Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	Phase 2a Proof-of-Concept, Multicenter, Randomized, Open Label Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of a Single Dose of the Combination M5717-pyronaridine as Chemoprevention in Asymptomatic Adults and Adolescents with *Plasmodium falciparum* Malaria Infection
Study Number:	MS201618_0034
Protocol Version:	01 March 2023/Version 1.0
Merck Compound:	M5717
Merck Registered Compound Name in Japan:	Not Applicable
Study Phase:	Phase 2a
Brief Title:	Efficacy, Safety, and PK of M5717 in Combination with Pyronaridine as Chemoprevention in Adults and Adolescents with Asymptomatic *Plasmodium falciparum* Infection
Acronym:	CAPTURE-2
Coordinating Investigator:	PPD [redacted]
Sponsor Name and Legal Registered Address:	Merck Healthcare KGaA, Darmstadt, Germany an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Strasse 250 Darmstadt, 64293, Germany
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Keywords	*Plasmodium falciparum*, chemoprevention, malaria, plasmodium eukaryotic translation elongation factor 2 (PeEF2), exposure response

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1 Protocol Summary

1.1 Synopsis

Clinical Study Protocol Title: Phase 2a Proof-of-Concept, Multicenter, Randomized, Open Label Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of a Single Dose of the Combination M5717-pyronaridine as Chemoprevention in Asymptomatic Adults and Adolescents with *Plasmodium falciparum* Malaria Infection.

Brief Title: Efficacy, Safety, and PK of M5717 in Combination with Pyronaridine as Chemoprevention in Adults and Adolescents with Asymptomatic *Plasmodium falciparum* Infection.

Rationale: CCI [redacted]

An optional substudy assessing the transmission blocking potential of the M5717-pyronaridine combination in humans (direct membrane feeding assay [DMFA] substudy) will be conducted.

Objectives and Estimands:

Objectives	Estimands/Endpoints	Ref. #
Primary		
To evaluate the time of protection of different doses of M5717 in combination with pyronaridine in adults and adolescents with asymptomatic falciparum malaria compared with the natural incidence of infection as measured in Cohort 4	**Endpoint**: Time to parasitemia since negative blood smear after treatment. **Population:** Asymptomatic adult and adolescent participants infected with *P. falciparum* **Treatment:** • Single dose 60 mg M5717 plus 720 mg pyronaridine (≥ 65 kg) or 540 mg pyronaridine (≥ 45 to < 65 kg) (Cohort 1) • Single dose 200 mg M5717 plus 720 mg pyronaridine (≥ 65 kg) or 540 mg pyronaridine (≥ 45 to < 65 kg) (Cohort 2) • Single dose 660 mg M5717 plus 720 mg pyronaridine (≥ 65 kg) or 540 mg pyronaridine (≥ 45 to < 65 kg) (Cohort 3) • 3 doses of Malarone® (in total 1,000 mg atovaquone plus 400 mg proguanil hydrochloride [proguanil]) to clear all parasites to measure the natural incidence of infection (Cohort 4)	1

Objectives	Estimands/Endpoints	Ref. #
	Intercurrent Event Strategy: • Intake of rescue medication: composite variable strategy, i.e. endpoint is considered as failure (=positive blood smear at the time of rescue medication intake) • Intake of antibiotics or other prohibited medication that impacts treatment effect (e.g. drug with antimalarial activity) at any timepoint: On-treatment strategy, i.e. time to parasitemia is censored at the time of antibiotics or prohibited medication intake • Experience of any event that affects absorption (e.g. vomiting within the first 24 hours after dosing): Treatment policy strategy, i.e. treatment effect is estimated regardless of intercurrent event (ICE) • Death due to malaria: Composite variable strategy • Death due to other reasons: On-treatment strategy, i.e. time to parasitemia is censored at the time of death **Population-Level Summary:** HRs estimated from Cox' Proportional Hazards Model for each dose of M5717 relative to Cohort 4	
Secondary		
To further evaluate the time of protection of different doses of M5717 in combination with pyronaridine in adults and adolescents with asymptomatic falciparum malaria compared with the natural incidence of infection as measured in Cohort 4	**Endpoint:** Incidence of parasitemia (positive blood smear) **Population:** See primary endpoint **Treatment:** See primary endpoint **Intercurrent Event Strategy:** • Intake of rescue medication: composite variable strategy, i.e. endpoint is considered as failure (=positive blood smear at the time of rescue medication intake) • Intake of antibiotics or other prohibited medication that impacts treatment effect (e.g. drug with antimalarial activity) at any timepoint: On-treatment strategy, i.e. time to parasitemia is censored at the time of antibiotics or prohibited medication intake • Experience of any event that affects absorption (i.e. vomiting within the study intervention absorptive period of 2 × median t_{max}): Treatment policy strategy, i.e. treatment effect is estimated regardless of ICE • Death due to malaria: Composite variable strategy • Death due to other reasons: On-treatment strategy, i.e. time to parasitemia is censored at the time of death **Population-Level Summary:** Proportion of participants with parasitemia using Kaplan-Meier estimates for each dose of M5717 and for each cohort	2
	Endpoint: Incidence of polymerase chain reaction (PCR)-adjusted parasitemia (thick smear/microscopy, after adjustment for parasitemia due to new infections as determined by genotyping using PCR techniques) **Population:** See primary endpoint **Treatment:** See primary endpoint **Intercurrent Event Strategy:** See Endpoint #2 **Population-Level Summary:** See Endpoint #2	3

Objectives	Estimands/Endpoints	Ref. #
	Endpoint: Incidence of PCR-adjusted parasitemia (thick smear/microscopy, after adjustment for parasitemia due to recrudescence as determined by genotyping using PCR techniques) **Population:** See primary endpoint **Treatment:** See primary endpoint **Intercurrent Event Strategy:** See Endpoint #2 **Population-Level Summary:** See Endpoint #2	4
To evaluate the parasite clearance time in adult and adolescent participants with asymptomatic falciparum malaria treated with different doses of M5717 in combination with pyronaridine	**Endpoint:** Parasite clearance time defined as time from dosing to the first negative (no parasites) blood film (microscopy) **Target Population:** See primary endpoint **Treatment:** See primary endpoint **Intercurrent Event Strategy:** See Endpoint #2 **Population-level Summary:** Median parasite clearance time as estimated by Kaplan-Meier method for each dose of M5717	5
To evaluate the safety and tolerability of different doses of M5717 in combination with pyronaridine in adult and adolescent participants with asymptomatic falciparum malaria	**Endpoint**: Incidence, severity, and seriousness of treatment-emergent adverse events, treatment-emergent study intervention related adverse events, as per Common Terminology Criteria for Adverse Events v5.0	6
To characterize the pharmacokinetic (PK) profile of the M5717-pyronaridine combination	PK parameters of M5717 and pyronaridine using noncompartmental analysis, as appropriate	7

Overall Design: This Phase 2a study is a multicenter, parallel, randomized, open label study. The study population will include adults and adolescents (≥ 12 and ≤ 55 years of age) with asymptomatic *P. falciparum* malaria.

Participants will be randomized to 1 of 4 cohorts (1:1:1:1 ratio). Participants in Cohorts 1 to 3 will be treated with a single dose of M5717 plus pyronaridine whereas participants randomized to Cohort 4 will be treated with 3 daily and consecutive doses of Malarone to clear infections and then estimate the natural incidence of infection during follow-up. Randomization will be stratified by site. Cohort 5 is a synthetic control cohort using external data from a clinical study that investigated Pyramax (pyronaridine-artesunate) among asymptomatic malaria-infected individuals (Dabira ED, Hachizovu S, Conteh B, et al. Clin Infect Dis. 2022 Jan 29;74(2):180-188.).

Brief Summary: This study will determine the time without infection, between clearance of infection following treatment and the end of follow-up (or up to a recurrent infection if occurring during the follow-up) in adults and adolescents with asymptomatic *P. falciparum* malaria at the time of recruitment and living in endemic countries. The purpose of the primary endpoint is to assess the time of protection against any parasite infections occurring after treatment with M5717 plus pyronaridine.

The maximum study duration per participant will be 12 weeks including a prescreening period of a maximum of 2 weeks and a follow-up period of up to 63 days (Day 64, Week 10).

Participants randomized to Cohorts 1 to 3 will receive single oral doses of the study interventions M5717 plus pyronaridine. Participants randomized to Cohort 4 will receive oral doses of the study intervention Malarone (fixed-dose combination of atovaquone-proguanil) on 3 consecutive days.

On Day 1 participants randomized to Cohorts 1 to 3 will be either hospitalized or stay in the vicinity of the sites for 24 hours for PK sampling and assessment of parasitemia until Day 2. Participants randomized to Cohort 4 will attend outpatient visits on Day 1 and Day 2. All participants will return to the sites on Day 3 and Day 4. From Day 8, study visits will take place every week until detection of parasitemia or until Day 64, whichever occurs first.

Number of Participants: Up to 192 participants will be randomly assigned to study intervention with a ratio of 1:1:1:1 to Cohorts 1 to 4, such that approximately 180 evaluable participants are anticipated to be obtained assuming a drop-out rate < 10% as observed in other malaria studies. This will result in 45 participants per treatment cohort. It is planned to use external data as an additional cohort (Cohort 5) to compare with actively enrolled participants.

Study Intervention Groups and Duration:

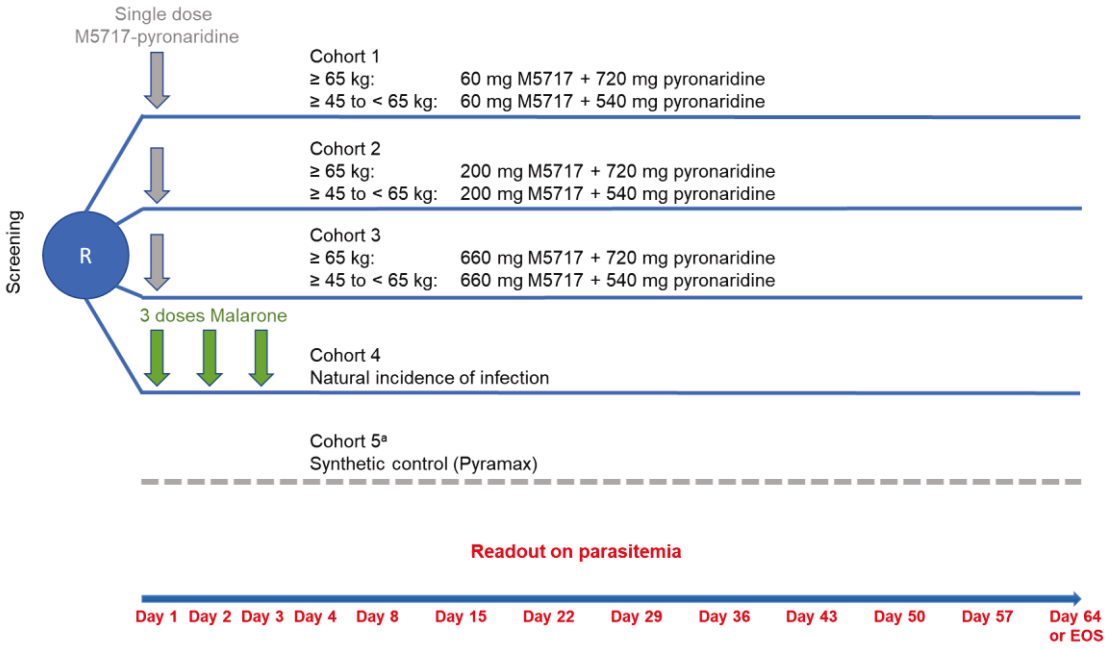
- Cohort 1: Single dose 60 mg M5717 plus 720 mg (participants ≥ 65 kg) or 540 mg (participants ≥ 45 to < 65 kg) pyronaridine
- Cohort 2: Single dose 200 mg M5717 plus 720 mg (participants ≥ 65 kg) or 540 mg (participants ≥ 45 to < 65 kg) pyronaridine
- Cohort 3: Single dose 660 mg M5717 plus 720 mg (participants ≥ 65 kg) or 540 mg (adolescents) pyronaridine (participants ≥ 45 to < 65 kg)
- Cohort 4: 3 doses of 1,000 mg/400 mg atovaquone – proguanil (Malarone) on 3 consecutive days

Data and Safety Monitoring /Other Committee: Yes

A Data Monitoring Committee (DMC) will evaluate the safety data of participants, if judged to be necessary by the Sponsor clinical team.

1.2 Schema

Figure 1 Schematic for the Proof-of-Concept Phase 2a Study: M5717 plus Pyronaridine for Chemoprevention



a Data will be obtained from a clinical study sponsored by Shin Poong Pharmaceuticals Co. Ltd. (ClinicalTrials.gov Identifier: NCT03814616) and published by Dabira ED, Hachizovu S, Conteh B, et al. Efficacy, Safety and Tolerability of Pyronaridine-artesunate in Asymptomatic Malaria-infected Individuals: a Randomized Controlled Trial. Clin Infect Dis. 2022;74(2):180-88. Data of the 1-day treatment arm of this clinical study will be used as Cohort 5

Note: A Data Monitoring Committee will evaluate the safety data of participants, if judged to be necessary by the Sponsor clinical team

1.3 Schedule of Activities

Table 1 Schedule of Activities – Cohorts 1 to 4

Assessments & Procedures	Outpatient	Outpatient/ Inpatient[a]		Outpatient					Notes
Visit Number	**Prescreening**	**Scr + Visit 1[a]**	**Visit 2[a]**	**Visit 3**	**Visit 4**	**Visits 5 to 12**	**Visit 13**	**Unscheduled Visit**	[a] Visit 1 and 2: Participants randomized to Cohorts 1 to 3 will remain in hospital or stay in the vicinity of the sites for 24 hours for PK sampling and assessment of parasitemia (see Table 2). Participants randomized to Cohort 4, will visit the clinic on Days 1, 2, and 3 for dosing in an outpatient setting
Timepoint	**Prescreening**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Week 2 to 9 (weekly visits starting at Day 8)**	**EOS (last visit) Week 10, Day 64[b]**	**Can be required due to AEs, and AESIs; follow-up of AEs and AESIs**	[b] Day 64 or day of completion or premature discontinuation. Participants will remain in the study until parasitemia or until Day 64, whichever comes first. All EOS evaluations will be completed before providing antimalarial rescue treatment if required.
Visit Window						± 1 day	± 2 days		
Prescreening consent	X								
Informed consent		X							
CCI [redacted]		[redacted]							[redacted].
Informed consent DMFA substudy		X							Additional informed consent for the DMFA substudy (optional, see Appendix 2).
Malaria diagnostics	X								For asymptomatic malaria (RDT as per standard of care).

