resistant to other anti-malarial medicines.

Malaria is an infectious mosquito-borne disease, spread to humans by the bite of the Anopheles mosquito. The mosquito carries parasites and injects them into the bloodstream when it bites a person.

The parasites infect red blood cells, causing fever, chills, a general feeling of unwell (malaise), cough, nausea, headaches, vomiting and diarrhoea. Not all symptoms need to be present to suggest that you have malaria.

Ask your doctor if you have any questions about why this medicine has been prescribed for you.
Your doctor may have prescribed it for another purpose.

This medicine is only available with a doctor's prescription.

It is not addictive.

Riamet is suitable for adults, adolescents, and children over 12 years of age who weigh 35 kg or more.

Before you take Riamet

When you must not take it

Do not take this medicine to prevent getting a malaria infection.

Do not take this medicine if you have a severe malaria infection.
Severe malaria is a malaria infection that affects the brain, lungs or kidneys.

Do not take Riamet if you are allergic to artemether or lumefantrine (the active ingredients) or to any of the other ingredients listed at the end of this leaflet.

If you think you may be allergic to Riamet, ask your doctor for advice.

Some of the symptoms of an allergic reaction may include:

- shortness of breath, wheezing or difficulty breathing
- swelling of the face, lips, tongue or other parts of the body
- rash, itching or hives on the skin.

Do not take Riamet if you are pregnant, think you are pregnant, or intend to become pregnant.
Riamet may affect your developing baby especially if you take it during the first three (3) months of pregnancy. There are potential serious consequences for the foetus. It may be possible for the doctor to give an alternative medicine during this time.

Take Riamet in the later stages of pregnancy only if clearly necessary.
Your doctor will discuss with you the potential risks and benefits of taking Riamet during pregnancy.

Use effective contraception measures to prevent pregnancy, before you take Riamet. If you are taking hormonal birth control medicine, you should also use an additional method of birth control.
Women who are capable of becoming pregnant are advised to use an effective method of contraception whilst on Riamet treatment, and until the start of the next menstruation after treatment.

Do not breast-feed while you are taking this medicine and for at least four (4) weeks after taking the last tablet.
It is not known if the active ingredient in Riamet passes into the breast milk and could affect your baby.

Do not take Riamet after the expiry date printed on the pack or if the packaging is torn or shows signs of tampering.
In that case, return it to your pharmacist.

Do not take Riamet until you tell your doctor about any other medical conditions that you have and any other medicines that you are taking before you start taking Riamet.
Your doctor may not want you to take Riamet or he/she may need to take special precautions if you have certain medical conditions or are taking certain medicines.

Before you start to take it

Tell your doctor if you have, or have ever had, any of the following:

- an abnormal electrical signal called "prolongation of the QT interval".
- a problem with your heart rhythm, heart rate, severe heart disease or any other heart problem
- a family history of heart rate or rhythm problems, or sudden death
- low blood electrolyte levels such as potassium or magnesium
- severe liver or kidney problems
- allergies to any other medicines, foods, dyes or preservatives.

Taking other medicines

Tell your doctor if you are taking, or have recently taken, any other medicines, including medicines that you buy without a prescription from a pharmacy, supermarket or health food shop.

Some medicines and Riamet may interfere with each other. Some of these medicines include:

- other medicines used to treat malaria
- anti-retroviral medicines or protease inhibitors (used to treat HIV infections or AIDS)
- hormonal birth control medication (as you should follow an additional method of birth control whilst taking Riamet)
- medicines used to treat an abnormal heart rhythm, rhythm disturbance or affect heart beat (e.g. flecainide, metoprolol)
- medicines that can have side effects on your heart, including some medicines used to treat depression or mental illnesses (such as imipramine, amitriptyline, clomipramine),
- rifampicin, an antibiotic used to treat leprosy or tuberculosis
- some antibiotic medicines (e.g. macrolides, fluoroquinolones, and imidazole)
- cisapride, a medicine used to treat stomach disorders (such as hyperacidity, reflux and ulcers)
- triazole antifungal agents (e.g. fluconazole, itraconazole)
- certain medicines used to treat allergies or inflammation (e.g. non-sedating antihistaminics such as terfenadine or astemizole)
- a variety of other medicines that are removed from your body through your liver
- certain medicines used to treat epilepsy (such as carbamazepine, phenytoin)
- St John's wort (Hypericum perforatum), a medicinal plant extract that is used to relieve some temporary feelings of sadness or low mood

You may need to take different amounts of your medicines or you may need to take different medicines. Your doctor and pharmacist have more information.

If you have not told your doctor about any of these things, tell him/her before you start taking this medicine.

How to take Riamet

Follow all directions given to you by your doctor and pharmacist carefully.
They may differ from the information contained in this leaflet.

If you do not understand the instructions on the label, ask your doctor or pharmacist for help.

How much to take

Your doctor will tell you exactly how many Riamet tablets to take.

For adults and children over 12 years of age who weigh 35 kg or more, the recommended course of treatment consists of 6 doses taken over 3 days.

Each of the 6 doses consists of four tablets (i.e. a total of 24 tablets are taken over 3 days).

Do not exceed the recommended dose.

When to take it

Start treatment at the time of diagnosis by a doctor.

Unless your doctor tells you otherwise, take the six doses over 3 days as follows:

1. Take the first dose (4 tablets) as soon as possible after malaria is diagnosed.
2. Take the second dose (4 tablets) 8 hours after the first dose.
3. Take the third dose (4 tablets) 24 hours (exactly one day) after the first dose.
4. Take the fourth dose (4 tablets) 36 hours after the first dose.
5. Take the fifth dose (4 tablets) 48 hours (exactly 2 days) after the first dose.
6. Take the sixth dose (4 tablets) 60 hours after the first dose.

To benefit from the full therapeutic effect, the full course of medication must be taken over the 60 hours at the intervals as indicated.

How to take it

***Swallow each dose (4 tablets) with* a full glass of water or with drinks rich in fat (e.g. milk).**

Do not break the tablets.

If possible, take the tablets with food or immediately after some food rich in fat.

If you are too unwell to eat, still take the tablets.
People with malaria often do not feel like eating, but you should try to eat normally as soon as you can tolerate food. Taking Riamet with food increases the amount of medicine that is absorbed into the body. This helps to kill the malaria parasite more effectively and reduces the risk of a relapse (a return of the malaria infection).

If you vomit within 1 hour of taking the tablets, take another dose as soon as you can. Then contact your doctor or pharmacist immediately. You may need to take another dose or get a prescription for more tablets.

If you are unsure about how much Riamet to take, or when to take it, please ask your doctor or pharmacist.

How long to take it

Continue taking Riamet tablets for the full course of treatment recommended by your doctor.
It is extremely important for you to take this medicine exactly as directed by your doctor and for the full course of treatment, even if you begin to feel better before you have finished the tablets. If you stop taking Riamet tablets too soon, your symptoms may return.

Do not miss any doses.
Falciparum malaria is a serious, life-threatening disease that requires complete cure.

If you forget to take it

If you miss a dose, take the missed dose as soon as you remember, and then go back to the schedule prescribed by your doctor.

Do not take a double dose to make up for the one that you missed.
Your chance of an unwanted side effect may be increased if you do.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

If you take too much (overdose)

If you think that you or anyone else may have taken too much Riamet, immediately:

- **telephone your doctor or the Poisons Information Centre (telephone 13 11 26),**
- ***or go to Accident and* Emergency at your nearest hospital**

Keep the telephone numbers for these places handy.

Do this even if there are no signs of discomfort or poisoning.
You may require medical attention.

Remember to take your medicine with you, and show it to your doctor or to the staff of the emergency unit.

If you have run out of tablets, take the empty packaging along with you.

While you are taking Riamet

Things you must do

Contact your doctor immediately if your condition worsens, or if you feel too unwell to eat and drink. Your doctor may want to perform a test called an electrocardiogram (ECG) and check the levels of electrolytes (such as potassium and magnesium) in your blood before and during treatment.

Tell your doctor if don't feel like eating while you are taking Riamet.
People with malaria usually don't feel like eating. However, eating may help to stop the malaria coming back.

Tell your doctor if you keep vomiting.
If you keep vomiting, the medicine may not work properly. Your doctor may need to give you another treatment.

Tell your doctor if your symptoms are not improving or if they become worse after starting Riamet.
This may mean that you need a different treatment for your malaria.