Assessments & Procedures	Outpatient	Outpatient/ Inpatient[a]		Outpatient					Notes
Visit Number	**Prescreening**	**Scr + Visit 1[a]**	**Visit 2[a]**	**Visit 3**	**Visit 4**	**Visits 5 to 12**	**Visit 13**	**Unscheduled Visit**	[a] Visit 1 and 2: Participants randomized to Cohorts 1 to 3 will remain in hospital or stay in the vicinity of the sites for 24 hours for PK sampling and assessment of parasitemia (see Table 2). Participants randomized to Cohort 4, will visit the clinic on Days 1, 2, and 3 for dosing in an outpatient setting
Timepoint	**Prescreening**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Week 2 to 9 (weekly visits starting at Day 8)**	**EOS (last visit)** **Week 10, Day 64[b]**	**Can be required due to AEs, and AESIs; follow-up of AEs and AESIs**	[b] Day 64 or day of completion or premature discontinuation. Participants will remain in the study until parasitemia or until Day 64, whichever comes first. All EOS evaluations will be completed before providing antimalarial rescue treatment if required.
Blood films (microscopy)		X	X	X	X	X	X		Thick and thin blood films will be collected at Visit 1 (predose) to confirm eligibility and at all visits. Cohorts 1 to 3: The exact timepoints on Days 1 to 2 are provided in Table 2. Cohort 4: Blood films should be examined at Screening, predose on Day 1, Day 2, and Day 3. Blood sampling for parasitemia will be done simultaneously with PK.
Inclusion/ exclusion criteria		X							
COVID-19 antigen test		X							The test will be conducted at Visit 1. Additional COVID-19 tests may be conducted as needed.
Demographic and medical history		X							
Randomization		X							

Assessments & Procedures	Outpatient	Outpatient/ Inpatient[a]		Outpatient					Notes
Visit Number	**Prescreening**	**Scr + Visit 1[a]**	**Visit 2[a]**	**Visit 3**	**Visit 4**	**Visits 5 to 12**	**Visit 13**	**Unscheduled Visit**	[a] Visit 1 and 2: Participants randomized to Cohorts 1 to 3 will remain in hospital or stay in the vicinity of the sites for 24 hours for PK sampling and assessment of parasitemia (see Table 2). Participants randomized to Cohort 4, will visit the clinic on Days 1, 2, and 3 for dosing in an outpatient setting
Timepoint	**Prescreening**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Week 2 to 9 (weekly visits starting at Day 8)**	**EOS (last visit)** **Week 10, Day 64[b]**	**Can be required due to AEs, and AESIs; follow-up of AEs and AESIs**	[b] Day 64 or day of completion or premature discontinuation. Participants will remain in the study until parasitemia or until Day 64, whichever comes first. All EOS evaluations will be completed before providing antimalarial rescue treatment if required.
M5717 plus pyronaridine dosing		X							Applicable to participants randomized to Cohorts 1 to 3. Participants randomized to Cohort 4 will not receive any treatment with M5717 and pyronaridine.
Malarone dosing		X	X	X					Only applicable to Cohort 4. Participants randomized to Cohort 4 will receive Malarone as per SmPC on Days 1 to 3 (4 tablets once a day for 3 days).
Physical examination		X	X	X	X	X	X	X	A complete physical examination will be done at screening and at the EOS Visit. At other time points an abbreviated examination will be performed (see Section 8.2.1).
Neurological physical examination		X	X	X	X	X	X	X	Will be done during screening and at every visit. Details are provided in Section 8.2.1.

Assessments & Procedures	Outpatient	Outpatient/ Inpatient[a]		Outpatient					Notes
Visit Number	**Prescreening**	**Scr + Visit 1[a]**	**Visit 2[a]**	**Visit 3**	**Visit 4**	**Visits 5 to 12**	**Visit 13**	**Unscheduled Visit**	[a] Visit 1 and 2: Participants randomized to Cohorts 1 to 3 will remain in hospital or stay in the vicinity of the sites for 24 hours for PK sampling and assessment of parasitemia (see Table 2). Participants randomized to Cohort 4, will visit the clinic on Days 1, 2, and 3 for dosing in an outpatient setting
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Pregnancy test		X					X		Female participants of childbearing potential: serum test at Screening. Urine test at EOS Visit or at premature discontinuation.
12-lead ECG		X[c]							Will include QTcF assessment as scheduled and as clinically indicated. All ECGs will be recorded in triplicate. [c] ECG assessments will be performed at Day1/Visit 1 prior to dosing and 2 hours postdose.
Vital signs		X[d]	X	X	X	X	X	X	Will include supine blood pressure and pulse rate. Vital sign measurements will be taken after the participant has been supine for ≥ 5 minutes. Taken at screening and at predose and at the timepoints listed. [d] Measurements on Day 1/Visit 1 will be taken predose, and 2 and 4 hours postdose, if applicable.

Assessments & Procedures	Outpatient	Outpatient/ Inpatient[a]		Outpatient					Notes
Visit Number	**Prescreening**	**Scr + Visit 1[a]**	**Visit 2[a]**	**Visit 3**	**Visit 4**	**Visits 5 to 12**	**Visit 13**	**Unscheduled Visit**	[a] Visit 1 and 2: Participants randomized to Cohorts 1 to 3 will remain in hospital or stay in the vicinity of the sites for 24 hours for PK sampling and assessment of parasitemia (see Table 2). Participants randomized to Cohort 4, will visit the clinic on Days 1, 2, and 3 for dosing in an outpatient setting
Timepoint	**Prescreening**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Week 2 to 9 (weekly visits starting at Day 8)**	**EOS (last visit)** **Week 10, Day 64[b]**	**Can be required due to AEs, and AESIs; follow-up of AEs and AESIs**	[b] Day 64 or day of completion or premature discontinuation. Participants will remain in the study until parasitemia or until Day 64, whichever comes first. All EOS evaluations will be completed before providing antimalarial rescue treatment if required.
Hematology, chemistry, and urinalysis		X[e]	X	X	X	X	X	X	Hematology, biochemistry, urinalysis as scheduled and when clinically indicated. A sample should be collected before rescue treatment administration if required. [e] If abnormalities are detected on Day 1 a follow-up sample will be taken on Day 2. If increase in ALT > 3 x ULN and/or TB > 2 x ULN, a follow-up is required including ALT, AST, ALP, and TB. Timing of the follow-up visits until resolution will be at the discretion of the Investigator.

Assessments & Procedures	Outpatient	Outpatient/ Inpatient[a]		Outpatient					Notes
Visit Number	**Prescreening**	**Scr + Visit 1[a]**	**Visit 2[a]**	**Visit 3**	**Visit 4**	**Visits 5 to 12**	**Visit 13**	**Unscheduled Visit**	[a] Visit 1 and 2: Participants randomized to Cohorts 1 to 3 will remain in hospital or stay in the vicinity of the sites for 24 hours for PK sampling and assessment of parasitemia (see Table 2). Participants randomized to Cohort 4, will visit the clinic on Days 1, 2, and 3 for dosing in an outpatient setting
Timepoint	**Prescreening**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Week 2 to 9 (weekly visits starting at Day 8)**	**EOS (last visit)** **Week 10, Day 64[b]**	**Can be required due to AEs, and AESIs; follow-up of AEs and AESIs**	[b] Day 64 or day of completion or premature discontinuation. Participants will remain in the study until parasitemia or until Day 64, whichever comes first. All EOS evaluations will be completed before providing antimalarial rescue treatment if required.
									If early clinical symptoms of liver toxicity or DILI (e.g. anorexia, nausea, fatigue, right upper abdominal discomfort, vomiting) are present the investigator should start a liver safety evaluation (see Appendix 6), unless there is an alternative explanation for the clinical symptoms and the liver enzyme increase.
Temperature		X (predose)	X (predose)	X (predose)	X	X	X	X	
Adverse events review		⇐==========⇒							
Concomitant medications review		⇐==========⇒							

Assessments & Procedures	Outpatient	Outpatient/ Inpatient[a]		Outpatient					Notes
Visit Number	**Prescreening**	**Scr + Visit 1[a]**	**Visit 2[a]**	**Visit 3**	**Visit 4**	**Visits 5 to 12**	**Visit 13**	**Unscheduled Visit**	[a] Visit 1 and 2: Participants randomized to Cohorts 1 to 3 will remain in hospital or stay in the vicinity of the sites for 24 hours for PK sampling and assessment of parasitemia (see Table 2). Participants randomized to Cohort 4, will visit the clinic on Days 1, 2, and 3 for dosing in an outpatient setting
Timepoint	**Prescreening**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Week 2 to 9 (weekly visits starting at Day 8)**	**EOS (last visit)** **Week 10, Day 64[b]**	**Can be required due to AEs, and AESIs; follow-up of AEs and AESIs**	[b] Day 64 or day of completion or premature discontinuation. Participants will remain in the study until parasitemia or until Day 64, whichever comes first. All EOS evaluations will be completed before providing antimalarial rescue treatment if required.
Rescue treatment		As per national treatment guidelines or medical judgment							All EOS evaluations will be completed before providing antimalarial rescue treatment, if required. Asymptomatic reinfections will be managed as per national guidelines or medical judgment
Malaria and severe malaria signs and symptoms		X	X	X	X	X	X		
CCI [redacted]		[redacted]			[redacted]	[redacted]	[redacted]		[redacted]
Gametocytemia		X (predose)	X (predose)	X (predose)	X	X	X		Samples will be taken predose and at every visit.

Assessments & Procedures	Outpatient	Outpatient/ Inpatient[a]		Outpatient					Notes
Visit Number	**Prescreening**	**Scr + Visit 1[a]**	**Visit 2[a]**	**Visit 3**	**Visit 4**	**Visits 5 to 12**	**Visit 13**	**Unscheduled Visit**	[a] Visit 1 and 2: Participants randomized to Cohorts 1 to 3 will remain in hospital or stay in the vicinity of the sites for 24 hours for PK sampling and assessment of parasitemia (see Table 2). Participants randomized to Cohort 4, will visit the clinic on Days 1, 2, and 3 for dosing in an outpatient setting
Timepoint	**Prescreening**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Week 2 to 9 (weekly visits starting at Day 8)**	**EOS (last visit)** **Week 10, Day 64[b]**	**Can be required due to AEs, and AESIs; follow-up of AEs and AESIs**	[b] Day 64 or day of completion or premature discontinuation. Participants will remain in the study until parasitemia or until Day 64, whichever comes first. All EOS evaluations will be completed before providing antimalarial rescue treatment if required.
PK blood sampling for M5717		X[f]	X[f]	X	X	X			[f] PK blood samples: The exact sampling timepoints at Days 1 to 2 are provided in Table 2. Not applicable for Cohort 4.
PK blood sampling for pyronaridine		X[g]	X[g]	X	X	X			[g] PK blood samples: The exact sampling timepoints at Days 1 to 2 are provided in Table 2. Not applicable for Cohort 4.
CCI [redacted]		[redacted]							[redacted].

AE = adverse event, AESI = adverse event of special interest, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, AT = aminotransferase, CNS = central nervous system, COVID-19 = Corona virus Disease 2019, DILI = drug-induced liver injury, DMFA = direct membrane feeding assay, ECG = electrocardiogram, EOS = end of study, PK = pharmacokinetic(s), QTcF = corrected QT interval by Fridericia's formula, RDT = rapid diagnostic test, RT-qPCR = real-time quantitative reverse transcription polymerase chain reaction, Scr = screening, SmPC = Summary of Product Characteristics, TB = total bilirubin, ULN = upper limit of normal.

Table 2 Pharmacokinetics and Blood Films: Sampling Timepoints on Days 1 and 2 – Cohorts 1 to 3

Assessment									**Notes**
Visit	**1**							**2**	
Day	**1**							**2**	**For subsequent PK blood sampling for M5717and pyronaridine refer to Table 1**
Window		**± 5min**	**± 10 min**	**± 20 min**	**± 30 min**	**± 30 min**	**± 60 min**	**± 120 min**	
Hours after M5717 + pyronaridine dose	**Pre**	**1h**	**2h**	**4h**	**6h**	**8h**	**12h**	**24h**	
PK blood sampling for M5717	X	X	X	X	X	X	X	X	Not applicable for Cohort 4.
PK blood sampling for pyronaridine	X	X	X	X	X	X	X	X	Not applicable for Cohort 4.
Blood films (microscopy)	X	X			X		X	X	Not applicable for Cohort 4.

PK = pharmacokinetic(s).

2 Introduction

M5717 is a first-in-class NCE targeting the *Plasmodium* cytosolic protein synthesis "Elongation Factor 2" for the treatment and prevention of malaria due to the activity in the liver and blood stage of the parasite life cycle.

Pyronaridine tetraphosphate is an antimalarial drug marketed in combination with artesunate as Pyramax for which the CHMP adopted a positive scientific opinion in accordance with Art 58 of (EC) Regulation 726/2004 on 16 February 2012. Pyronaridine is a drug that interferes with the digestive system of *P. falciparum* and *P. berghei* and inhibits the production of complexes with β-hematin to enhance hematin-induced human blood cell lysis (Croft 2012).

M5717 and pyronaridine are intended to be developed as a fixed-dose combination for either the treatment of acute uncomplicated malaria or for the prevention of symptomatic malaria in populations living in endemic areas. The initial step of the clinical development plan of the combination is to generate initial safety, efficacy, and exposure data in symptomatic malaria patients and asymptomatic, malaria-infected individuals through the conduct of 2 Phase 2a PoC studies (CAPTURE-1 and CAPTURE-2) to prioritize the final indication for Phase 2b and Phase 3.

There is a clear need to accelerate the development of dedicated drug combinations for malaria prevention. A reduction of > 50% of malaria cases was observed in regions where malaria preventive treatments were systematically applied (Cairns 2012) leading to a significant reduction in mortality in the population. WHO has recently published new treatment policies to reinforce the use of chemoprevention (WHO Guidelines for Malaria, 2022), which combined with the increasing development of resistance against the 2 main standards of care, highlights the need for dedicated new therapies.

This study aims to leverage on the liver and blood stage activity of M5717, to develop for the first time a malaria drug combination directly intended for prevention, such as SMC and iPT. The study will open the path to develop a combination where the doses of the respective partner drug will have been selected based on preventive efficacy, exposure, and safety. Detailed information on the chemistry, pharmacology, efficacy, and safety of M5717 and pyronaridine is in the respective IBs.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

2.2 Background

Human malaria is an acute febrile infection caused by Plasmodium parasite species especially P. falciparum, P. vivax, P. malariae, P. ovale, and P. knowlesi. According to the latest estimates, there were about 247million cases of malaria and an estimated 619,000 deaths worldwide in 2022 (WHO Malaria Report, 2022). Most deaths (77%) occur among children < 5 years of age, most of them living in sub-Saharan Africa.