Tell your doctor immediately if you find out that you are pregnant while taking Riamet.

If you are about to be started on any new medicine, remind your doctor and pharmacist that you are taking Riamet.

Tell any doctor, dentist or pharmacist who treats you that you are taking Riamet.

Things you must not do

Do not give this medicine to anyone else, even if their condition seems similar to yours.

Do not use it to treat any other complaints unless your doctor tells you to.

Things to be careful of

If you feel ill again, especially if you develop a fever after finishing your treatment, see your doctor immediately.
A further course of treatment with Riamet may be necessary if the malaria infection returns (i.e. you have a relapse) or you are reinfected with Plasmodium falciparum after having been cured.

Avoid grapefruit juice whilst taking this medicine.

Be careful driving, operating machinery or doing jobs that require you to be alert while you are taking Riamet until you know how it affects you.
This medicine may make some people feel sleepy, dizzy or weak. If you have any of these symptoms, do not drive or do anything else that could be dangerous.

Side effects

Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking Riamet.
All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects. You may not be able to tell the difference between side effects of Riamet and the symptoms of malaria itself.

Do not be alarmed by these lists of possible side effects.
You may not experience any of them. Most of the side effects are mild to moderate and will generally disappear after a few days to a few weeks from treatment.

Ask your doctor or pharmacist to answer any questions you may have.

Tell your doctor if you notice any of the following and they worry you:

- headache, loss of appetite
- stomach pain
- stomach problems
- nausea (feeling sick) or vomiting
- diarrhoea
- unusual tiredness or general weakness
- difficulty sleeping or sleepiness
- aching muscles or joints
- unsteadiness when walking
- tingling or numbness of the hands or feet
- sore throat
- cough
- fever
- shivering
- itching on the skin or a rash

Tell your doctor immediately if any of the following happen:

- decreased feeling of sensitivity (especially of the skin)
- abnormal walk or inability to co-ordinate body movements
- sudden signs of allergy such as rash, itching or hives on the skin; swelling of the face, lips, tongue or other parts of the body; wheezing or troubled breathing
- unusual bleeding or bruising under the skin
- feeling of fast or irregular heart beat (palpitations)
- dizziness, lightheadedness, fainting or near fainting
- involuntary muscle contractions, sometimes in rapid spasms
- unexplained persistent nausea
- signs of a possible liver problem such as persistent pain in the upper right abdomen, yellowing of the skin and/or eyes, dark urine or pale bowel motions.

Some side effects may not give you any symptoms and can only be found when tests are done. Some of these side effects include:

- heart rhythm disturbances (called QTc prolongation or abnormal ECG heart tracing)

Tell your doctor if you notice anything else that is making you feel unwell.

Some people may have other side effects not yet known or mentioned in this leaflet.

After taking Riamet

Storage

Keep your medicine in the original container until it is time to take a dose.

Store it in a cool dry place.

Do not store Riamet or any other medicine in the bathroom or near a sink.

Do not leave it in the car or on window sills.

Keep this medicine where children cannot reach it.
A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your doctor tells you to stop taking this medicine or the expiry date has passed, ask your pharmacist what to do with any medicine you have left over.

Product description

What it looks like

Riamet tablets are yellow, round, flat tablets marked with N/C and a score line on one side and CG on the other side. Each carton contains 24 tablets.

Ingredients

Active Ingredients
Each RIAMET tablet contains:

- artemether 20 mg and
- lumefantrine 120 mg.

Inactive Ingredients
RIAMET tablets also contain:

- cellulose - microcrystalline (E460)
- croscarmellose sodium
- hypromellose (E 464)
- magnesium stearate (E 572)
- polysorbate 80
- silica-colloidal anhydrous

Riamet tablets do not contain lactose, sucrose, gluten, tartrazine or any other azo dyes.

Sponsor

Riamet tablets are supplied in Australia by:
NOVARTIS Pharmaceuticals Australia Pty Limited
ABN 18 004 244 160
54 Waterloo Road
North Ryde NSW 2113
Telephone: 1 800 671 203
Web site: www.novartis.com.au

® = Registered Trademark

This leaflet was prepared in July 2012

Australian Registration Number:
Riamet tablet: AUST R 90011

CCI

Appendix 10 Protocol Amendment History

Version Number	Type	Version Date
1.0	Original Protocol	30 Sep 2019
2.0	Amendment	05 Feb 2020
3.0	Amendment	20 Jul 2020

The information for the current amendment is on the title page.

Protocol Version 3.0 (20 July 2020)

This amendment is nonsubstantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

The current Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2) pandemic can pose a challenge to integrity of the trials, protection of participants' rights, safety and wellbeing and the safety of clinical trial staff. Therefore, risk mitigation strategies will be put in place for this trial following the Central Committee on Research Involving Human Subjects (CCMO) guidance, Conditions (re)start studies in clinical research units, dated 24 June 2020. These mitigation strategies will be kept in place and evaluated on an ongoing basis for the duration of this trial, or until there is a consensus that the period of the SARS-CoV-2 outbreak in the Netherlands has passed. If the dynamics of the SARS-CoV-2 outbreak change in such a way that the safety of the trial participants and clinical trial staff or integrity of the data collected during this clinical trial cannot be guaranteed the trial will be halted. To prevent SARS-CoV-2 infections among trial participants, measures and procedures based on the advice issued by the Dutch National Institute for Public Health and the Environment (RIVM) and COVID-19 measures declared by the Dutch government will be adhered to as outlined in the CCI site-specific COVID-19 Standard Operating Procedure (SOP).

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis (Study Intervention Groups and Duration) 1.3 Schedule of Activities (Tables 1 and 3) 2.3 Benefit/Risk assessment 8.2.2 Vital Signs	COVID-19 risk assessment added per CCMO guidance	To protect trial participants and staff during SARS-CoV-2 outbreak.
5.1 Inclusion Criteria 5.2 Exclusion Criteria	COVID-19 risk mitigation strategies added per CCMO guidance	To protect trial participants and trial staff during the SARS-CoV-2 outbreak.

Section # and Name	Description of Change	Brief Rationale
5.3 Lifestyle Considerations 6.5.1 Rescue Medicine 7.2 Participant Discontinuation/Withdrawal from the Study		
Appendix 1 Abbreviations	Abbreviations added	To clarify abbreviations used in this amendment.
Appendix 11 COVID-19 Risk Assessment and Mitigation Strategies	Added	To describe risk assessment and mitigation strategies during COVID-19 pandemic.
2.3 Benefit/Risk assessment	Sentence removed	Correction to protocol
Throughout document	'Subject' replaced with 'participant', where applicable	For consistency

Protocol Version 2.0 (05 February 2020)

This amendment is nonsubstantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

The original protocol had already been submitted and approved by the responsible independent ethics committee (IEC). However, during the implementation activities the site found a few administrative items that need to be adopted for logistical reasons, particularly allowing randomization to be performed also on Day -1 (instead of only pre-challenge Day 1), and widening the time window for PK and 12-Lead ECG at later time points to better accommodate qPCR sample analysis at the LUMC Laboratory on the same day. Also, there were a few incorrect entries in the tables due to reformatting that had to be corrected.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis (Study Intervention Groups and Duration) 1.3 Schedule of Activities (Tables 1 and 3) 6.3.1 Study Intervention Assignment	Added that randomization may occur on either Day -1 or Day 1.	For logistical reasons in order to allow sufficient time for completion of randomization procedures.
1.1 Synopsis (Study Intervention Groups and Duration)	Clarified that participants will be hospitalized for 2 nights.	Wording revised for clarification purposes.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (Tables 1 and 3)	Incorrect entries due to reformatting corrected to be consistent with protocol text.	Minor; therefore, have not been summarized.
1.3 Schedule of Activities (Table 5)	Allowed time windows for certain scheduled time points widened.	Time windows for PK and 12-Lead ECG at later time points have been widened to better accommodate qPCR sample analysis at the LUMC Laboratory on the same day.
8.2.4 Clinical Safety Laboratory Assessments Appendix 7	Added that blood fasting state samples will be optional from Day 6 onwards.	Mandatory fasted status for lab assessments required only during Screening and Day 1 Predose visits to confirm eligibility. If needed for specific reasons it may be requested by the investigator from Days 6 to 33.
Throughout	Minor editorial and document formatting revisions.	Minor; therefore, have not been summarized.