Prevention of clinical malaria or infection is one of the key strategies to decrease the malaria burden. For this purpose, there is a limited number of medications available for use in high-risk populations in malaria endemic areas. Most efforts in malaria drug development have focused on case management; the development of new treatments targeting prevention and transmission are becoming increasingly important. The latest WHO report has highlighted for the first time in decades a rise in the number of malaria cases and deaths, highlighting, and reinforcing the need for innovative approaches for prevention and treatment.

SMC, consisting of providing a full treatment at monthly intervals in areas where transmission is highly seasonal, has been endorsed since 2012 by the WHO Technical Expert Group on Preventive Chemotherapy and has resulted in a significant decrease of malaria morbidity among children under 5. The current standard for SMC is the combination SPAQ that is administered over 3 days every month for 3 to 4 months. In a systematic review (Meremikwu 2012), SMC with SPAQ was directly compared with no treatment in 7 studies with a total of 12,589 children. All studies were conducted in West Africa, and 6 of 7 studies were restricted to children < 5 years of age. In comparison with no intervention, SMC:

- prevented up to 75% of malaria episodes (rate ratio, 0.26; 95% CI, 0.17;0.38; 6 studies, 9,321 participants),
- prevented up to 75% of severe malaria episodes (rate ratio, 0.27; 95% CI, 0.10;0.76; 2 studies, 5,964 participants), and
- may reduce mortality (risk ratio, 0.66; 95% CI, 0.31;1.39; 6 studies, 9,533 participants).

These recent successes observed with chemopreventive therapies, as well as the RTS,S vaccine, led the WHO to publish new guidelines and policies emphasizing the central role of chemoprevention and elimination strategies (interventions in the final phase of elimination and prevention of re-establishment) (WHO Guidelines for Malaria, 2022). New targeted indication or use-cases have been defined. Different combination drugs should be used for treatment and prevention in a defined region. Chemoprevention strategies include the intermittent preventive treatment of malaria in pregnancy, perennial malaria chemoprevention (PMC), SMC, intermittent preventive treatment in school aged children, postdischarge malaria chemoprevention and mass

drug administration for malaria burden and transmission reduction, and mass relapse prevention. The last 2 interventions apply to the entire population including adults and adolescents.

To date, all drugs available for chemoprevention have been developed and registered for the treatment of uncomplicated malaria and were then repositioned for malaria prevention. To support the ambitious goal of the WHO to eliminate malaria and to address a large unmet medical need, there is a demand for accelerating the development of new antimalaria drugs such as M5717 with preventive, prophylactic, and transmission blocking potential.

M5717 is a Merck compound with a potent and novel spectrum of antimalarial activity against multiple lifecycle stages of the Plasmodium parasite (Baragaña 2015). M5717 is an inhibitor of the PeEF2 that is involved in protein synthesis in all parasite lifecycle stages. Pyronaridine is a synthetic antimalarial drug first synthesized in China in 1970 that targets hematin formation by inhibiting β-hematin production and facilitating the accumulation of toxic hematin in the digestive vacuole of the parasite (Croft 2012, Bailly 2021).

Recent nonclinical in vitro and in vivo studies of the combination of M5717 and pyronaridine showed a positive interaction between the 2 drugs (Rottmann 2020). The chemopreventive activity of M5717 alone was assessed in a clinical, sequential, double-blind, randomized, placebo-controlled *P. falciparum* sporozoite challenge study (Study MS201618_0003). Single different doses of M5717 administered after direct venous inoculation of *P. falciparu*m sporozoites to healthy adult malaria-naïve participants demonstrated a full protective effect at 100 mg and 200 mg, while at lower doses a delayed time to parasitemia was shown compared to placebo.

The efficacy, safety, and exposure of the combination of M5717 and pyronaridine in African adults and adolescent patients with acute uncomplicated malaria will be evaluated in a parallel Phase 2a study (Study MS201618_0033 [CAPTURE 1]).

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of M5717, pyronaridine, and atovaquone-proguanil hydrochloride (Malarone) may be found in Section 4.2 and the respective IBs (M5717, pyronaridine) and SmPC (Malarone).

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

CCI [redacted]

2.3.2 Benefit Assessment

The combination of M5717 plus pyronaridine has never been used in patients with asymptomatic *P. falciparum* malaria. There is evidence supporting the efficacy and safety of pyronaridine, as it is a component of Pyramax (artesunate-pyronaridine combination). Pyramax received a positive opinion in 2012 from the EMA and is currently recommended by the WHO as standard of care for the treatment of acute uncomplicated malaria. Pyramax has been evaluated in a study in The Gambia showing positive outcomes in terms of protection at Day 64 in asymptomatic *P. falciparum* malaria patients at 1-, 2-, and 3-day treatment regimens (Dabira 2022).

The combination of M5717 and pyronaridine will be assessed in parallel at higher doses in the Phase 2a Study MS201618_0033 (CAPTURE-1) for the treatment of acute uncomplicated malaria patients. In CAPTURE-1, the blood stage efficacy, safety, and exposure will be assessed and closely monitored through a staggered dose-increase strategy with intermediate assessment by a DMC. The same DMC will closely monitor the safety of CAPTURE-2.

There is no routine screening for asymptomatic malaria. Hence, most patients and their attending healthcare providers are unaware of the condition, unless it is identified as an incidental finding in the context of other investigations. Given that there is currently no recommendation for the medical management of this condition, the current study's SoA (see Section 1.3) and follow-up procedures provide a level of care that is beyond what patients would normally receive.

2.3.3 Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk in participants in this study, the potential risks identified in association with M5717 and pyronaridine are justified by the anticipated benefits that may be afforded to adult and adolescent participants with asymptomatic *P. falciparum* malaria.

3 Objectives and Estimands

Objectives	Estimands/Endpoints	Ref. #
Primary		
To evaluate the time of protection of different doses of M5717 in combination with pyronaridine in adults and adolescents with asymptomatic falciparum malaria compared with the natural incidence of infection as measured in Cohort 4	**Endpoint:** Time to parasitemia since negative blood smear after treatment **Population:** Asymptomatic adult and adolescent patients infected with *P. falciparum* **Treatment:** • Single dose 60 mg M5717 plus 720 mg pyronaridine (≥ 65 kg) or 540 mg pyronaridine (≥ 45 to < 65 kg) (Cohort 1) • Single dose 200 mg M5717 plus 720 mg pyronaridine (≥ 65 kg) or 540 mg pyronaridine (≥ 45 to < 65 kg) (Cohort 2) • Single dose 660 mg M5717 plus 720 mg pyronaridine (≥ 65 kg) or 540 mg pyronaridine (≥ 45 to < 65 kg) (Cohort 3)	1

Objectives	Estimands/Endpoints	Ref. #
	• 3 doses of Malarone (1,000 mg atovaquone plus 400 mg proguanil hydrochloride [proguanil]) to clear all parasites to measure the natural incidence of infection (Cohort 4) **Intercurrent Event Strategy:** • Intake of rescue medication: composite variable strategy, i.e. endpoint is considered as failure (=positive blood smear at the time of rescue medication intake) • Intake of antibiotics or other prohibited medication that impacts treatment effect (e.g. drug with antimalarial activity) at any timepoint: On-treatment strategy, i.e. time to parasitemia is censored at the time of antibiotics or prohibited medication intake • Experience of any event that affects absorption (e.g. vomiting within the first 24 hours after dosing): Treatment policy strategy, i.e. treatment effect is estimated regardless of ICE. • Death due to malaria: Composite variable strategy • Death due to other reasons: On-treatment strategy, i.e. time to parasitemia is censored at the time of death **Population-Level Summary:** HRs estimated from Cox' Proportional Hazards Model for each dose of M5717 relative to Cohort 4	
Secondary		
To further evaluate the time of protection of different doses of M5717 in combination with pyronaridine in adults and adolescents with asymptomatic falciparum malaria compared with the natural incidence of infection as measured in Cohort 4	**Endpoint:** Incidence of parasitemia (positive blood smear). **Population:** See primary endpoint **Treatment:** See primary endpoint **Intercurrent Event Strategy:** • Intake of rescue medication: composite variable strategy, i.e. endpoint is considered as failure (=positive blood smear at the time of rescue medication intake) • Intake of antibiotics or other prohibited medication that impacts treatment effect (e.g. drug with antimalarial activity) at any timepoint: On-treatment strategy, i.e. time to parasitemia is censored at the time of antibiotics or prohibited medication intake • Experience of any event that affects absorption (i.e. vomiting within the study intervention absorptive period of 2 x median t_{max}): Treatment policy strategy, i.e. treatment effect is estimated regardless of ICE • Death due to malaria: Composite variable strategy • Death due to other reasons: On-treatment strategy, i.e. time to parasitemia is censored at the time of death **Population-Level Summary:** Proportion of participants with parasitemia using Kaplan-Meier estimates for each dose of M5717 and for each cohort	2
	Endpoint: Incidence of PCR-adjusted parasitemia (thick smear/microscopy, after adjustment for parasitemia due to new infections as determined by genotyping using PCR techniques). **Population:** See primary endpoint **Treatment:** See primary endpoint **Intercurrent Event Strategy:** See Endpoint #2	3

Objectives	Estimands/Endpoints	Ref. #
	Population-Level Summary: See Endpoint #2	
	Endpoint: Incidence of PCR-adjusted parasitemia (thick smear/microscopy, after adjustment for parasitemia due to recrudescence as determined by genotyping using PCR techniques). **Population:** See primary endpoint **Treatment:** See primary endpoint **Intercurrent Event Strategy:** See Endpoint #2 **Population-Level Summary:** See Endpoint #2	4
To evaluate the parasite clearance time in adults and adolescents with asymptomatic falciparum malaria treated with different doses of M5717 in combination with pyronaridine	**Endpoint:** Parasite clearance time defined as time from dosing to the first negative (no parasites) blood film (microscopy) **Target Population:** See primary endpoint **Treatment:** See primary endpoint **Intercurrent Event Strategy:** See Endpoint #2 **Population-level Summary:** Median parasite clearance time as estimated by Kaplan-Meier method for each dose of M5717	5
To evaluate the safety and tolerability of different doses of M5717 in combination with pyronaridine in adults and adolescents with asymptomatic falciparum malaria	**Endpoint**: Incidence, severity, and seriousness of TEAEs, treatment-emergent study intervention related AEs, as per CTCAE v 5.0	6
To characterize the PK profile of the M5717-pyronaridine combination	PK parameters of M5717 and pyronaridine using noncompartmental analysis, as appropriate.	7

4 Study Design

4.1 Overall Design

Study Design	Phase 2a, PoC, parallel, randomized, open label study (see Section 1.2)
Control Method	• Randomization • Incidence rate of infection • Synthetic control cohort (Pyramax)
Single or Multicenter	Multicenter
Study Population Type	Adult and adolescent patients ≥ 12 to ≤ 55 years of age with asymptomatic *P. falciparum* malaria

Level and Method of Blinding	Open label
Bias Minimalization Method(s)	Evaluators blinded (microscopists and laboratory personnel performing the microscopy and PCR)
Study Intervention Assignment Method	Randomization stratified by site
Data and Safety Monitoring /Other Committee:	Yes (see Appendix 3)
Total Duration of Study Participation per Participant	A maximum of 12 weeks (including a prescreening period of a maximum of 2 weeks). See Section 1.3. Participants randomized to Cohorts 1 to 3 will be treated with a single dose of M5717 plus pyronaridine. Participants randomized to Cohort 4 will be treated with 3 daily and consecutive doses of Malarone. Participants will be followed up until Day 64 (Week 10) or until recurrent infection, whichever occurs first. Cohort 5 is a synthetic control cohort using external data from a completed clinical study that investigated the efficacy, safety, and tolerability of Pyramax in asymptomatic *P. falciparum* malaria patients (Dabira 2022). Data from participants treated with the 1-day Pyramax regimen and followed up until Day 64 will be used.
DMFA Substudy	The gametocidal activity of the M5717- pyronaridine combination will be assessed in vivo at selected sites (see Appendix 2)
Provisions for Study Extension or Entry into Roll-over Studies	Not applicable.

Adaptive Aspects of Study Design	Safety stopping criteria: If one of the criteria is met, the current study will be put on hold until it has been established that the benefit-risk of the combination is optimal 1. Liver toxicity signals: > 1 participant present any of the following criteria: a. Presence of Hy's law criteria (ALT and/or AST > 3 × ULN, and elevation of serum TB to > 2 × ULN, without initial findings of cholestasis [elevated serum ALP], with no other reason to explain the combination of increased transaminases and TB). b. CTCAE v5.0 ≥ Grade 3 ALT or AST increases, that do not return to normality or below 1.5 × the ULN at the end of follow-up (28 days after first treatment). c. CTCAE v5.0 ≥ Grade 3 ALT or AST increases accompanied by posttreatment established coagulation disorder at any time (INR ≥ 1.5) not related to another underlying condition. 2. CNS signals: a. if ≥ 1 participant present persistent severe study intervention-related CNS disorders considered AEs that do not resolve within 2 weeks after the onset, or b. if ≥ 2 participants present persistent severe study intervention-related CNS AEs irrespectively of the recovery status, or c. if ≥ 1 participants experience a serious study intervention-related CNS AE. 3. SUSAR Grade 4 or higher according to the CTCAE v5.0.

4.2 Scientific Rationale for Study Design

M5717 is active against all dividing stages of the malaria parasites, including both blood and liver stages. This unique feature allows the development of this molecule for both malaria therapy and prevention. The current study aims to provide initial information on parasite clearance in asymptomatic malaria-infected individuals and the duration of protection. This information will be collected by testing M5717 in combination with pyronaridine in asymptomatic carriers of *P. falciparum.*

The outcome of this study will determine if the M5717 plus pyronaridine combination is suitable for further development as monthly chemoprevention as defined in the WHO malaria treatment guidelines (WHO Guidelines for Malaria, 2022). The main objective of the current Phase 2a study is to assess for how long the combination will prevent the appearance of parasites in the peripheral blood (microscopy) of asymptomatic malaria-infected individuals. This will support the definition

of the optimal dose regimen (dosing interval and dosing frequency of the combination) for Phase 2b and Phase 3 studies.

The duration of chemoprevention will probably be influenced by multiple factors, including the liver and blood stage activity of M5717 and the blood stage activity of pyronaridine. 3 different doses of M5717 will be evaluated in combination with pyronaridine (dosed according to SmPC). The intention is to better understand the contribution of M5717 to the combination, in extending the duration of protection against new parasite infections after treatment. The robust nature of the primary endpoint permits an open label design, although the laboratory personnel evaluating the blood samples will be blinded to the study intervention.

The contribution of M5717 alone to the duration of protection will be further investigated by a synthetic control cohort (Cohort 5) using the data from a clinical study (ClinicalTrials.gov Identifier: NCT03814616) comparing 1- to 3-day treatment regimens of Pyramax (fixed-dose combination tablets of 180 mg pyronaridine and 60 mg artesunate). Artesunate has a short half-life (Morris 2011) and, therefore, the long-term protective effect against parasite reappearance is most likely due to pyronaridine. The additional effect of M5717 on the time to parasitemia can be assessed by matching the data of this Phase 2a study with the data of the 1-day regimen arm; for a methodological description see Section 9. In order to make the use of external data feasible, key aspects of the design of this Phase 2a study were aligned with those of the external study wherever possible (e.g. inclusion-/exclusion criteria, time points of assessments).

In 1 trial arm, participants will be treated with Malarone (Cohort 4) to determine the natural incidence of infection in the different study areas. Malarone is a fixed-dose combination of atovaquone and proguanil with antimalarial activity on liver and blood stages; half-lives of the components are short (2 to 3 days for atovaquone and approximately 1 day for proguanil; see SmPC for details). Participants in Cohort 4 will receive Malarone on 3 consecutive days to clear all parasites to simulate a cohort of uninfected patients without drug protection after a couple of days. Alternatively, the natural incidence of infection could be evaluated retrospectively using existing epidemiological data. However, the drawback of this approach is that infection rates vary significantly by year. Another alternative to the Malarone cohort could be that noninfected adults and adolescents could be recruited into the study. However infected individuals are more likely to be reinfected for various reasons. Including positive individuals will increase the probability of having parasitemia during the time of follow up. Considering the drawbacks of the alternative approaches mentioned, Malarone treatment was chosen as the most appropriate option to assess the natural infection rates.

Utilization of an active control cohort consisting of either SPAQ or any other ACTs would not be appropriate at the current stage of clinical development as these drug combinations would all provide protection over 3 weeks against recurrent infections. The currently available data are not sufficient to support repeated M5717 plus pyronaridine dose regimens; indeed, definition of the dose regimen is the purpose of the current study.

CCI [redacted] The study population of adults and adolescents has been selected based on the expected safety profile of the M5717 plus pyronaridine

combination as well as the safety profile of M5717 in healthy volunteers. Pyronaridine is approved for children weighing ≥ 20 kg and adults in combination with artesunate (Pyramax SmPC). Safety of adults and adolescents will be ensured by multiple risk mitigation measures (e.g. safety monitoring, entry criteria, DMC, predefined AESIs). It is well known that over time malaria patients develop protective immunity, and the risk of clinical malaria decreases with age. Severe malaria, at least in countries where transmission is moderate, is extremely rare in adolescents and adults.

The study interventions M5717 and pyronaridine will be administered as single doses based on the long-lasting activity of the M5717-pyronaridine combination, thereby potentially improving the dosing regimen currently considered as standard of care for SMC, which currently requires a 3-day treatment.

The scientific rationale for the substudy is provided in Appendix 2.

4.2.1 Participant Input into Design

Not applicable.

CCI [redacted]

[redacted]

4.4 End of Study Definition

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

A participant has completed the study if he/she has completed all the study visits including the last visit or the last scheduled procedure shown in Section 1.3. If a participant has recurrent parasitemia

before the end of follow-up (Day 64, Week 10), they will attend the EOS Visit and will be considered as having completed the study.

5 Study Population

The study population consists of African adults and adolescents ≥ 12 years old, with asymptomatic *P. falciparum* infection. Potential participants will be identified by screening the local population for malaria.

The criteria in Sections 5.1 and 5.2 are designed to enroll only individuals who are appropriate for the study; thereby, ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions are considered when deciding whether an individual is suitable for this study. Eligibility criteria for the substudy are provided in Appendix 2.

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 individual's routine medical care, the Investigator will confirm that the individual has provided written informed consent, as indicated in Appendix 3.

5.1 Inclusion Criteria

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

Category	Criterion
Age	1. Are ≥ 12 and ≤ 55 years of age at the time of signing the informed consent.
Type of Participant and Disease Characteristics	2. Are patients with asymptomatic *P. falciparum* malaria with no fever or other sign of acute uncomplicated malaria and, with microscopic confirmation using Giemsa-stained thick film, and a parasitemia of ≥ 40 to ≤ 10,000 asexual parasites/μL of blood. 3. Axillary temperature < 37.0ºC or oral/tympanic/rectal temperature < 37.5ºC; without history of fever during the previous 48 hours.
Weight	4. Have a body weight ≥ 45 kg.

Sex and Contraception/ Barrier Requirements	5. "All sexes allowed" The Investigator confirms that each participant agrees to use appropriate contraception and barriers, if applicable. The contraception, barrier, and pregnancy testing requirements are below. Contraceptive use will be consistent with local regulations on contraception methods for those participating in clinical studies. **Male study participants:** Agree to the following during M5717, pyronaridine, or Malarone study intervention period and for ≥ 120 days after the last dose of study intervention: a. Refrain from donating fresh unwashed semen PLUS, either: b. Abstain from intercourse with a partner of childbearing potential. **OR** c. Use an external condom: o When having sexual intercourse with a partner of childbearing potential, who is **not** currently pregnant, and instruct the partner to use a highly effective contraceptive method with a failure rate of <1% per year, as described in Appendix 4, since a condom may break or leak. **Female study participants:** o Is **not** breastfeeding. o Is **not** pregnant (i.e. has a negative serum pregnancy test, as required by local regulations, within 24 hours before the first dose of M5717, pyronaridine, or Malarone). o Is not a POCBP. **OR** o If a POCBP, uses a highly effective contraceptive method (i.e. with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 4: 1. Before the first dose of the M5717, pyronaridine, or Malarone, if using hormonal contraception: o Has completed ≥ one 4-week cycle of an oral contraception pill and either had or has begun her menses; **OR**, o Has used a depot contraceptive or extended-cycle oral contraceptive ≥ 28 days and has a documented negative pregnancy test using a highly sensitive assay. 2. During the M5717, pyronaridine, or Malarone period. 3. After the study intervention period (i.e. after the last dose of M5717, pyronaridine, or Malarone is administered) for ≥ 62 days, corresponding to the time needed to eliminate

Category	Criterion
	any study intervention(s) (5 terminal half-lives of 155 hours) plus 30 days (a menstrual cycle) after the last dose of M5717, pyronaridine, or Malarone (and agree not to donate eggs [ova, oocytes] for reproduction during this period). The Investigator evaluates the effectiveness of the contraceptive method in relationship to the first dose of M5717, pyronaridine, or Malarone. The Investigator reviews the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a participant with an early undetected pregnancy.
Informed Consent	6. Are capable of giving signed informed consent, as indicated in Appendix 3, which includes compliance with the requirements and restrictions listed in the ICF and this protocol.

5.2 Exclusion Criteria

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

Category	Criterion
Medical Conditions	1. Any condition, including any uncontrolled disease state other than asymptomatic *P. falciparum* malaria, that in the Investigator's opinion constitutes an inappropriate risk or a contraindication for participation in the study or that could interfere with the study objectives, conduct, or evaluation. 2. Known history or evidence of clinically significant disorders such as: cardiovascular, respiratory (including active tuberculosis), hepatic, renal, gastrointestinal, immunological (including known HIV-AIDS), neurological (including auditory), endocrine, infectious (including COVID-19), malignancy, psychiatric, history of convulsions, or other abnormality (including head trauma). 3. Any disease requiring chronic treatment. 4. Preplanned surgery during the study. 5. Mixed *Plasmodium* infections as per thin film microscopy results. 6. Known liver abnormalities, liver cirrhosis (compensated or decompensated), known active or history of hepatitis B or C (testing not required), underlying hepatic injury or known

Category	Criterion
	severe liver disease, known gallbladder, or bile duct disease, acute or chronic pancreatitis, or severe malnutrition.
Prior/Concomitant Therapy	7. Previous treatment with pyronaridine as part of a combination therapy during the last 3 months. 8. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days or until the expected PD effect has returned to Baseline, whichever is longer. 9. Prior antimalarial therapy or antibiotics with antimalarial activity within a minimum of their 5 plasma half-lives (or within 4 weeks of screening if half-life is unknown). 10. Patients taking medications prohibited by the protocol.
Prior/Concurrent Clinical Study Experience	11. Previous participation in any malaria vaccine study or received malaria vaccine in any other circumstance during the last 3 months.
Diagnostic Assessments	12. Serum creatinine levels ≥ 2 × ULN. 13. AST and/or ALT > 1.5 × ULN, regardless of the level of TB. 14. AST/ALT > 1.0 and ≤ 1.5 × ULN and TB is > 1.5 × ULN. 15. TB > 2 × ULN, regardless of the level of AST/ALT. 16. A marked Baseline prolongation of QTc interval > 450 msec applying the Fridericia's correction. 17. Known disturbances of electrolyte balance, ≥ Grade 2 according to the CTCAE v5.0, e.g. hypokalemia, hypocalcemia, or hypomagnesemia. 18. Moderate to severe anemia (hemoglobin level < 8 g/dL). 19. Severe malnutrition as reflected by a mid-upper arm circumference < 18 cm for adolescents (Hadush 2021) or defined as a BMI < 18.5 kg/m^2 for adults. 20. Severe vomiting, defined as > 3 times in the 24 hours prior to enrollment in the study or inability to tolerate oral treatment, or severe diarrhea defined as ≥ 3 watery stools per day.
Other Exclusions	21. Known history of hypersensitivity, allergic or adverse reactions to pyronaridine or M5717; contraindications to atovaquone and/or proguanil (Malarone SmPC).

Category	Criterion
	22. Known history or current substance abuse.

5.3 Lifestyle Considerations

Participants will be required to adhere to the COVID-19 measures and procedures outlined in the site-specific COVID-19 SOPs.

5.3.1 Meals and Dietary Restrictions

Participants will abstain from consuming 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 final dose.

Participants will not be allowed food or water from 2 hours prior until 2 hours after study intervention dose (4 hours in total).

5.3.2 Caffeine, Alcohol, Tobacco, and Cannabinoid

During each dosing period, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g. coffee, tea, cola drinks, and chocolate) for 8 hours before the start of dosing until after collection of the final PK and/or PD sample.

During each dosing period, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and/or PD.

During each dosing period, participants will abstain from cannabinoid-containing products for 24 hours before the start of dosing until after collection of the final PK and/or PD.

Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinical unit.

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).

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

5.5 Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

Not applicable.

6 Study Intervention(s) and Concomitant Therapies

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(s) Administered

Intervention Name	M5717	Pyronaridine tetraphosphate	Atovaquone – proguanil hydrochloride
Intervention Description	On Day 1 participants will receive a single dose of M5717 of either 60, 200, or 660 mg in loose combination with a single dose of pyronaridine	On Day 1 participants will receive a single dose of 720 mg (participants ≥ 65 kg) or 540 mg (participants ≥ 45 to < 65 kg) pyronaridine irrespective of the dose of M5717	Participants in Cohort 4 will receive 3 doses of atovaquone – proguanil on Days 1, 2, and 3
Type	Drug	Drug	Drug
Dose Formulation	Capsules* (containing granules to be dispersed in water) *M5717 dose formulation is capsules, containing granules to be dispersed in water; it is also referred as hard capsules or sprinkle capsules.	Tablet	Tablet
Unit Dose Strength(s)	100 mg capsules, 30 mg capsules	180 mg tablets	250/100 mg fixed-dose combination
Dose	60 mg, 200 mg, 660 mg	720 mg, 540 mg	1,000/400 mg
Dosage Regimen	1 day treatment regimen	1-day treatment regimen	3-day treatment regimen (4 tablets per day)
Route of Administration	Oral, fasting condition	Oral, fasting condition	Oral
Use	Experimental	Experimental	Control
IMP or NIMP/AxMP	IMP	IMP	IMP
Sourcing	M5717 will be provided by the Sponsor	Pyronaridine to be supplied by Shin Poong Pharmaceuticals	Atovaquone proguanil will be provided by the Sponsor; sourced via qualified vendor/CDMO.
[redacted]	CCI [redacted]	[redacted]	[redacted]

Intervention Name	M5717	Pyronaridine tetraphosphate	Atovaquone – proguanil hydrochloride
Current/Former Name(s) or Alias(es)	M5717: MSC2576186A		Atovaquone-proguanil; Malarone

Study Arm(s)

Arm Name	Single dose 60 mg M5717 plus 720 mg (participants ≥ 65 kg) or 540 mg (participants ≥ 45 to < 65 kg) pyronaridine	Single dose 200 mg M5717 plus 720 mg (participants ≥ 65 kg) or 540 mg (participants ≥ 45 to < 65 kg) pyronaridine (Cohort 2)	Single dose 660 mg M5717 plus 720 mg (participants ≥ 65 kg) or 540 mg (adolescents) pyronaridine (participants ≥ 45 to < 65 kg) (Cohort 3)	3 doses of 1,000 mg/ 400 mg atovaquone – proguanil on 3 consecutive days (Cohort 4)
Arm Type	Experimental	Experimental	Experimental	Control
Arm Description	Participants randomized to Cohort 1 will receive a single dose of 60 mg M5717 and a single dose of 720 mg (participants ≥ 65 kg) or 540 mg (participants ≥ 45 to < 65 kg) pyronaridine in loose combination. Participants will be followed up until detection of parasitemia since parasite clearance defined as positive parasite blood smear or until Day 64, whichever comes first.	Participants randomized to Cohort 2 will receive a single dose of 200 mg M5717 and a single dose of 720 mg (participants ≥ 65 kg) or 540 mg (participants ≥ 45 to < 65 kg) pyronaridine in loose combination. Participants will be followed up until detection of parasitemia since parasite clearance defined as positive parasite blood smear or until Day 64, whichever comes first.	Participants randomized to Cohort 3 will receive a single dose of 660 mg M5717 and a single dose of 720 mg (participants ≥ 65 kg) or 540 mg (participants ≥ 45 to < 65 kg) pyronaridine in loose combination. Participants will be followed up until detection of parasitemia since parasite clearance defined as positive parasite blood smear or until Day 64, whichever comes first.	Participants randomized to Cohort 4 will receive 3 doses of 1,000/400 mg atovaquone - proguanil on 3 consecutive days. Participants will be followed up until detection of parasitemia since parasite clearance defined as positive parasite blood smear or until Day 64, whichever comes first to define the natural incidence of infection at the study sites.
Associated Intervention Labels	M5717 plus pyronaridine	M5717 plus pyronaridine	M5717 plus pyronaridine	Malarone

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 will 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 Study Reference Manual.
- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply it. All study intervention(s) will be stored in a secure, environmentally controlled, and monitored (manual or automated) area, per the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- For preparation and administration detailed guidance and information are provided in the Pharmacy manual.
- 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) will not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be redispensed 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 Study Reference Manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

Participants will be randomly assigned to Cohorts 1, 2, 3, or 4. Randomization to the cohorts will be stratified by site with a ratio of 1:1:1:1 to Cohorts 1, 2, 3, and 4 using a computer-generated randomization list integrated in the electronic data capturing system. Randomization lists will be generated by using randomization blocks of appropriate size.