Appendix 11 COVID-19 Risk Assessment and Mitigation Strategies

The current SARS-CoV-2 pandemic can pose a challenge to integrity of the trials, protection of participants' rights, safety and wellbeing and the safety of clinical trial staff. Therefore, risk mitigation strategies will be put in place for this trial following the CCMO guidance "*Conditions (re)start studies in clinical research units"* dated 24 June 2020. These mitigation strategies will be kept in place and evaluated on an ongoing basis for the duration of this trial, or until there is a consensus that the period of the SARS-CoV-2 outbreak in the Netherlands has passed. If the dynamics of the SARS-CoV-2 outbreak change in such a way that the safety of the trial participants and clinical trial staff or integrity of the data collected during this clinical trial cannot be guaranteed the trial will be halted.

COVID-19 RISK ASSESSMENT

Risk for Trial Participants and Trial Staff

Healthy participants in the current study fall in a low risk category for complications of COVID-19, the disease caused by the SARS-CoV-2 virus. To prevent SARS-CoV-2 infections among trial participants, measures and procedures based on the advice issued by the Dutch National Institute for Public Health and the Environment (RIVM) and COVID-19 measures declared by the Dutch government will be adhered to as outlined in the CCI site-specific COVID-19 SOP. Site trial staff in direct contact and/or within 1.5 m distance of study participants will receive additional protection via the use of Personal Protective Equipment (PPE). All trial participants will be screened for SARS-CoV-2 with a PCR: 1) prior to the/each admission at the clinical unit with at least one overnight stay, and; 2) in case of symptoms possibly related to COVID-19. Healthy participants will be excluded from the study when tested positive for SARS-CoV-2.

Protection of Trial Integrity

Adherence to the protocol and CCI site-specific COVID-19 SOP protects the integrity of the data collected during this clinical trial, as well as participants' data protection rights.

Impact of M5717 and *Plasmodium falciparum* Sporozoite (PfSPZ) Challenge on COVID-19 Disease

Based on the mechanism of action of the investigational drug and the available information in the Investigators Brochure, there is currently no reason to believe that the investigational drug could 1) increase the susceptibility of trial participants to the SARS-CoV-2 virus, or 2) worsen or mask any COVID-19 signs, symptoms or complications.

While *P. falciparum* infection may cause harm when high levels of parasitemia are present in the blood, our study design is such that any breakthrough infection is observed in a very early stage (i.e., very low parasitemia) as compared with a person who has been symptomatic for several days. There is no evidence to expect any increased susceptibility or worsening of clinical symptoms from COVID-19 when co-infected with a low burden of *P. falciparum* parasitemia and vice versa. We do recognize that symptoms of COVID-19, especially fever and malaise, may overlap with

symptoms of *P. falciparum* infection. Criteria for SARS-CoV-2 testing during the *P. falciparum* infection phase are noted in a later section of this appendix.

COVID-19 Contingency Plan

Any participant that presents with COVID-19-related symptoms and/or has a positive SARS-CoV-2 PCR will be excluded from (further) participation in the trial and will receive follow-up medical attention per CCI site-specific COVID-19 SOP.

COVID-19 RISK ASSESSMENT MEASURES

SARS-CoV-2 Screening

Upon admission to the clinical research unit in the morning of Day -1, a nasopharyngeal and throat swab will be taken to test for SARS-CoV-2 infection. Participants will be required to fast for 1 hour prior to the nasopharyngeal and throat swab. Samples will be sent to NMDL-LCPL lab for qPCR analysis. Only participants with a negative SARS-CoV-2 qPCR analysis prior to first dosing will be included in the study.

Participants that test positive for a SARS-CoV-2 infection prior to PfSPZ challenge will be withdrawn from the study and will be replaced. Participants that test positive for a SARS-CoV-2 infection after the PfSPZ challenge will immediately receive mandatory antimalarial rescue medication and follow-up assessments to ensure participant's safety and complete cure from the investigational malaria challenge (see Section 6.5.1), before being withdrawn from the study. Participants withdrawn due to a SARS-CoV-2 infection may be replaced after consultation with the Sponsor. Participants with a SARS-CoV-2 infection will be followed-up according to CCI site-specific COVID-19 SOP.

COVID-19 Arrival Checklist and Temperature Measurement

Trial participants will be requested to come to the clinic only if they have no symptoms that could indicate a COVID-19 infection and if they have not been in contact with a COVID-19 patient for at least 14 days. A standard checklist and temperature measurement will be used upon arrival at the clinic.

Exclusion of Participants with a Risk Factor for a COVID-19 Infection

As per protocol, only healthy participants without underlying conditions comprising a risk factor for a COVID-19 infection will be recruited into the study. Furthermore, participants >45 years, participants with a BMI ≥30 and cardiovascular, respiratory or immune system disorders will be excluded per protocol eligibility criteria. Exclusion of these participants will be safeguarded via COVID-19 specific validation rules in the Promasys study database.

COVID-19 Lifestyle Restrictions

Trial participants will be required to adhere to the measures and procedures outlined in CCI site-specific COVID-19 SOP, based on the advice issued by the Dutch National Institute for Public

Health and the Environment (RIVM) and COVID-19 measures declared by the Dutch government, to prevent SARS-CoV-2 infections among trial participants and clinical site staff.

COVID-19 After PfSPZ infection

SARS-CoV-2 screening will be performed whenever symptoms of COVID-19 develop that cannot be explained by a blood-stage malaria infection. This means that a nasopharyngeal swab will be taken by the study team 1) when symptoms occur that do not match with a malaria infection (e.g. coughing, sneezing, rhinitis); 2) when symptoms occur during the asymptomatic malaria liver-stage phase from infection up until day 6; 3) on any day thereafter when symptoms (mainly fever and malaise) occur but the PCR for *P. falciparum* remains negative or 4) when symptoms persist for 3 days after malaria rescue treatment. Should SARS-CoV-2 infection be identified in a participant that is infected with *P. falciparum*, then prompt initiation of rescue treatment with Malarone will be initiated according to the study specific procedures regarding rescue treatment. These procedures have been implemented in the LUMC SOP 'L-CHIC Clinical trials, procedures for visits during the COVID-19 pandemic'.

The sponsor will enlist the following laboratory for SARS-CoV-2 PCR testing:

PPD

Contact person: PPD
Telephone: PPD

Appendix 12 Sponsor Signature Page

Study Title:	A Phase Ib, Randomized, Double-Blind, Placebo Controlled, Sequential Study of Single Oral Doses of M5717 to Explore the Chemo-prophylactic Activity of M5717 in a Controlled *Plasmodium falciparum* Sporozoite Challenge Model in Healthy Participants
Regulatory Agency Identifying Numbers:	EudraCT: 2019-003414-14
Clinical Study Protocol Version:	03 December 2020/4.0

I approve the design of the clinical study:

PPD

Signature

PPD

Date of Signature

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

Appendix 13 Protocol Co-Lead Signature Page

Study Title:	A Phase Ib, Randomized, Double-Blind, Placebo Controlled, Sequential Study of Single Oral Doses of M5717 to Explore the Chemo-prophylactic Activity of M5717 in a Controlled *Plasmodium falciparum* Sporozoite Challenge Model in Healthy Participants
Regulatory Agency Identifying Numbers:	EudraCT: 2019-003414-14
Clinical Study Protocol Version:	03 December 2020/4.0

I approve the design of the clinical study:

PPD

Sign

PPD

Date of Signature

Name, academic degree:	PPD
Function / Title:	PPD
Institution:	Merck Institute for Pharmacometrics
Address:	PPD
Telephone number:	PPD
Fax number:	Not Applicable
E-mail address:	PPD

Appendix 14 Principal Investigator Signature Page

Study Title:	A Phase Ib, Randomized, Double-Blind, Placebo Controlled, Sequential Study of Single Oral Doses of M5717 to Explore the Chemo-prophylactic Activity of M5717 in a Controlled *Plasmodium falciparum* Sporozoite Challenge Model in Healthy Participants
Regulatory Agency Identifying Numbers:	EudraCT: 2019-003414-14
Clinical Study Protocol Version:	03 December 2020/4.0
Site Number:	01

I approve the design of the clinical study, am responsible for the conduct of the study at this site and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

PPD

Date of Signature

Name, academic degree:	PPD
Function/Title:	PPD
Institution:	PPD
Address:	PPD
Telephone number:	PPD
Fax number:	Not Applicable
E-mail address:	PPD