Participants will be assigned a unique number (randomization number) in ascending numerical order at each study site. The randomization number encodes the participant's assignment to 1 of the 4 cohorts of the study, per the randomization schedule generated prior to the study. Open label study intervention will be labeled with a unique medication number.

6.3.2 Blinding

This study will be open label.

Microscopists and laboratory personnel performing the microscopy and PCR will be blinded to minimize bias.

6.4 Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, a second member of the study site staff will confirm the dose preparation.

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. A member of the study site staffs other than the person administering the study intervention will confirm the study intervention dose and study participant identification at the time of dosing. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5 Dose Modification

A single dose 60, 200, or 660 mg M5717 is selected as the dose to be evaluated in Cohorts 1, 2, and 3, respectively. This dose will be administered together with pyronaridine. The pyronaridine dose in Cohorts 1 to 3 will be based on participants' body weight: 720 mg pyronaridine for participants with a body weight ≥ 65 kg and 540 mg for participants with a body weight from ≥ 45 kg to < 65 kg.

Participants in Cohort 4 will be treated with 4 Malarone tablets (1,000 mg atovaquone and 400 mg proguanil) as a single dose for 3 consecutive days according to the SmPC.

Details on the justification for selecting the doses are provided in Section 4.3.

No dose modifications are permitted at the participant level. The DMC will have the option to recommend dose adjustments for pyronaridine. The DMC created for CAPTURE-1 will continue to monitor CAPTURE-2.

6.6 Continued Access to Study Intervention After the End of the Study

The Sponsor will **not** provide any additional care to participants after they leave the study because such care would not differ from what is normally expected for patients with asymptomatic *P. falciparum* malaria.

6.7 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 will be considered an overdose.

Even if not associated with an AE, SAE, or AESI, any overdose is recorded in the CRF and reported to global patient safety in an expedited manner. Overdoses are reported on an SAE and Overdose Report Form, following the procedure in Appendix 5.

The effects of a 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.

No case of overdosage with Pyramax has been reported. In cases of suspected overdosage symptomatic and supportive therapy should be given as appropriate, and transaminases (AST and ALT) should be monitored. If there are significant rises, then serial total and direct bilirubin values should also be obtained to determine whether there is any change in liver function.

There is insufficient experience to predict the consequences or suggest specific management of Malarone overdose. However, in the reported cases of atovaquone overdose, the observed effects were consistent with known undesirable effects of the drug (SmPC Malarone). If overdose occurs, the participant should be monitored, and standard supportive treatment applied.

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

6.8 Concomitant Therapy

Record in the CRF all concomitant therapies (e.g. medicines or nondrug interventions) used from the signing of the ICF until completion of the study at the timepoints specified in the SoA, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information. For nondrug interventions, record the name, the indication, and dates administered.

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

Participants will 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 5half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

Ibuprofen, at doses of ≤ 1,600 mg/24 hours, is permitted for use across the study. Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor if required. Paracetamol for fever is permitted when the temperature is ≥ 38.0°C.

6.8.1 Rescue Medicine

The following circumstances warrant discontinuation from the study and the implementation of rescue medication:

1. Development of acute uncomplicated *P. falciparum* malaria, or severe malaria in the presence of parasitemia at any time during the study.

2. Development of acute uncomplicated *P. vivax* or other species malaria in the presence of parasitemia at any time during the study.

3. Vomiting the replacement dose within 2 hours of intake. (Note: If the participant vomits a dose within 1 hour of intake it may be replaced once).

4. Asymptomatic parasitemia after administration of study intervention should be managed as per national treatment guidelines or medical judgment.

Rescue treatment involves therapy with an effective antimalarial available locally, either ACTs, or artesunate injection based on investigator assessment of severity of malaria symptoms. Administration may be orally or parenterally depending on the participant's clinical condition.

The exact rescue regimen and route of administration must be recorded in the CRF on the concomitant medication page together with the start and end dates of the rescue medication applied. These participants will not be replaced.

6.8.2 Permitted Medicines

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.

6.8.3 Prohibited Medicines

The following products are considered as prohibited medication during the participant's participation in the study:

1. Antimalarial compounds or products with antimalarial activity (macrolides, trimethoprim sulfamethoxazole, dapsone, rifampin, and cyclins) except for ophthalmic use (see Appendix 7).

2. Medicines with mitochondrial toxicity, such as valproate and antiretroviral medicines should be avoided due to risk of overlap toxicity (see Appendix 8; Will 2019).

3. Medicines with photosensitivity risk such as tetracycline, doxycycline, nalidixic acid, voriconazole, amiodarone, hydrochlorothiazide, naproxen, piroxicam, chlorpromazine, and thioridazine (see Appendix 9; Drucker 2011).

4. Strong CYP3A4 inducers or strong CYP3A4 inhibitors (FDA guidance for drug development and drug interactions 2020).

Participants will not be withdrawn from the study due to the use of prohibited medication and the follow-up will be completed.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the entire study is specified in Appendix 3.

7.1 Discontinuation of Study Intervention

Malarone will be administered on 3 consecutive days in line with the SmPC for Cure. Participants will be discontinued from Malarone treatment if they experience an allergic reaction. In this case Malarone should be discontinued promptly (SmPC Malarone). In the event of an allergic reaction, the Investigator or treating physician should use appropriate clinical judgment for the treatment. In case of symptomatic malaria at the time of Malarone discontinuation, participants will be treated with rescue medication at the discretion of the Investigator. The study interventions M5717 and pyronaridine cannot be discontinued since single doses will be administered in this study.

If study intervention is permanently discontinued, the participant will not remain in the study to be evaluated for parasitemia. The SoA indicates data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.2 Participant Discontinuation/Withdrawal from the Study

A participant may discontinue from the study at any time, at their own request or at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons (e.g. disruption of operations due to natural disasters, interruption of lab, or facility accreditation, participant moving to another country, resignation of key staff").

At the time of study discontinuation, 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.

If the participant revokes consent for 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.

If a participant requests the destruction of any biological samples still remaining, the Investigator will document this in the site study records and inform the Sponsor. The samples will be destroyed.

In case of safety events or laboratory abnormalities deemed clinically significant by the Investigator and related to the drug administration, participants might be followed up for the required period until the event is resolved or becomes stable, even if discontinuation from the study is applicable.

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 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 will be taken if a participant fails to return to the clinic for a required study visit:

The site will 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 will continue in the study.

Before a participant is deemed "lost to follow-up", the Investigator or designee will 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 or caretaker (where allowed by local regulations) for information. These contact attempts will be documented in the participant's medical record.

If the participant continues to be unreachable, he/she will be deemed as "lost to follow-up".

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the SoA.
- **No** protocol waivers or exemptions are allowed.

- Immediate safety concerns are discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant will 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 will 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 3.
- 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, were performed within the time frame defined in the SoA, and if reviewed, and approved by the Sponsor.
- About 180 mL of blood total will be taken throughout the study: approximately 130 mL for the main study and 50 mL for the DMFA substudy. Up to 38 mL of blood may be drawn at certain visits: approximately 26 mL for the main study and 12 mL for the DMFA substudy. Taking into consideration a potential 20% increase in blood volume due to unforeseen events leading to blood draws the total blood volume may reach a maximum of 220 mL per adult or adolescent participant. All efforts will be made to minimize blood volumes. These blood samples will be used for the following purposes: clinical laboratory tests, PK, CCI [redacted]
- Where allowed by local law/regulations, samples collected during this clinical study may be transferred to a biobank and used for future research outside the clinical protocol when additional consent for this purpose is given. Transfer to the biobank will be documented and any testing of coded biobank samples will **not** be reported in the CSR.
- The long-term storage of samples after study completion for future research may be performed will all sample types collected in the study (e.g. PK, CCI [redacted]) if the participant consents to optional future medical research.

8.1 Efficacy Assessments and Procedures

Assessment of Primary Efficacy Endpoint

The primary efficacy endpoint of the study is the time to parasitemia since negative blood smear after treatment. For endpoint assessment it will be irrelevant whether the recurrent parasite detected after treatment is genetically the same strain present at baseline or a new one.

Assessment of Secondary and CCI [redacted]

For the definitions of secondary and CCI [redacted] endpoints please refer to Table 3.

In addition to the time to parasitemia since negative blood smear after treatment, incidence of parasitemia or prevalence of gametocytes will be assessed and summarized as proportion of participants with parasitemia or gametocytemia. In addition to the primary analysis, the incidence of new infections and recrudescence will be assessed by PCR.

Assessments for the DMFA substudy are provided in Appendix 2.

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, 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.

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 64 [± 2 days]). At other time points an abbreviated physical examination will 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 specific neurological assessment will be performed including motor function and balance, sensory function, gait, coordination, reflexes (including osteotendinous and pupilar reflex), cranial nerves assessment (special attention to optic, oculomotor and trochlear) and mental status. This neurological physical examination will be done at Screening and at every visit.

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

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

Investigators will pay special attention to clinical signs of liver toxicity, e.g. jaundice.

8.2.2 Vital Signs

Vital signs will be measured in supine position at timepoints indicated in the SoA (Table 1).

Blood pressure and participant's position during measurement; pulse; respiratory rate; temperature and location of measurement, weight, and height (at Baseline only) will be measured and recorded.

Blood pressure and pulse measurements will be preceded by ≥ 5 minutes of rest for the participant in a quiet setting without distractions (e.g. television, cell phones) and measured with an automated device. Manual techniques will be used only if an automated device is not available.

At visits where multiple assessments and procedures are to be done at the same timepoint, the vital signs should be done before blood sampling for laboratory tests.

8.2.3 Electrocardiograms

12-lead ECG will be performed at Screening only as indicated in the SoA (Table 1).

Triplicate 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically measures heart rate, PR, RR, QRS, QT, and QTcF.

8.2.4 Clinical Safety Laboratory Tests

Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 10 at the timepoints listed in the SoA. All samples will 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

The tests will be performed by a local laboratory.

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 will review each laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE, unless it does **not** meet the AE definition, as specified in Appendix 5. The laboratory reports will be filed with the source documents.

Pregnancy testing (serum or highly sensitive urine) will be conducted as indicated in the SoA (see Section 1.3).

Additional serum or urine pregnancy testing may be conducted at any time during the study to establish the absence of pregnancy, at the Investigator's discretion or if local regulations require them.

8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting

- The definitions of an AE, SAE, and AESI are in Appendix 5.

- The Investigator and any qualified designees (e.g. Subinvestigators) are responsible for detecting, documenting, and recording events that meet the definition of an AE, SAE, or AESI. The Investigator remains responsible for following up all AEs, as specified in Section 8.3.2.
- Requests for follow-up will usually be made via the Sponsor or CRO-designated study team member, although in exceptional circumstances the global patient safety department may contact the Investigator directly to obtain further information or to discuss the event.
- The method of recording, evaluating, and assessing causality of AEs, SAEs, and AESIs and the procedures for completing and transmitting SAE reports are in Appendix 5.
- All AEs, SAEs, and AESIs will be collected from the signing of the ICF until the End of Study Visit at the timepoints specified in the SoA (Section 1.3). Beyond this reporting period, any new unsolicited SAEs that the Investigator spontaneously reports to the Sponsor will be collected and processed. 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".
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance will this exceed 24 hours, as indicated in Appendix 5. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available using the same procedure that was used for the initial report.
- Investigators are not obligated to actively solicit information on AEs, SAEs, or AESIs after the end of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator will promptly notify the Sponsor.

8.3.1 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 of who report it (by the participant or observed by the Investigator).

Care will be taken not to introduce bias when detecting AEs, SAE, and/or AESIs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

The method of recording, evaluating, and assessing causality of AEs, SAEs, and AESIs and the procedures for completing and transmitting SAE reports are in Appendix 5.

All SAEs must be additionally documented and reported using the appropriate Report Form as specified in Appendix 5.

8.3.2 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE/AESI report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs (as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Reasonable attempts to obtain this information will be made and documented. It is also the Investigator's responsibility to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is in Appendix 5.

8.3.3 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of an SAE (particularly life-threatening and deaths) is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

Individual Case Safety Reports will be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators within 15 days.

An Investigator or Subinvestigator who receives an Individual Case Safety Report describing a SUSAR or other specific safety information (e.g. Emerging Safety Issue Report, summary or listing of SAEs/SUSARs) from the Sponsor will read it and confirm completion of this activity. This information will be filed in the Investigator's Site File, and the IRB/IEC will be notified, if appropriate, according to applicable local laws/regulations and site SOPs.

8.3.4 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until ≥ 120 days for female partners of male participants and ≥ 62 days for female participants.
- If a pregnancy is reported, the Investigator will record the pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication, or elective termination of a pregnancy will be reported as an AE or SAE. Adverse pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered and reported as SAEs. A spontaneous abortion (occurring at < 22 weeks gestational age) or stillbirth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.

- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date for a healthy newborn. In case of a congenital anomaly or other illness of the newborn, follow-up will continue until the illness has resolved or there is a definite outcome of the event.
- Any post study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as specified in Section 8.3.3. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partner he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.
- Prior to continuation of study intervention following pregnancy, the following will occur:
  - The Sponsor and the relevant IRB/IEC give written approval
  - The participant gives signed informed consent
  - The Investigator agrees to monitor the outcome of the pregnancy and the status of the participant and her offspring

8.3.5 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

DREs and/or DROs should not be reported to the Global safety database.

The following DREs are common in participants with malaria and can be serious/ life-threatening:

- Severe *P.falciparum* malaria, is defined as ≥ 1 of the following, occurring in the absence of an identified alternative cause and in the presence of *P.falciparum* asexual parasitemia.
  - Impaired consciousness: A Glasgow coma score < 11 in adults or a Blantyre coma score < 3 in children.
  - Prostration: Generalized weakness so that the person is unable to sit, stand, or walk without assistance.
  - Multiple convulsions: > 2 episodes within 24 hours.
  - Acidosis: A base deficit of > 8 mEq/L or, if not available, a plasma bicarbonate level of < 15 mmol/L or venous plasma lactate ≥ 5 mmol/L. Severe acidosis manifests clinically as respiratory distress (rapid, deep, labored breathing).
  - Hypoglycemia: Blood or plasma glucose < 2.2 mmol/L (< 40 mg/dL).
  - Severe malarial anemia: Hb concentration ≤ 5 g/dL or a hematocrit of ≤ 15% in children < 12 years of age (< 7 g/dL and < 20%, respectively, in adults) with a parasite count > 10,000/µL.

- Renal impairment: Plasma or serum creatinine > 265 µmol/L (3 mg/dL) or blood urea > 20 mmol/L.
- Jaundice: Plasma or serum bilirubin > 50 µmol/L (3 mg/dL) with a parasite count > 100,000/ µL.
- Pulmonary edema: Radiologically confirmed or oxygen saturation < 92% on room air with a respiratory rate > 30/min, often with chest indrawing and crepitations on auscultation.
- Significant bleeding: Including recurrent or prolonged bleeding from the nose, gums, or venipuncture sites; hematemesis or melena.
- Shock: Compensated shock is defined as capillary refill ≥ 3s or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as SBP < 70 mmHg in children or < 80 mmHg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill).
- Hyperparasitemia: *P. falciparum* parasitemia > 10%.

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of a SAE. These events will be recorded within 24 hours.

However, if either of the following conditions applies, then the event will be recorded and reported as an AE/SAE (instead of a DRE):

- The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

- The Investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.3.6 Adverse Events of Special Interest

Liver events (AT increase, TB increase) and CNS events will be considered AESIs and specifically followed-up through laboratory surveillance and a specific physical examination at specific visits during the follow-up. All those events should be reported to the Sponsor within 24 hours of knowledge and appropriate updates should be provided when new information becomes available.

For this study, AESI(s) include only the following:

- Liver events will be monitored through LFTs that will include the 2 ATs, ALT, and AST, as well as TB and ALP. Specific details regarding the values confirmation, follow-up, and monitoring frequency are provided in Appendix 6.
- Neurological events will be monitored through specific neurological clinical examinations, detailed in Section 8.2.1. This neurological physical examination will be done at Screening and at every visit. If additional tests or assessments (such as CT, MRI, lumbar punction) are required to further evaluate neurological abnormalities detected, those will be done at the discretion of the Investigator.

8.4 Pharmacokinetics

8.4.1 Blood Sampling and Bioanalysis

PK sampling timepoints are provided in the SoA (Section 1.3). Blood samples will be taken for participants randomized to Cohorts 1 to 3 during the dosing day (Day 1, Visit 1) and at each subsequent visit to assess the PK of M5717 and pyronaridine. The exact sampling timepoints at Day 1 to 2 (24 hour sampling after dosing) are provided in Table 2.

- Samples are collected only where allowed by local law/regulations.
- The actual date and time (24 hour clock time) of:
  - Each sample collection
  - Study intervention administration prior to sample collection

  will be recorded in the eCRF to determine the elapsed time of sampling in relation to the administration of study intervention.
- Additional samples may be collected during the study if warranted and agreed upon between the Investigator and the Sponsor. The sampling timing may be altered during the study based on newly available data (e.g. to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The quantification of M5717 and pyronaridine in whole blood will be performed using validated assay methods. Concentrations will be used to evaluate the PK of M5717 and pyronaridine.
- Remaining samples collected for bioanalytical measurements may also be used for evaluation of safety or efficacy aspects related to concerns arising during or after the study, CCI [redacted] of metabolites of study intervention, or CCI [redacted] during or after the study. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.
- Details on processes for collection and handling of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

8.4.2 PK Parameters

The following PK parameters for M5717 and pyronaridine will be calculated, when appropriate:

Symbol	Definition
$AUC_{0-\infty}$	The AUC from time zero (= dosing time) up to infinity with extrapolation of the terminal phase.
CL/F	The apparent total body clearance following extravascular administration.
C_{max}	Maximum observed concentration.
$t_{½}$	Apparent terminal half-life. $t_{½} = \ln(2)/\lambda_z$.
t_{max}	The time to reach the C_{max} in a dosing interval.
V_Z/F	The apparent volume of distribution during the terminal phase following extravascular administration.

Symbol	Definition
$AUC_{0\text{-}tlast}$	The AUC from time zero (= dosing time) to the time of the last quantifiable concentration (t_{last}).
$AUC_{0\text{-}tlast}$/Dose	The dose normalized $AUC_{0\text{-}tlast}$.
$AUC_{0\text{-}\infty}$/Dose	The dose normalized $AUC_{0\text{-}\infty}$.
C_{max}/Dose	The dose normalized C_{max}.

Other PK parameters might be added based on emerging data. Details will be provided in the IAP.

Details on PK sampling for M5717 and pyronaridine are provided in Section 8.4.1.

Concentration data may be used for integrated data analyses across studies, such as population PK and exposure response analyses of PD biomarker, efficacy, and/or safety analyses and reported separately from the main CSR.

CCI [redacted]

[redacted]

[redacted]

8.7 Immunogenicity Assessments

Not applicable.

8.8 Medical Resource Utilization and Health Economics

Healthcare resource utilization data are not collected in this study.

9 Statistical Considerations

Details of the analysis of efficacy, safety, and PK will be presented in the IAP, which will be finalized before the database is locked for analysis.

Statistical considerations for the DMFA substudy are provided in Appendix 2.

9.1 Statistical Hypotheses

This study is an exploratory PoC study with no formal confirmatory analysis. All analyses will be descriptive. No confirmatory hypothesis testing is planned, so no adjustment for multiple testing is necessary.

9.2 Sample Size Determination

Actively Enrolled Study Cohorts (Cohorts 1 to 4)

In total, 192 participants will be randomly assigned to study intervention with a ratio of 1:1:1:1 to Cohorts 1 to 4, such that approximately 180 evaluable participants are anticipated to be obtained assuming a drop-out rate < 10% as observed in other malaria studies. This will result in 45 participants per treatment cohort.

In order to investigate the time of protection of M5717 plus pyronaridine (see Section 2.1), it is important to show that with the highest dose of M5717 at least an effect comparable to Pyramax (pyronaridine+artesunate) over 63 days can be shown.

Within a clinical study by use of Pyramax for which results are reported in Dabira 2022, 3 different dose regimens of Pyramax were compared with respect to number of patients with parasitemia over 63 days (1-, 2-, and 3-day regimen). For the 1 day regimen the same dose of pyronaridine as planned for this study was administered (540 mg/720 mg according to body weight) to asymptomatic individuals with *P. falciparum* infection. Out of 96 participants of the 1-day regimen arm 84.4% remained without parasitemia at Day 63. Since a slightly higher proportion of participants without parasitemia is expected for M5717 plus pyronaridine, a proportion of 87% will be assumed in the following.

In Sukwa 1999 results of a randomized, double-blind, placebo-controlled field study to determine the efficacy of Malarone for prevention are reported. In this study, asymptomatic volunteers residing in a highly malarious area of Zambia were first treated with a 3 day treatment regimen of Malarone to clear all parasites (same approach as for Cohort 4 in this study). After liver and blood stage parasite cure, participants were randomized to receive daily treatment with either Malarone or Placebo over 70 days. In the Placebo group of 111 participants the proportion of participants without parasitemia at Day 70 was 63%.

Assuming, thus, cumulative % Survival for the Control (=natural infection cohort) and the highest dose group of M5717 plus pyronaridine combination to be 63% and 87%, a HR of 0.29 is expected (i.e. a 71% reduction of the risk for a parasitemia event in participants treated with the M5717 plus pyronaridine combination as compared to participants of Cohort 4). Basing the estimation on a Log-rank test given accrual and study duration to be 2 months each, the expected total number of events is 21 (which are expected to be distributed over both cohorts according to a HR of 0.29) and, with a total sample size of 90 participants, the estimated power is 80% with an assumed type 1 error of $\alpha = 0.05$.

Synthetic Control Cohort

It is planned to use external data as an additional cohort (Cohort 5) to compare with actively enrolled participants (for details on the data please refer to Section 3).

To minimize bias due to potential imbalances of confounding factors between external and study data, a PS matching will be used for balancing the multivariate baseline covariate data (the selection of covariates will be described in the IAP) across treatment groups. The PS matching will be done separately by treatment cohort since descriptive comparisons against the synthetic control arm will also be done by cohort. In order to end up with comparable cohort sizes at least approximately 35 participants should have a match per cohort. In case the number of identified matches falls below 35 the respective cohort will not be used for comparison to the synthetic

control arm from the external study. In case the number of matches is < 35 for all cohorts the use of the synthetic control arm will not be performed at all.

Matching of the external data will be performed after database lock and unblinding. Further details on the matching algorithm and the use of calipers will be defined in the IAP.

9.3 Analysis Sets

The Analysis Sets are specified in Table 3.

Table 3 Analysis Sets

Analysis Set	Description
FAS	The FAS will include all randomized participants. Participant will be analyzed according to the treatment assigned at randomization as per the Intention-to-Treat (ITT) principle.
SAF	All participants who were administered any dose of any study intervention. Analyses will consider participants as treated.
PK Analysis Set	All participants, who receive 1 dose of study intervention, have no clinically important protocol deviations or important events affecting PK, and provide ≥ 1 measurable postdose concentration. Participants will be analyzed per the actual study intervention they received. All PK analyses will be based on this analysis set.

9.4 Statistical Analyses

This Section provides a description of the statistical methods to be used to analyze efficacy, safety, and other endpoints. Prior to locking the database, a detailed IAP will be finalized. All details of the statistical analyses not covered by the following sections will be described in the IAP.

Unless otherwise specified, the FAS will be the primary analysis set for all efficacy analyses. The SAF will be used for all safety data reporting.

Continuous variables will be analyzed by displaying the number of available observations, mean, SD, median, lower and upper quartiles, and minimum, and maximum values. Where applicable, 95% CIs will be provided.

Ordinal variables will be summarized by frequency tables, including the number of available observations, median, and lower and upper quartiles.

Qualitative variables will be analyzed by frequency tables.

9.4.1 Efficacy Analyses

In Table 4 only main analyses are described for the primary and secondary efficacy endpoints. Additional sensitivity and subgroup analyses will be planned in the IAP.

Table 4 Summary of Main Statistical Analyses – Efficacy

Reference #	Category	Statistical Analysis
Primary		
1 – Time to parasitemia since negative blood smear after treatment	Main	Time to parasitemia since negative blood smear after treatment will be analyzed. HRs will be estimated from a Cox Proportional Hazards model separately for the 3 dose groups of M5717 plus pyronaridine compared to Cohort 4 together with 95% CIs. Additionally, Kaplan-Meier curves will be provided to descriptively compare the time to parasitemia between the treatment groups.
Secondary		
2 - Incidence of parasitemia	Main	The proportion of participants with parasitemia will be estimated from Kaplan-Meier curves and displayed by treatment group together with 95% CIs.
CCI [redacted]		
[redacted]	[redacted]	[redacted]

9.4.1.1 Efficacy Analyses Related to Primary Objective

Per ICH E9(R1), Addendum on Estimands and Sensitivity Analysis in Clinical Trials (November 2019), the primary estimand targeting the primary objective is defined by the following attributes:

- **Variable (endpoint):** The primary endpoint is the time to parasitemia since parasite clearance (randomization) defined as the time without a positive blood smear.
- **Treatment:** Intervention of interest is single dose of either 60 mg M5717 + 720 mg pyronaridine (≥ 65 kg) or 540 mg pyronaridine (≥ 45 to < 65 kg), 200 mg M5717 + 720 mg pyronaridine (≥ 65 kg) or 540 mg pyronaridine (≥ 45 to < 65 kg), or 660 mg M5717 + 720 mg pyronaridine (≥ 65 kg) or 540 mg pyronaridine (≥ 45 to < 65 kg).
- **Target population:** The target population is defined as the population of patients targeted by the clinical question. In this exploratory PoC study the target population is defined by adult and adolescent patients with asymptomatic *P. falciparum* malaria.
- **Strategies for handling ICEs:** A composite variable strategy, i.e. the primary endpoint is considered as failure (positive blood smear) is applied if participants take rescue medication after intake of study intervention or if they discontinue the study due to malaria induced death. In case participants experience any event that effects the absorption of the study intervention (e.g. vomiting within the study intervention absorptive period of 2 times median T_{max}), a treatment policy strategy is applied as to which the treatment effect is estimated regardless of the ICE. An on-treatment strategy is considered for participants with documented intake of antibiotics or other prohibited medication that impacts the treatment effect (e.g. drug with antimalarial activity) at any timepoint or if participants die from other reasons than malaria, i.e. the time parasitemia since parasite clearance is censored at the time of antibiotics or prohibited medication intake and at the time of death, respectively.

- **Population-level summary:** The population-level summary of the primary endpoint is the HR for the different dose groups in comparison to the natural incidence of infection as measured in Cohort 4. HRs together with 95% CIs will be estimated from Cox Proportional Hazard models. Details of the models and potential factors or covariates to be included will be described in more detail within the IAP.

9.4.1.2 Efficacy Analyses Related to Secondary Objectives

For the secondary endpoints incidence of parasitemia (positive blood smear), and incidence of PCR-adjusted parasitemia (new infections and recrudescence), similar estimand attributes as for the primary endpoint apply. For incidence of gametocytemia, a treatment policy strategy will be applied in case of intake of antibiotics or prohibited medications and in case of malabsorption of study treatment. Events of death due to malaria and to other causes will be handled according to a composite variable and on-treatment strategy, respectively.

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis set. The safety analyses are described in Table 5.

AEs will be classified using the most recent MedDRA version at time of the analysis to determine SOC, PT, and SMQs.

Table 5 Summary of Main Statistical Analyses – Safety

Reference #	Category	Statistical Analysis Methods
Secondary		
6 - Incidence, severity, and seriousness of TEAEs, treatment-emergent study intervention related AEs, as per CTCAE v5.0	Main	Frequency and percentage of participants by SOC and PT.

TEAEs are defined as AEs which started at or after the administration of IMP (study treatment) or which started prior to the first administration of IMP but worsened after the dose intake, until the last scheduled assessment will be regarded as treatment-emergent, but before established rescue antimalarial treatment is administered, if required. Treatment-related AEs are those rated by the Investigator as "definitely", "probably" or "possibly" related. All AEs will be documented, and will include the Investigator term, the preferred term, start, and end date of AE, duration (days), severity, drug relationship, action taken, and outcome. Liver signals (AT increase, TB increase) and CNS signals will be considered AESIs and specific follow-up will be performed, through laboratory surveillance, and a specific physical examination at specific visits during the follow-up.

Abnormal laboratory findings and other abnormal investigational findings should not be reported as SAEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation, or are considered otherwise medically important by the Investigator.

Examples of medically important findings include:

- Requirement for treatment or any other therapeutic intervention.
- Necessity for further diagnostic evaluation (excluding repetition of the same procedure to confirm the abnormality).
- Association with clinical signs or symptoms that may have a significant clinical impact, as determined by the Investigator.
- Clinically significant changes (as assessed by the Investigator) of any laboratory parameter throughout the study (compared to the last assessment prior to trial treatment).

Note: if the abnormal results were already present at baseline with the same severity, it will be recorded as medical history.

9.4.3 Other Analyses

Demographics and medical history will be analyzed descriptively.

The PK and CCI [redacted] are described in Table 6.

Details on the PK and CCI analyses will be in the IAP that will be finalized before database lock. CCI

Details on the analyses performed in the optional DMFA substudy (reduction of infectivity of gametocytes, mosquito infectivity parameters, and gametocyte parameters) are provided in Appendix 2. The results of the substudy will be reported separately.

Table 6 Summary of Statistical Analyses – PK and CCI

Reference #	Category	Statistical Analysis Methods
Secondary		
7 – PK	PK parameters (in Section 8.4)	Summary statistics of PK parameters will be provided. For PK parameters no estimand attributes have been defined. Detailed descriptions of PK analyses will be part of an annex to the IAP. All PK analyses will be performed on the PK Analysis Set.
CCI		

9.4.4 Sequence of Analyses

No interim analyses are planned for this study. There will be one final analysis after completion of the main study and one final analysis after completion of the DMFA substudy.

10 References

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11 Appendices

Appendix 1 Abbreviations

ACT	artemisinin-based combination therapy
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AESI	adverse events of special interest
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	aminotransferase
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CNS	central nervous system
COVID-19	Corona Virus Disease 2019
CRF	case report form
CRO	Contract Research Organization
CSR	clinical study report
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DMFA	direct membrane feeding assay
DRE	disease-related events
DRO	disease-related outcome

ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EOS	end of study
FAS	full analysis set
FIH	first in human
GCP	Good Clinical Practice
Hb	hemoglobin
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormonal replacement therapy
IAP	integrated analysis plan
IB	Investigator's Brochure
IC_{50}	half maximal inhibition concentration
IC_{99}	Approximately 100-fold greater than IC_{50} concentration
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IMP	investigational medicinal product
INR	international normalized ratio
iPT	intermittent preventive therapy
IPTsc	intermittent preventive treatment in school aged children
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LAM	lactational amenorrhea method
LFT	liver function test
MDA	mass drug administration

MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NASH	Nonalcoholic fatty liver disease
NCE	new chemical entity
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCT	National Clinical Trial number
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	Nonsteroidal anti-inflammatory drug
PACTR	Pan African Clinical Trials Registry
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PDMC	Post discharge malaria chemoprevention
PeEF2	plasmodium eukaryotic translation elongation factor 2
PGx	pharmacogenetic
PK	pharmacokinetic(s)
PMC	perennial malaria chemoprevention
PoC	Proof-of-concept
POCBP	participant of childbearing potential
PS	Propensity Score
PT	preferred term
QTcF	corrected QT interval by Fridericia' formula
QTL	quality tolerance limit
RDT	rapid diagnostic test
RT-qPCR	real-time quantitative reverse transcription PCR
SAE	serious adverse event
SAF	safety analysis set
SARI	serotonin antagonist and reuptake inhibitor
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
Scr	Screening

SD	standard deviation
SMC	seasonal malaria chemoprevention
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA query
SoA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
SPAQ	sulfadoxine-pyrimethamine plus amodiaquine
SUSAR	suspected unexpected serious adverse reactions
TA	Therapeutic Area
TB	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO	World Health Organization

Appendix 2 Substudy to Evaluate the Efficacy of the Combination M5717 Plus Pyronaridine Versus Malarone to Reduce Post-treatment *P. Falciparum* Transmission (DMFA Substudy)

Table 7 Schedule of Activities – DMFA Substudy (Cohorts 1 to 4)

Assessments & Procedures	**Outpatient/ Inpatient[a]**		**Outpatient**				**Notes**
Visit Number	**Screening and Visit 1[a]**	**Visit 2[a]**	**Visit 3**	**Visit 4**	**Visits 5 to 12**	**Visit 13**	[a] Visit 1 and 2: Participants randomized to Cohorts 1 to 3 will remain in the hospital or vicinity of the site for 24 hours.
Timepoint	Day 1	Day 2	Day 3	Day 4	Week 2 to 9 (weekly visits starting at Day 8)	EOS (last visit) Week 10, Day 64[b]	[b] Day 64 or day of completion or premature discontinuation. Participants will remain in the study until parasitemia or until Day 64, whichever comes first.
Visit Window					± 1 day	± 2 days	
Informed consent and eligibility for the substudy	X						
Venous blood sampling for DMFA	X[c]	X	X	X	X[d]	X[d]	[c] Predose and 1 h after the first dose. [d] DMFA will only be performed if the participant is infectious to mosquitoes on any of the 2 preceding feeding days.
Venous blood sampling for DMFA after MACS	X[e]	X					[e] Predose and 1 h after the first dose.
Venous blood sampling for gametocyte assessments	X[f]	X	X	X	X	X	[f] Predose and 1 h after the first dose.

DMFA = direct membrane feeding assay, EOS = end of study, MACS = magnetic cell sorting

CCI [redacted]

Substudy Design

This substudy is an ancillary study to the main study. Additional blood samples will be taken for participants enrolled into the substudy (see Table 7).

Substudy Population

Individuals who were randomized to Cohorts 1 to 4 of the main study will be approached to identify if they are willing to be involved in this substudy. Participation in this substudy is entirely voluntary. A participant's decision to participate or to not participate in the substudy will not affect their participation, care, or treatment in the main study.

Participants are eligible to be included in the substudy if in addition to the eligibility criteria of the main study (see Section 5.1 and 5.2) all of the following criteria apply.

Inclusion criteria:

1. *P. falciparum* gametocyte carriage confirmed by microscopy with a minimum gametocyte density of 2 per 500 WBC (~32 per µL) at the time of randomization in the main and substudy

Exclusion criteria:

1. Administration of immunoglobulin and/or any blood products within the 3 months preceding the study participation

2. Any finding that would in the Investigator's opinion interfere with study participation

Objectives and Endpoints of the Substudy

Mosquito infectivity will be assessed at 3 levels: the mean number of oocysts in a sample of mosquitoes (i.e. oocyst density), the proportion of mosquitoes in a given assay infected with any number of oocysts (i.e. mosquito infection rate), and the relation between infectivity of the study participants and infectivity of mosquitoes. These different aspects of mosquito infectivity are translated into primary and secondary/CCI as described in below table. All analyses of mosquito infectivity will be conducted on all participants who are infectious at baseline (i.e. with a minimum gametocyte density of 2 per 500 WBC (~32 per µL at randomization).

Objectives	Estimands/Endpoints	Ref. #
Primary		
To assess the intra-individual reduction of infectivity of gametocytes (in terms of mosquito infection rate) following administration of Malarone alone or M5717 plus pyronaridine (single dose regimen) at Day 2 (24 hours) compared to pretreatment (Day 1)	**Endpoint:** Percent reduction in the mosquito infection rate of mosquitoes fed with Day 2 (24 hours post treatment) blood sample and mosquitoes fed with Day 1 (pretreatment) blood sample. The mosquito infection rate is defined by the proportion of mosquitoes in an assay infected with any number of oocysts. **Population-level summary:** Arithmetic mean by dose cohort with 95% CI	S1
Secondary		
To assess the intraindividual reduction of infectivity of gametocytes (in terms of mosquito infection rate) following administration of Malarone alone or M5717 plus pyronaridine (single dose regimen) at all feeding timepoints post treatment compared to pretreatment (Day 1)	**Endpoint:** Percent reduction in the mosquito infection rate of mosquitoes at different feeding timepoints and mosquitoes fed with Day 1 (pretreatment) blood sample. The mosquito infection rate is defined by the proportion of mosquitoes in an assay infected with any number of oocysts. **Population-level summary:** Arithmetic mean by dose cohort with 95% CI	S2
To assess the intraindividual reduction of infectivity of gametocytes (in terms of oocyst intensity) following administration of Malarone alone or M5717 plus pyronaridine (single dose regimen) at all feeding timepoints post treatment compared to pretreatment (Day 1)	**Endpoint:** Difference in the mean number of oocysts in a sample of mosquitoes at different feeding timepoints and mean number of oocysts in a sample of mosquitoes fed with Day 1 (pretreatment) blood sample. **Population-level summary:** Geometric mean by dose cohort with 95% CI	S3

Objectives	Estimands/Endpoints	Ref. #
To assess differences in gametocyte prevalence following administration of Malarone alone or M5717 plus pyronaridine (single dose regimen) at all feeding timepoints post treatment compared to pretreatment (Day 1)	**Endpoint:** Difference in gametocyte prevalence at all feeding timepoints determined by molecular assays and gametocyte prevalence at Day 1. Gametocyte prevalence is defined by the percentage of study participants that are carriers of gametocytes. **Population-level summary:** Arithmetic mean of differences in proportions by dose cohort with 95% CI	S4

CCI

Substudy Assessments and Procedures

Mosquito feeding assays

Membrane feeding will be performed to determine infectivity to locally reared female *Anopheles coluzzii* mosquitoes, as described in detail in online protocols (Goncalves 2017, Reuling 2017).

The blood sample for feeding will be obtained prior to study intervention administration where applicable. On Day 1 and Day 2, additional heparinized blood will be taken and enriched using the MACS gametocyte enrichment method (Reuling 2017). The gametocytes enriched blood will be used for duplicate feeding assay.

Oocyst assessments

Fully fed mosquitoes will be kept at 27°C to 29°C with access to glucose solution for approximately one week (6 – 8 days) prior to dissection and assessment for the presence and density of oocysts by 2 independent microscopists blinded to study arms. Infected guts will be stored for later PCR confirmation of oocysts

CCI [redacted]

[redacted]

[redacted]

[redacted]

Blinding

Parasitologists and laboratory personnel performing the microscopy, the membrane feeding assays and PCR will be blinded with respect to dose cohorts to minimize bias.

Statistical Considerations for the Substudy

This substudy is fully exploratory. All analyses conducted will be of descriptive nature. Details on the planned analyses will be described in the IAP together with the description of planned analyses for the main study. Definitions of estimands and intercurrent events were not considered for this substudy, since endpoints are based on measures of the DMFA based on blood samples of the participants. Study participants are not directly involved in any measurement for the substudy.

Substudy References

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Appendix 3 Study Governance

Financial Disclosure

Investigators and Subinvestigators 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, including the risks, and benefits, to the participant or his/her legally authorized representative (where allowed by local laws and regulations) and answer all questions on the study, using a language chosen so that the information can be fully and readily understood by laypersons.
- The participant and/or the participant's parent(s) or guardian/legally authorized representative will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification.
- Participants and/or the participant's parent(s) or guardian/legally authorized representative will be informed that their participation is voluntary.
- Participants or their guardian/legally authorized representative (where allowed by local laws and regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; ICH guidelines; privacy and data protection requirements, where applicable; and the IRB/IEC or study site.
- The medical record will 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 will also sign the ICF.
- If the participant and/or the participant's parent(s) or his/her guardian/legally authorized representative is (are) illiterate, an impartial witness must be present during the information session. The witness will explain to the participants and/or parent or guardian/legally authorized representative the information contained in the written document and ask to give verbal consent to participate in the study and/or have his/her child participating in the study. Consent of the participants and/or participant's parent or guardian/legally authorized representative will be confirmed by his/her fingerprint on the form; the witness will sign and date the form.
- The original signed and dated declaration of informed 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 copy of the signed and dated information and ICF(s) should be provided to the participants or one of the participant's parents or his/her guardian/legally authorized representatives prior to participation.
- If the ICF is updated during their participation in the study, participants, and/or the participant's parent(s) or his/her guardian/legally authorized representative will be reconsented to the most current, approved version.

Data Protection

- Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing participant data. The Sponsor will assign a unique identifier to participants after obtaining their and/or their participant's parent(s) or his/her guardian/legally authorized representative informed consent. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor will inform participants and/or the participant's parent(s) or their guardian/legally authorized representative that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure will also be explained to the participant and/or the participant's parent(s) or his/her guardian/legally authorized representative, and pregnant partners (if applicable) who will be required to give consent for their data to be used, as specified in the informed consent.
- The participant and/or the participant's parent(s) or his/her guardian/legally authorized representative will be informed that the participant's 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 Coordinating Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH GCP. The Coordinating 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.

Details of structures and associated procedures will be defined separately in Study Reference Manual, Safety Management Plan, IAP, Laboratory Manual, Pharmacy Manual, CRF Completion Guidelines, Monitoring Plan, and DMC Charter.

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

A DMC will be charged with reviewing safety of M5717 and pyronaridine on an ad hoc basis if deemed necessary by the Sponsor clinical team.

Further details on the DMC composition, processes, and decision criteria will be provided in the DMC charter that will be available before the start of enrollment.

The Sponsor's Global Patient Safety department, or its designated representatives, will supervise drug safety and the timeline for reporting of AEs, SAEs, and AESIs to all concerned parties in accordance with the applicable guidelines, laws, and regulations. In the event of a nonserious AESI, the Investigator will complete the AESI Report Form and send it to the Sponsors/designees within a maximum of 24 hours after becoming aware of the event. Names, addresses, telephone-,

and fax numbers for AESI reporting will be included on the Report Form. Additional details for reporting of AESIs are 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 CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (e.g. advertisements) will be submitted to an IRB/IEC for review and approve 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 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.

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Clinical Study Report

After study completion, the Sponsor will write a clinical study report in consultation with the Coordinating Investigator and any Steering Committee or other relevant study-appointed committees or groups.

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.
- 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 participant privacy and intellectual property. In addition, the study results will be made publicly available by means of a CSR synopsis in accordance with privacy legislation and rules. Other researchers can, by following the appropriate Merck Healthcare KGaA processes, gain access to the data for additional analysis or information as part of EFPIA/PhRMA commitment to Responsible Data Sharing. Merck Healthcare 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 Healthcare 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.

Study participants might be provided with the results of the medical examinations at request. After finalization of the study, 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 Study Reference Manual.
- The Investigator will maintain accurate documentation (source data) that supports the information in the CRF.
- The Investigator will 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.
- QTLs will be predefined and documented in the Study Reference Manual to help support the identification of systematic issues that could potentially impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important deviations from the QTL thresholds and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy, including definition of study critical data items and processes (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 Study Reference Manual.
- 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. Details will be outlined in Data Management documents and procedures.
- 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.
- The Investigator will retain records and documents, including signed ICFs, pertaining to the conduct of this study 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 will maintain source documents that support the data recorded in the CRFs.
- Data recorded on CRFs that are transcribed from source documents will be consistent with the source documents or the discrepancies will be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records will be available.
- 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 and its origin is found in ICH GCP Guideline E6 Chapter 1.51.

Study and Site Start and Closure

The study start date is when the first participant signs the Informed Consent Form.

Study and Site Closure

The Investigator may initiate site closure at any time, provided there is reasonable cause and enough notice is given in advance of the intended closure.

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.
- Sponsor discontinuation of the study due to an unacceptable risk, any relevant toxicity, or negative change in the risk/benefit assessment.
- If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any third-party service providers of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the participants and assure appropriate participant therapy and/or follow-up.

Appendix 4 Contraception and Barrier Requirements

Definitions:

POCBP:
A participant is of childbearing potential (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 M5717, pyronaridine, or Malarone, consider additional evaluation.

Postmenopause:

Postmenopause is defined as no menses for 12 months without an alternative medical cause.

- A participant on HRT and whose menopausal status are in doubt will be required to use one of the nonestrogen 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.

Permanent sterilization:

For this study, permanent sterilization includes:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

For individuals 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.

Contraception Guidance:

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods That Have Low User Dependency • Implantable progestogen-only hormone contraception associated with inhibition of ovulation • IUD • IUS • Bilateral tubal occlusion • Azoospermic partner (vasectomized or due to a medical cause) Azoospermia is a highly effective contraceptive method provided the partner is the sole sexual partner of the POCBP and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days. Documentation can come from the site personnel's review of the individual's medical records, medical examination, or medical history interview.

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 M5717, pyronaridine, or Malarone. 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:

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, 1) barrier methods (external or internal condom with or without spermicide; cap, diaphragm, or sponge with spermicide) in addition to hormonal contraception or 2) a non-hormonal IUD must be used. If locally required, in accordance with 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 LAM are not acceptable methods of contraception for this study. External and internal condoms cannot be used together (due to risk of failure from friction).

Appendix 5 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

AE Definition

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether considered related to the study intervention or not. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.
Events Meeting the AE Definition
• Any abnormal laboratory test results (e.g. hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital signs measurements), including those that worsen from baseline and are judged to be more severe than expected for the participant's condition per the Investigator's medical and scientific judgment, are considered clinically significant in the medical and scientific judgment of the Investigator (e.g. not related to progression of underlying disease, but may be leading to study intervention discontinuation). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfil the definition of an AE or SAE.
Events NOT Meeting the AE Definition
• Unless judged by the Investigator to be more severe than expected for the participant's condition, any clinically significant abnormal laboratory findings, other abnormal safety assessments that are associated with the underlying disease, the disease/disorder being studied within the expectedness for participant's condition, as judged by the Investigator. • Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

SAE Definition

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (e.g. hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death.

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE will be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization must be documented and reported as SAEs.

d. Results in persistent disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is **not** intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

f. Other situations

- Medical or scientific judgment will be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events are usually considered as serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Any suspected transmission of an infectious agent via a study intervention is also considered an SAE for reporting purposes, as specified below for reporting SAEs and AESIs.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- As needed, Sponsor may ask for copies of certain medical records (e.g. autopsy reports, supplemental lab reports, documents on medical history/concomitant medications, discharge letters), as supporting source documentation. All participant identifiers, except the participant number, will be redacted on these copies before submission to Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- Specific guidance is in the CRF Completion and Monitoring Conventions.

Assessment of Intensity

The Investigator will assess the intensity of each AE and SAE reported during the study.

An event is defined as "serious" when it meets ≥ 1 of the predefined criteria specified in the definition of an SAE, NOT when it is rated as severe.

Investigators will reference the NCI-CTCAE, version 5.0 (publication date: 27 Nov 2017), a descriptive terminology that can be used for AE reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If the severity for an AE is not specifically graded by NCI-CTCAE, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5, using his or her best medical judgment.

The 5 general grades are:

- Grade 1 or Mild
- Grade 2 or Moderate

- Grade 3 or Severe
- Grade 4 or Life-threatening
- Grade 5 or Death

Any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria specified below.

If death occurs, the primary cause of death or event leading to death will be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (e.g. sudden death, unexplained death), the death per se might then be reported as an SAE.

Assessment of Causality

- The Investigator will assess the relationship between study intervention and each AE/SAE occurrence:
  - Unrelated: Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention. A reasonable alternative explanation will be available.
  - Related: Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the study intervention.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator will document in the medical notes that he/she has reviewed the AE/SAE and assessed causality.
- There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor or its designee. To meet the reporting timeline, the causality assessment is not required for the initial report.
- The Investigator may change his/her causality assessment after considering follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The Investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE, as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Sponsor/designee with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The Investigator will submit any updated SAE data to Sponsor/designee within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting by an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE in multicenter studies to the Sponsor or its designee will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE form, specified below, to report the event within 24 hours. • The site will enter into the electronic system the SAE data within 24 hours after becoming aware of the event. It is expected that the Investigator/Subinvestigator signs off this data in the system and any relevant associated data (e.g. additional laboratory tests, medical records, diagnostic reports, histopathological examinations, or consultation with other health care professionals) will be entered as soon as it becomes available. • After the study is completed at a site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to the Sponsor's safety department. • By exception, an SAE (or follow-up information) may be reported by telephone. The site will complete the electronic SAE data entry immediately thereafter.
SAE Reporting by a Paper Form
• SAE reporting on a paper report form may be used in single center studies in addition to the standard electronic CRF and as a back-up method for an EDC system failure. The form includes completion instructions for the Investigator, names, addresses, and telephone and fax numbers. All information from the paper form will be transcribed into the electronic form as soon as the system becomes available.

- Facsimile transmission (fax to mail) of the paper form or any follow-up information is the preferred method for transmission and will be done within 24 hours to the Sponsor or its designee.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the form within 24 hours after becoming aware of the event.
- Additional documents (e.g. laboratory reports, autopsy report, hospital discharge letter) and relevant pages from the CRF may be required in addition (e.g. medical history, concomitant medication). The data provided will be consistent with the information in the CRF.

Reporting of AESIs

- For a nonserious AESI, the site will complete the specific AESI report form and notify the Sponsor immediately (within 24 hours), using the same process for reporting SAEs, as specified above.
- For a serious AESI, the site will complete an SAE report form, using the SAE reporting process, specified above.

Reporting of Pregnancies

- Pregnancy will be reported whether related to the study intervention using the applicable paper form.
- The applicable form will be used to report if an abnormal outcome of the pregnancy occurs and the child/fetus sustains an event.
- Facsimile transmission (fax to mail) of the paper form or any follow-up information is the preferred method for transmission and will be done within 24 hours to the Sponsor or its designee.

Appendix 6 Liver Safety: Suggested Actions and Follow-up Assessments

The DILI will be defined as follows:

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

An increase of serum ALT or AST to > 3 × ULN should be followed by repeat testing within 48 to 72 hours of all 4 of the usual serum measures (ALT, AST, ALP, and TB) 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 > 3 × ULN and/or TB is > 2 × ULN.

If symptoms persist or repeat testing shows AT > 3 × ULN 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 2 or 3 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. INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.

All study participants showing possible DILI should be followed until all abnormalities return to normal or to the Baseline state.

Appendix 7 Prohibited Concomitant Medications with Antimalarial Activities

Within 6 weeks prior to Screening:

- Piperaquine
- Mefloquine
- Naphthoquine
- Sulphadoxine-pyrimethamine

Within 4 weeks prior to Screening:

- Amodiaquine
- Chloroquine
- Hydroxychloroquine and all other 4-aminoquinolines
- Pyronaridine
- Tafenoquine

Within 14 days prior to Screening:

- All Artemisinin derivatives including artemether, artemether, artesunate, and dihydroartemisinin
- Quinine
- Halofantrine
- Lumefantrine
- Quinidine
- Arterolane
- Proguanil
- Chlorproguanil
- Primaquine
- Atovaquone
- Pentamidine
- Clindamycin
- Rifampin
- Dapsone and all sulphones
- All sulfonamides (sulphonamides) or sulfonamide containing preparations including co-trimoxazole (trimethoprim-sulfamethoxazole)

- All tetracycline class antibiotics including minocycline, erythromycin, azithromycin, and doxycycline
- Quinolone antibiotics including fluoroquinolones
- Azithromycin and all other macrolides
- Erythromycin and all other macrolides

Within 7 days prior to Screening:

- Any herbal products or traditional medicines
- From Screening
- Ketoconazole
- Praziquantel
- Albendazole
- Mebendazole
- Metronidazole

Appendix 8 Drug-induced Mitochondrial Activity

Each drug class contains drugs with more and less observed mitochondrial toxicity.

Drug Class	Rank Order of Toxicity Observed (High to Low)	Target Organ
Antidiabetic (thiazolidinediones)	Rosiglitazone Pioglitazone	Liver
Cholesterol lowering (statins)	Simvastatin Atorvastatin Fluvastatin	Muscle
Antidiabetic (biguanides)	Metformin	Lactic acidosis
Antidepressant/anxiety (SARIs)	Trazodone Buspirone	Liver
Antilipidemic (fibrates)	Gemfibrozil Ciprofibrate Fenofibrate	Liver
Pain medication (NSAIDs)	Meloxicam Dichlofenac Piroxicam Acetylsalicylic acid	Liver, intestine
Antibiotics (fluoroquinolones)	Levofloxicin Ciprofloxicin	Liver
Antiepileptics	Valproate	Liver
NRTIs	Zidovudine Stavudine Zalcitabine Lamivudine Abacavir Tenofovir	Liver, lactic acidosis
Anticancer (topoisomerase inhibitors)	Doxorubicin	Heart

NRTI = nucleoside reverse transcriptase inhibitor, NSAID = nonsteroidal anti-inflammatory drug, SARI = serotonin antagonist and reuptake inhibitor.

Appendix 9 Drug-induced Photosensitivity

The following drugs will be prohibited:

- Amiodarone
- Cefotaxime
- Chlorpromazine
- Ciprofloxacin
- Dapsone
- Diltiazem
- Doxycycline
- Efavirenz
- Furosemide
- Hydrochlorothiazide
- Hydroxychloroquine
- Isoniazid
- Itraconazole
- Methyldopa
- Nalidixic acid
- Naproxen
- Nifedipine
- Ofloxacin
- Piroxicam
- Pyrazinamide
- Quinapril
- Quinidine
- Quinine
- Ramipril
- Rilmenidine
- Sparfloxacin
- Tetracycline
- Thiazides
- Thioridazine
- Tilisolol
- Triamterene
- Trimethoprim
- Voriconazole

Appendix 10 Clinical Laboratory Tests

The protocol-required clinical laboratory assessments are in the following table:

All study-required safety laboratory assessments will be performed by a local laboratory.

Laboratory Assessment	Parameter	Notes
Biochemistry	Alanine Aminotransferase	
	Alkaline Phosphatase	If elevated, consider measuring the alkaline phosphatase isoenzymes
	Aspartate Aminotransferase	
	Total Bilirubin	
	Calcium	
	Chloride	
	Creatinine	
	Glucose	
	Potassium	
	Sodium	
	Protein	
Hematology	Hematocrit	
	Hemoglobin	
	Leukocytes with Differential: Neutrophils (absolute/%) Lymphocytes (absolute/%) Monocytes (absolute/%) Eosinophils (absolute/%) Basophils(absolute/%)	
	Platelets	
	Reticulocytes	
Routine Urinalysis	Specific gravity, pH, glucose, protein, blood, ketones, nitrite, leukocytes by dipstick.	
	Microscopic examination (if blood or protein is abnormal).	
Contraception and Pregnancy	Serum hCG pregnancy test (as needed for a POCBP).	

CCI [redacted] [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Appendix 12 Sponsor Signature Page

Study Title:	Phase 2a Proof-of-Concept, Multicenter, Randomized, Open Label Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of a Single Dose of the Combination M5717-pyronaridine as Chemoprevention in Asymptomatic Adults and Adolescents with *Plasmodium falciparum* Malaria Infection
Regulatory Agency Identifying Numbers:	To be assigned
Clinical Study Protocol Version:	01 March 2023/Version 1.0

I approve the design of the clinical study:

PPD

PPD

PPD

Name, Academic Degree:	PPD
Function/Title:	PPD
Institution:	Healthcare – Global Research & Development – Clinical Measurement Sciences
Address:	Frankfurter Str. 250, Postcode: F130/132, 64293 Darmstadt, Germany
General Merck Phone Number:	+06151 720
General Merck Fax Number:	Not applicable
E-mail address:	PPD

PPD

Appendix 13 Coordinating Investigator Signature Page

Study Title:	Phase 2a Proof-of-Concept, Multicenter, Randomized, Open Label Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of a Single Dose of the Combination M5717-pyronaridine as Chemoprevention in Asymptomatic Adults and Adolescents with *Plasmodium falciparum* Malaria Infection
Regulatory Agency Identifying Numbers:	To be assigned
Clinical Study Protocol Version:	01 March 2023/Version 1.0
Site Number:	

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, ICH GCP (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

PPD

Signature Date of Signature

Name, academic degree:	PPD
Function/Title:	PPD
Institution:	PPD
Address:	PPD

PPD

Fax number:	Not applicable
E-mail address:	PPD

PPD

Appendix 14 Principal Investigator Signature Page

Study Title:	Phase 2a Proof-of-Concept, Multicenter, Randomized, Open Label Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of a Single Dose of the Combination M5717-pyronaridine as Chemoprevention in Asymptomatic Adults and Adolescents with *Plasmodium falciparum* Malaria Infection
Regulatory Agency Identifying Numbers:	To be assigned
Clinical Study Protocol Version:	01 March 2023/Version 1.0
Site Number:	

I 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, ICH GCP (Topic E6) and all applicable Health Authority requirements and national laws.

_____ _____

Signature Date of Signature

Name, academic degree:

Function/Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address: