Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	Phase IIa Proof of Concept, Multicenter, Randomized, Open-label Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of the Combination M5717 plus Pyronaridine Administered Once Daily for 1 or 2 Days to Adults and Adolescents with Acute Uncomplicated *Plasmodium falciparum* Malaria
Study Number:	MS201618_0033
Protocol Version:	02 November 2022/Version 3.0
Merck Compound:	M5717
Merck Registered Compound Name in Japan:	Not Applicable
Study Phase:	IIa
Short Title:	Phase IIa Proof of Concept Study of M5717-Pyronaridine in Adults and Adolescents with acute uncomplicated *Plasmodium falciparum* Malaria
Coordinating Investigator:	PPD
Sponsor Name and Legal Registered Address:	Merck Healthcare KGaA, Darmstadt, Germany an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Str. 250 64293, Darmstadt, Germany
Regulatory Agency Identifying Numbers:	PACTR: to be assigned Clinical Trials.gov: NCT to be assigned
Keywords:	Plasmodium eukaryotic translation Elongation Factor 2 (PeEF2), exposure response, Plasmodium mutants, polymerase chain reaction (PCR), Adequate Clinical and Parasitological Response (ACPR)

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	05 Apr 2022
2.0	Global Amendment to the Original Protocol	27 Jul 2022
3.0	Global Amendment to Protocol Version 2.0	02 Nov 2022

Protocol Version 3.0 (02 November 2022)

Overall Rationale for the Amendment

The overall rationale for this amendment was to address minor comments from the regulatory authority and ethics committees.

The following elements of the protocol were revised:

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (Table 1) Section 2.3.1 Risk Assessment Section 5.2 Exclusion Criteria	A COVID-19 antigen test was added to the SoA and it was clarified that only patients with a negative COVID-19 antigen test at screening are eligible.	To clarify that COVID-19 antigen tests will be performed at screening and as needed as requested by the regulatory authority.
CCI [redacted]	[redacted]	[redacted]
Section 6.6 Continued Access to Study Intervention after the End of the Study	Rescue treatment will not be provided by the Sponsor, but locally available medications will be used as specified in Section 6.8.1.	To correct an error.
Section 8.4 Pharmacokinetics CCI [redacted]	Blood sample volumes were removed.	To clarify that blood volumes will be specified in the laboratory manual.
Appendix 2 Study Governance (Informed Consent Process)	Participants who are rescreened will be required to sign a new ICF if the rescreening occurs later than 7 days after the initial screening visit.	To correct an error.
Throughout	Minor editorial and document formatting revisions	Minor; therefore, have not been summarized.

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1 Protocol Summary

1.1 Synopsis

Protocol Title: Phase IIa Proof of Concept, Multicenter, Randomized, Open-label Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of the Combination M5717 plus Pyronaridine Administered once Daily for 1 or 2 Days to Adults and Adolescents with Acute Uncomplicated *Plasmodium falciparum* Malaria

Short Title: Phase IIa Proof of Concept Study of M5717-Pyronaridine in Adults and Adolescents with acute uncomplicated *Plasmodium falciparum* Malaria

Rationale: Artemisinin-based combination therapies (ACTs) have been the gold standard for acute uncomplicated *P. falciparum* malaria, but the increasing reports of emergent resistant strains to artemisinin-related compound therapies makes it necessary to look for new therapeutic tools. In this context, the current study intends to explore in a Proof of Concept the safety, preliminary efficacy, and pharmacokinetics (PK) of M5717 (free base) in combination with pyronaridine (tetraphosphate). An ACT containing combination pyronaridine-artesunate (Pyramax) will be used as internal control, mainly for safety purposes.

Objectives and Endpoints/Estimands:

Part A – Safety/PK Run-in

Objectives	Estimands/Endpoints	Ref. #
Primary		
To evaluate the safety and tolerability of the M5717-pyronaridine combination in adult participants with acute uncomplicated malaria due to *P. falciparum*	**Endpoint:** Incidence, severity, and seriousness of study intervention-related treatment-emergent adverse events (TEAEs), as per Common Terminology Criteria for Adverse Events (CTCAE) v 5.0 Additional endpoints related to safety and tolerability up to Day 29 (± 2 days): laboratory assessments, electrocardiograms (ECGs), and vital signs.	1
Secondary		
To characterize the PK of M5717 and pyronaridine in adult participants with acute uncomplicated malaria due to *P. falciparum*	**Endpoint:** • PK profiles for M5717 and pyronaridine • PK parameters of M5717 and pyronaridine such as $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}24}$, C_{max}, $t_{½}$, t_{max}, CL/F, V_Z/F, when data permits	2
To describe the clinical efficacy of the M5717-pyronaridine combination in adult participants with acute uncomplicated malaria due to *P. falciparum*	**Endpoint:** Early treatment failure (ETF) defined as meeting any of the following: • Danger signs or severe malaria 1, 2, or 3 days after treatment, in the presence of parasitemia • Parasitemia 2 days after treatment higher than on day of treatment, irrespective of axillary temperature • Parasitemia 3 days after treatment with axillary temperature ≥ 37.5°C • Parasitemia 3 days after treatment ≥ 25% of count on day of treatment **Target Population:** Adult patients with acute uncomplicated malaria due to *P. falciparum* **Treatment:** Single dose M5717 330 mg plus pyronaridine 360 mg	3

Objectives	Estimands/Endpoints	Ref. #
	Intercurrent Event Strategy: • Intake of rescue medication before or at Day 4: Composite variable strategy, i.e., endpoint is considered as failure (= presence of ETF) • Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity) before or at Day 4: Principal Stratum strategy, i.e., treatment effect is estimated within the principal stratum of participants that potentially don't experience the intercurrent event (ICE) • Experience of any event that affects absorption (i.e., vomiting within the study intervention absorptive period of 2 × median t_{max}) or immune response (severe immunocompromised participants): Treatment policy strategy, i.e., treatment effect is estimated regardless of intercurrent event or Principal Stratum strategy • Premature study discontinuation before or at Day 4 due to lack of efficacy: Composite variable strategy • Death due to malaria before or at Day 4: Composite variable strategy **Population-level Summary:** ETF rate, i.e., proportion of participants with ETF.	
	Endpoint: Late clinical failure (LCF) defined as: • Danger signs or severe malaria in the presence of parasitemia on any day between 4 and 28 days after treatment (i.e., between Days 5 and 29) in participants who did not previously meet any of the criteria of ETF • Presence of parasitemia on any day between 4 and 28 days after treatment with axillary temperature ≥ 37.5°C in participants who did not previously meet any of the criteria of ETF **Target Population:** See endpoint 3 **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** • Intake of rescue medication between 4 and 28 days after treatment: Composite variable strategy, i.e., endpoint is considered as failure (= presence of LCF) • Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity) between 4 and 28 days after treatment: Principal Stratum strategy, i.e., treatment effect is estimated within the principal stratum of participants that potentially don't experience the ICE • Experience of any event that affects absorption (i.e., vomiting within the study intervention absorptive period of 2 × median t_{max}) or immune response (severe immunocompromised participants): Treatment policy strategy, i.e., treatment effect is estimated regardless of intercurrent event or Principal Stratum strategy • Premature study discontinuation between 4 and 28 days after treatment due to lack of efficacy: Composite variable strategy • Death due to malaria between 4 and 28 days after treatment: Composite variable strategy **Population-level Summary:** LCF rate, i.e., proportion of participants with LCF	4

Objectives	Estimands/Endpoints	Ref. #
	Endpoint: Late parasitological failure (LPF) defined as: Presence of parasitemia on any day between 7 and 28 days after treatment (i.e., between Days 8 and 29) with axillary temperature < 37.5°C in participants who did not previously meet any of the criteria of ETF or LCF **Target Population:** See endpoint 3 **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** • Intake of rescue medication between 7 and 28 days after treatment: Composite variable strategy, i.e., endpoint is considered as failure (= presence of LPF) • Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity) between 7 and 28 days after treatment: Principal Stratum strategy, i.e., treatment effect is estimated within the principal stratum of participants that potentially don't experience the ICE • Experience of any event that affects absorption (i.e., vomiting within the study intervention absorptive period of 2 × median t_{max}) or immune response (severe immunocompromised participants): Treatment policy strategy, i.e., treatment effect is estimated regardless of intercurrent event or Principal Stratum strategy • Premature study discontinuation between 7 and 28 days after treatment due to lack of efficacy: Composite variable strategy • Death due to malaria between 7 and 28 days after treatment: Composite variable strategy **Population-level Summary:** LPF rate, i.e., proportion of participants with LPF	5
	Endpoint: Crude (polymerase chain reaction [PCR]-uncorrected) Adequate Clinical and Parasitological Response (ACPR) 14, 28, and 42 days after treatment defined as absence of parasitemia (thick smear/microscopy), irrespective of axillary temperature, in participants who did not previously meet any of the criteria of ETF, LCF, or LPF **Target Population:** See endpoint 3 **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** • Intake of rescue medication at any timepoint: Composite variable strategy, i.e., endpoint is considered as treatment failure • Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity) at any timepoint: Principal Stratum strategy, i.e., treatment effect is estimated within the principal stratum of participants that potentially don't experience the ICE • Experience of any event that affects absorption (i.e., vomiting within the study intervention absorptive period of 2 × median t_{max}) or immune response (severe immunocompromised participants): Treatment policy strategy, i.e., treatment effect is estimated regardless of intercurrent event or Principal Stratum strategy • Premature study discontinuation at any timepoint due to lack of efficacy: Composite variable strategy • Death due to malaria at any timepoint: Composite variable strategy **Population-level Summary:** Crude ACPR rate at each timepoint, i.e., proportion of participants with Crude ACPR at each timepoint	6

Objectives	Estimands/Endpoints	Ref. #
	Endpoint: PCR-adjusted ACPR 14, 28, and 42 days after treatment defined as absence of parasitemia (thick smear/microscopy, after adjustment for parasitemia due to new infections as determined by genotyping using PCR techniques), irrespective of axillary temperature, in participants who did not previously meet any of the criteria of ETF, LCF, or LPF. **Target Population:** see endpoint 3 **Treatment:** see endpoint 3 **Intercurrent Event Strategy:** See endpoint 3 **Population-level Summary:** PCR-adjusted ACPR rate at each timepoint, i.e., proportion of participants with PCR-adjusted ACPR at each timepoint	7
	Endpoint: Crude (PCR-uncorrected) efficacy 8 days after treatment, defined as absence of parasitemia (thick smear/microscopy) in participants who did not previously meet any of the criteria of ETF or LCF **Target Population:** See endpoint 3 **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** See endpoint 3 **Population-level Summary:** Crude efficacy rate, i.e., proportion of participants with crude (PCR-uncorrected) efficacy 8 days after treatment (Day 9)	8
	Endpoint: PCR-adjusted efficacy 8 days after treatment as defined as absence of parasitemia (thick smear/microscopy, after adjustment for parasitemia due to new infections as determined by genotyping using PCR techniques) in participants who did not previously meet any of the criteria of ETF or LCF **Target Population:** See endpoint 3 **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** see endpoint 3 **Population-level Summary:** PCR-adjusted efficacy rate, i.e., proportion of participants with PCR-adjusted efficacy 8 days after treatment (Day 9)	9
	Endpoint: Parasite reduction rate (PRR) defined as decrease in viable parasites over 48 hours, corresponding to 1 asexual parasite life cycle **Target Population:** See endpoint 3 **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** see endpoint 3 **Population-level Summary:** Geometric mean of the PRR	10
	Endpoint: Fever clearance time defined as the time from first dosing to the first measurement of an axillary temperature < 37.5°C for 2 consecutive temperature readings plus confirmed normal temperature 24 hours after the first normal body temperature reading **Target Population:** Adult patients with acute uncomplicated malaria due to *P. falciparum* with an increased axillary temperature (≥ 37.5°C) **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** • Intake of rescue medication: Composite variable strategy, i.e., time to fever clearance is censored at Day 29 • Intake of concomitant medications as a continuous treatment that have an impact on fever: Composite variable strategy, i.e., time to fever clearance is censored at Day 29	11

Objectives	Estimands/Endpoints	Ref. #
	• Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity): Composite variable strategy, i.e., time to fever clearance is censored at Day 29 • Experience of any event that affects absorption (i.e., vomiting within the study intervention absorptive period of 2 × median t_{max}) or immune response (severe immunocompromised participants): Treatment policy strategy, i.e., treatment effect is estimated regardless of intercurrent event or Principal Stratum strategy • Premature study discontinuation due to lack of efficacy: On-treatment strategy, i.e., time to fever clearance is censored at the day of the last available body temperature assessment • Death due to malaria: On-treatment strategy, i.e., time to fever clearance is censored at the day of the last available body temperature assessment **Population-level Summary:** Median fever clearance time as estimated by Kaplan-Meier method	
	Endpoint: Parasite clearance time defined as time from dosing to the first negative (no parasites) film (microscopy) **Target Population:** See endpoint 3 **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** see previous endpoint with the exception of intake of concomitant medications, which is not an ICE for parasite clearance time. Censoring will be done at the day of the last available microscopy assessment. **Population-level Summary:** Median parasite clearance time as estimated by Kaplan-Meier method	12
	Endpoint: Time to recrudescence, defined as the time from primary cure to the re-emergence of the same parasite strain that originated the primary infection **Target Population:** Adult patients with acute uncomplicated malaria due to *P. falciparum* who are primarily cured **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity) at any timepoint: Principal Stratum strategy, i.e., treatment effect is estimated within the principal stratum of participants that potentially don't experience the ICE **Population-level Summary:** Median time to recrudescence as estimated by Kaplan-Meier method	13
	Endpoint: Time to re-infection, defined as the time from primary cure to the re-emergence of a different parasite strain that originated the primary infection **Target Population:** See endpoint 3 **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity) at any timepoint: Principal Stratum strategy, i.e., treatment effect is estimated within the principal stratum of participants that potentially don't experience the ICE **Population-level Summary:** Median time to re-infection as estimated by Kaplan-Meier method	14

Objectives	Estimands/Endpoints	Ref. #
	Endpoint: Time to re-emergence, defined as the time from primary cure to having recrudescence or re-infection (the first one that occurs) **Target Population:** see endpoint 3 **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity) at any timepoint: Principal Stratum strategy, i.e., treatment effect is estimated within the principal stratum of participants that potentially don't experience the ICE **Population-level Summary:** Median time to re-emergence as estimated by Kaplan-Meier method	15

Part B – Randomized, Open-label

Objectives	Estimands/Endpoints	Ref. #
Primary		
To describe clinical efficacy of the M5717-pyronaridine combination and of Pyramax in adult and adolescent participants with acute uncomplicated malaria due to *P. falciparum*	**Endpoint**: PCR-adjusted ACPR 28 days after first treatment (i.e., on Day 29) defined as absence of parasitemia (thick smear/microscopy, after adjustment for parasitemia due to new infections as determined by genotyping using PCR techniques), irrespective of axillary temperature, in participants who did not previously meet any of the criteria of ETF, LCF, or LPF	19
	Target Population: Adult and adolescent patients with acute uncomplicated malaria due to *P. falciparum* **Treatment:** • Single dose M5717 660 mg/500 mg (adolescents < 45 kg) plus pyronaridine 720 mg (≥ 65 kg), 540 mg (≥ 45 to < 65 kg), or 360 mg (≥ 24 to < 45 kg) (Cohorts B0 and B1) • 2-day regimen of M5717 660/500 mg plus pyronaridine 720 mg (≥ 65 kg), 540 mg (≥ 45 to < 65 kg), or 360 mg (≥ 24 to < 45 kg) (Cohort B2) • 3-day regimen of Pyramax (pyronaridine-artesunate) 720/240 mg (≥ 65 kg), 540/180 mg (≥ 45 to < 65 kg), or 360/120 mg (≥ 24 to < 45 kg) (Cohort B3) **Intercurrent Event Strategy:** • Intake of rescue medication: Composite variable strategy, i.e., endpoint is considered as treatment failure (= presence of parasitemia) • Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity) at any timepoint: Principal Stratum strategy, i.e., treatment effect is estimated within the principal stratum of participants that potentially don't experience the ICE • Experience of any event that affects absorption (i.e., vomiting within the study intervention absorptive period of 2 × median t_{max}) or immune response (severe immunocompromised participants): Treatment policy strategy, i.e., treatment effect is estimated regardless of intercurrent event or Principal Stratum strategy • Premature study discontinuation due to lack of efficacy: Composite variable strategy • Death due to malaria: Composite variable strategy **Population-level Summary:** PCR-adjusted ACPR rate, i.e., proportion of participants achieving PCR-adjusted ACPR at Day 29	

Objectives	Estimands/Endpoints	Ref. #
Secondary		
To describe the clinical and parasitological efficacy of the M5717-pyronaridine combination and of Pyramax in adult and adolescent participants with acute uncomplicated malaria due *to P. falciparum*	**Endpoint:** ETF **Target Population:** See endpoint 19 **Treatment:** See endpoint 19 **Intercurrent Event Strategy:** See endpoint 3 **Population-level Summary:** See endpoint 3	20
	Endpoint: LCF **Target Population:** See endpoint 19 **Treatment:** See endpoint 19 **Intercurrent Event Strategy:** See endpoint 4 **Population-level Summary:** See endpoint 4	21
	Endpoint: LPF **Target Population:** see endpoint 19 **Treatment:** see endpoint 19 **Intercurrent Event Strategy:** See endpoint 5 **Population-level Summary:** See endpoint 5	22
	Endpoint: Crude (PCR-uncorrected) ACPR 14, 28 and 42 days after treatment **Target Population:** See endpoint 19 **Treatment:** See endpoint 19 **Intercurrent Event Strategy:** See endpoint 6 **Population-level Summary:** See endpoint 6	23
	Endpoint: PCR-adjusted ACPR 14 and 42 days after treatment **Target Population:** see endpoint 19 **Treatment:** see endpoint 19 **Intercurrent Event Strategy:** see endpoint 7 **Population-level Summary:** see endpoint 7	24
	Endpoint: Crude (PCR-uncorrected) efficacy 8 days after treatment **Target Population:** See endpoint 19 **Treatment:** See endpoint 19 **Intercurrent Event Strategy:** See endpoint 8 **Population-level Summary:** See endpoint 8	25
	Endpoint: PCR-adjusted efficacy 8 days after treatment **Target Population:** See endpoint 19 **Treatment:** See endpoint 19 **Intercurrent Event Strategy:** See endpoint 9 **Population-level Summary:** See endpoint 9	26
	Endpoint: PRR **Target Population:** See endpoint 19 **Treatment:** See endpoint 19 **Intercurrent Event Strategy:** See endpoint 10 **Population-level Summary:** See endpoint 10	27
	Endpoints: Fever clearance time **Target Population:** Adult and adolescent patients with acute uncomplicated malaria due to *P. falciparum* with an increased axillary temperature (≥ 37.5°C) **Treatment:** See endpoint 19 **Intercurrent Event Strategy:** See endpoint 11 **Population-level Summary**: See endpoint 11	28

Objectives	Estimands/Endpoints	Ref. #
	Endpoint: Parasite clearance time **Target Population:** See endpoint 19 **Treatment:** See endpoint 19 **Intercurrent Event Strategy:** See endpoint 12 **Population-level Summary**: See endpoint 12	29
	Endpoint: Time to recrudescence **Target Population:** See endpoint 19 **Treatment:** See endpoint 19 **Intercurrent Event Strategy:** See endpoint 13 **Population-level Summary:** See endpoint 13	30
	Endpoint: Time to re-infection **Target Population:** See endpoint 19 **Treatment:** See endpoint 19 **Intercurrent Event Strategy:** See endpoint 14 **Population-level Summary:** See endpoint 14	31
	Endpoint: Time to re-emergence **Target Population:** See endpoint 19 **Treatment:** See endpoint 19 **Intercurrent Event Strategy:** See endpoint 15 **Population-level Summary:** See endpoint 15	32
To evaluate the safety and tolerability of the M5717-pyronaridine combination in adult and adolescent participants with acute uncomplicated malaria due to *P. falciparum*	**Endpoint:** Incidence, severity, and seriousness of study intervention-related TEAEs, as per CTCAE v 5.0 Additional endpoints related to safety and tolerability up to Day 2 (± 2 days): laboratory assessments, ECGs, and vital signs.	33
To characterize the PK of M5717 and pyronaridine in adult and adolescent participants with acute uncomplicated malaria due to *P. falciparum* in Cohorts B0, B1 and B2.	**Endpoint:** • PK profiles for M5717 and pyronaridine in Cohorts B0, B1 and B2. • PK parameters of M5717 and pyronaridine such as $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}24}$, C_{max}, $t_{½}$, t_{max}, CL/F, V_Z/F, when data permits	34

Overall Design: This is a Phase IIa Proof of Concept, randomized, open-label, multicenter study designed to evaluate the safety, efficacy, and PK of the combination M5717 plus pyronaridine in adults and adolescents (≥ 12 and ≤ 55 years of age) with a diagnosis of acute uncomplicated *P. falciparum* malaria.

The study will consist of 2 parts:

- Part A: small safety/PK run-in group of 12 adults with acute uncomplicated *P. falciparum* malaria designed to monitor safety and exposure. After the Internal Data Monitoring Committee (IDMC) review on safety stopping criteria assessment, Part B will continue at the planned or adjusted dose based on exposure in Part A.
- Part B: designed as a randomized, open-label study including adults and adolescents (≥ 12 and ≤ 55 years of age). Before the randomization, a Cohort B0 composed of 25 adults and adolescents will serve as the basis to ensure the 1-day dosing leads to the expected exposures.

After the IDMC decision on the Cohort B0 safety, efficacy, and PK, 25, 50, and 25 participants will be randomized to Cohorts B1, B2, and B3.

Brief Summary:

The purpose of this study is to evaluate the safety, efficacy, and PK of the combination M5717 plus pyronaridine in participants with acute uncomplicated *P. falciparum* malaria. Pyramax will act as an internal control providing reference safety data and a benchmark for the efficacy evaluation.

Study details include:

- The endpoint selected for the assessment of efficacy (primary endpoint in Part B) is PCR-adjusted Adequate Clinical and Parasitological Response (ACPR) 28 days after first treatment (i.e., on Day 29) defined as absence of parasitemia (thick smear/microscopy, after adjustment for parasitemia due to new infections as determined by genotyping using PCR techniques), irrespective of axillary temperature, in participants who did not previously meet any of the criteria of early treatment failure (ETF), late clinical failure (LCF), or late parasitological failure (LPF).
- Study Duration: 42 (± 2) days.
- Treatment Duration: 1-day (Part A, Part B: Cohorts B0 and B1) or 2-day treatment (Cohort B2) with M5717 plus pyronaridine or 3-day treatment (Cohort B3) with Pyramax (pyronaridine-artesunate).
- Visit Frequency: 4 continuous days (72 hours post first dose) in the hospital after admission followed by 5 out-patient visits on Days 8, 15, 22, 29, and 43 (or day of premature discontinuation).

Number of Participants:

- Part A: As a safety/PK run-in cohort, it was considered acceptable to include 12 adult participants following the recommendations done for ascending dose Phase I studies. No formal sample size calculation was done for this part. In addition, the sample size is deemed adequate for obtaining relevant PK information.
- Part B: 50 participants per experimental cohort. CCI [redacted]. Simulations showed that with 50 participants and an expectation value of 95% of participants achieving PCR-adjusted ACPR 28 days after first treatment, the lower bound of its 95% confidence interval (based on Wilson's score method) is expected to be approximately 85%. The expected PCR-adjusted ACPR rate 28 days after first treatment for the combination of M5717 and pyronaridine was supported by a simulation from a PK/pharmacodynamic (PD) model that predicted a PCR-adjusted ACPR rate between 92% and 99% (based on an optimistic scenario with parasitemia on Day 2 higher than at Baseline and parasitemia on Day 3 ≥ 25% of count at Baseline). CCI [redacted]

CCI [redacted]

Study Intervention Groups and Duration:

Part A:

- Safety run-in cohort: 1-day dosing once daily of 330 mg M5717 given in combination with 360 mg pyronaridine.

Part B:

- Cohort B0: 1-day dosing once daily of M5717 plus pyronaridine:

  M5717
  - Adults and adolescents ≥ 45 kg: 660 mg
  - Adolescents < 45 kg: 500 mg

  Pyronaridine
  - ≥ 24 to < 45 kg: 360 mg
  - ≥ 45 to < 65 kg: 540 mg
  - ≥ 65 kg: 720 mg

After completion of Cohort B0 and evaluation by the IDMC participants will be randomized 1:2:1 to:

- Cohort B1: 1-day dosing once daily of M5717 plus pyronaridine:

  M5717
  - Adults and adolescents ≥ 45 kg: 660 mg
  - Adolescents < 45 kg: 500 mg

  Pyronaridine
  - ≥ 24 to < 45 kg: 360 mg
  - ≥ 45 to < 65 kg: 540 mg
  - ≥ 65 kg: 720 mg

- Cohort B2: 2-day dosing (once daily for 2 consecutive days) of M5717 plus pyronaridine:

  M5717
  - Adults and adolescents ≥ 45 kg: 660 mg
  - Adolescents < 45 kg: 500 mg

  Pyronaridine
  - ≥ 24 to < 45 kg: 360 mg
  - ≥ 45 to < 65 kg: 540 mg
  - ≥ 65 kg: 720 mg

- Cohort B3: 3-day dosing (once daily for 3 consecutive days) of Pyramax (pyronaridine-artesunate):

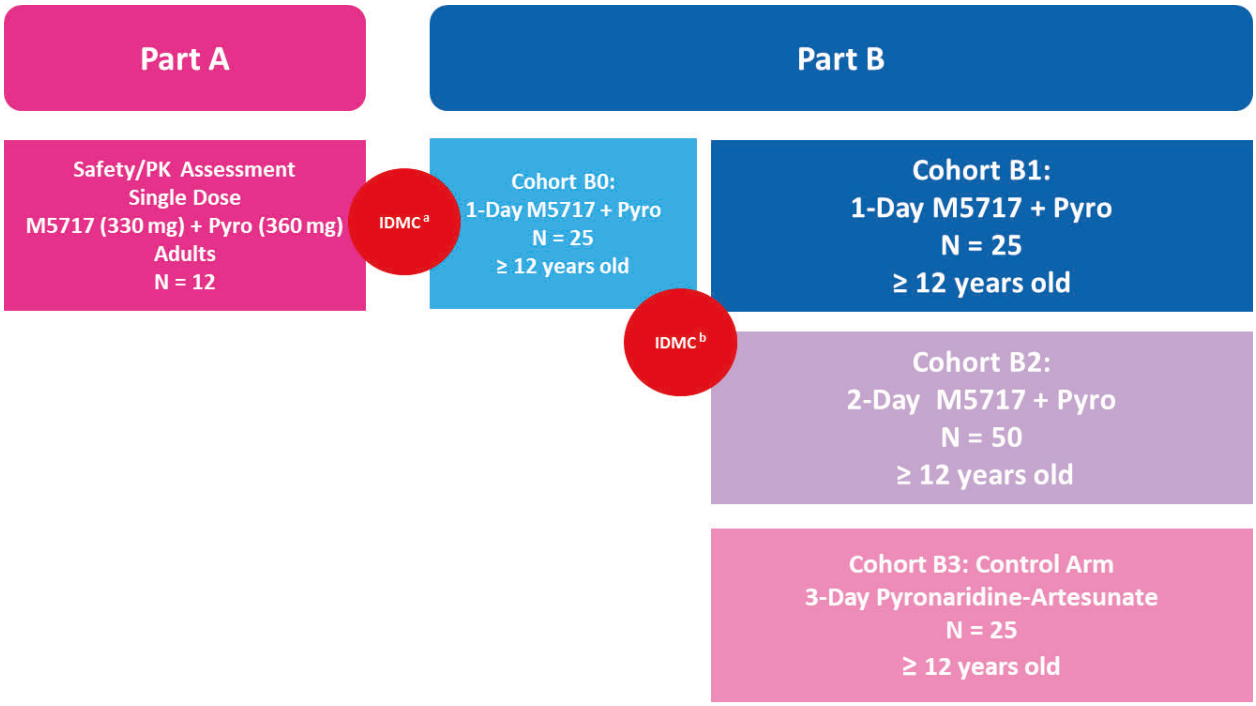
  Pyramax (pyronaridine-artesunate)
  - ≥ 24 to < 45 kg: 360/120 mg
  - ≥ 45 to < 65 kg: 540/180 mg
  - ≥ 65 kg: 720/240 mg

After completion of Part A and of Cohort B0 in Part B, the IDMC will have the option to recommend dose adjustments.

Involvement of Special Committee(s): Yes

An IDMC will evaluate the study safety and the benefit-risk assessment for the study progression to the next study stages.

1.2 Schema



IDMC=Internal Data Monitoring Committee, Pyro=pyronaridine. SmPC=Summary of Product Characteristics.

a. Escalation from Part A to Part B based on safety stopping criteria assessment (IDMC review) and potential dose adjustment based on exposure in Part A.

b. After completion of Cohort B0 and safety stopping criteria and exposure assessment (IDMC review), randomization in Part B (1:2:1 ratio in Cohorts B1, 2, and 3, respectively, stratified by site) will be opened.

M5717 free base dose, as a 660 mg flat dose for adults and adolescent participants with a body weight ≥ 45 kg. M5717 free base dose, as a 500 mg flat dose for adolescent participants with a body weight ≥ 24.0 to < 45 kg.

Pyronaridine administered according to the following weight bands: Participants' body weight ≥ 24 to < 45 kg: 360 mg; Participants' body weight ≥ 45 to < 65 kg: 540 mg; Participants' body weight ≥ 65 kg: 720 mg as specified in the SmPC for Pyramax.

Pyronaridine-artesunate to be administered according to the weight bands specified in the SmPC.

1.3 Schedule of Activities

Table 1 Schedule of Activities

Assessments & Procedures		Hospitalization				Out-patient Visits					Unscheduled Visit[a]	Notes
Visit Number	**SCR**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9/ EOS**	[a] An unscheduled visit can be required due to AEs, increase in ATs, or CNS events.	[b] Dosing within 6 hours of disease diagnosis (at a maximum of 12 hours). [c] Hospitalization for 4 continuous days (72 hours post first dose). [d] Day 29, or day at premature discontinuation (Note: All Day 29 study evaluations will be done before antimalarial rescue treatment is provided).
Day	**Day 1 (-12h)[b]**	**Day 1 (Dosing)**	**Day 2**	**Day 3**	**Day 4 (72h post)[c]**	**Day 8**	**Day 15**	**Day 22**	**Day 29[d]**	**Day 43**		
Visit Window	-	-	-	-	-	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days		
Informed consent	X											
Pharmacogenetic informed consent	X											Additional and separate informed consent form for pharmacogenetic (optional).
Inclusion/exclusion criteria	X											
COVID-19 antigen test	X											The test will be conducted at screening. Additional COVID-19 tests may be conducted as needed.
Demographic and medical history	X											
Physical examination	X				X[e]					X		[e] Physical examination will be done before discharge from hospital.
Neurological physical examination	X		X[f]	X	X	X	X	X[g]	X[g]	X	X	[f] If not performed on Day 1 due to malaria symptoms, should then be performed on Day 2. If abnormalities are detected it should be repeated at the next visit.

Assessments & Procedures		Hospitalization				Out-patient Visits					Unscheduled Visit[a]	Notes
Visit Number	**SCR**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9/ EOS**	[a] An unscheduled visit can be required due to AEs, increase in ATs, or CNS events.	[b] Dosing within 6 hours of disease diagnosis (at a maximum of 12 hours). [c] Hospitalization for 4 continuous days (72 hours post first dose). [d] Day 29, or day at premature discontinuation (Note: All Day 29 study evaluations will be done before antimalarial rescue treatment is provided).
Day	**Day 1 (-12h)[b]**	**Day 1 (Dosing)**	**Day 2**	**Day 3**	**Day 4 (72h post)[c]**	**Day 8**	**Day 15**	**Day 22**	**Day 29[d]**	**Day 43**		
Visit Window	**-**	**-**	**-**	**-**	**-**	**± 1 day**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**		
												[g] Assessment will be performed until neurological AESIs are resolved
Pregnancy test	X									X		WOCBP: serum test at Screening. Urine test at Day 43 or at withdrawal. Additional pregnancy tests may be conducted as needed.
Vital signs	X	X	X	X	X	X	X	X	X	X	X	Includes supine blood pressure and pulse rate. The exact assessment timepoints during the hospitalization period are provided in Table 2.
12-lead ECG	X	X			X				X			Will include QTcF assessment. 2, 4, and 8h postdose on Day 1. Predose ECG will be recorded in single, all other ECGs in triplicate. The exact assessment timepoints during the hospitalization period are provided in Table 2.

Assessments & Procedures		Hospitalization				Out-patient Visits					Unscheduled Visit[a]	Notes
Visit Number	**SCR**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9/ EOS**	[a] An unscheduled visit can be required due to AEs, increase in ATs, or CNS events.	[b] Dosing within 6 hours of disease diagnosis (at a maximum of 12 hours). [c] Hospitalization for 4 continuous days (72 hours post first dose). [d] Day 29, or day at premature discontinuation (Note: All Day 29 study evaluations will be done before antimalarial rescue treatment is provided).
Day	**Day 1 (-12h)[b]**	**Day 1 (Dosing)**	**Day 2**	**Day 3**	**Day 4 (72h post)[c]**	**Day 8**	**Day 15**	**Day 22**	**Day 29[d]**	**Day 43**		
Visit Window	**-**	**-**	**-**	**-**	**-**	**± 1 day**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**		
Hematology, coagulation, chemistry, and urinalysis	X			X		X			X		X AT follow-up (chemistry including ALT, AST, TB, and coagulation [optional if suspicion of drug-related ATs increased])	A sample should be collected before rescue treatment administration. If increase in: AT levels > 3 × ULN and/or TB > 2 × ULN, confirmation of abnormality will be required within 48-72h including ALT, AST, ALP, and TB, and afterwards weekly follow-up will be required at minimum; 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 the same follow-up protocol indicated previously when any increase of AT and TB is present, unless there is an alternative explanation for the clinical symptoms and the liver enzymes increase.
Randomization		X										
Dosing		X	X[h]	X[i]								[h] Day 2 dosing applicable for Cohort B2 (2-day) in

Assessments & Procedures		Hospitalization				Out-patient Visits					Unscheduled Visit[a]	Notes
Visit Number	**SCR**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9/ EOS**	[a] An unscheduled visit can be required due to AEs, increase in ATs, or CNS events.	[b] Dosing within 6 hours of disease diagnosis (at a maximum of 12 hours). [c] Hospitalization for 4 continuous days (72 hours post first dose). [d] Day 29, or day at premature discontinuation (Note: All Day 29 study evaluations will be done before antimalarial rescue treatment is provided).
Day	**Day 1 (-12h)[b]**	**Day 1 (Dosing)**	**Day 2**	**Day 3**	**Day 4 (72h post)[c]**	**Day 8**	**Day 15**	**Day 22**	**Day 29[d]**	**Day 43**		
Visit Window	**-**	**-**	**-**	**-**	**-**	**± 1 day**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**		
												Part B and Cohort B3 (Pyramax). [i] Day 3 dosing applicable for Cohort B3 (Pyramax). Day 2 and 3 dosing will each be 24 hours post each previous dose.
Temperature	X	X	X	X	X	X	X	X	X	X	X	The exact assessment timepoints during the hospitalization period are provided in Table 2.
Adverse events		⇐========== Continuous ==========⇒										
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	
Rescue treatment			As required									Rescue malaria treatment to be administered beginning Day 43 in Part A or as required.
Assessments only performed if the participant has been enrolled:												
Malaria and severe malaria signs and symptoms	X	X	X	X	X	X	X	X	X	X	X	
Blood films (microscopy)	X	X	X	X	X	X	X	X	X	X	X	Thick and thin blood films will be collected at Screening to confirm inclusion/exclusion criteria.

Assessments & Procedures		Hospitalization				Out-patient Visits					Unscheduled Visit[a]	Notes
Visit Number	SCR	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9/ EOS	[a] An unscheduled visit can be required due to AEs, increase in ATs, or CNS events.	[b] Dosing within 6 hours of disease diagnosis (at a maximum of 12 hours).
Day	Day 1 (-12h)[b]	Day 1 (Dosing)	Day 2	Day 3	Day 4 (72h post)[c]	Day 8	Day 15	Day 22	Day 29[d]	Day 43		[c] Hospitalization for 4 continuous days (72 hours post first dose).
Visit Window	-	-	-	-	-	± 1 day	± 2 days	± 2 days	± 2 days	± 2 days		[d] Day 29, or day at premature discontinuation (Note: All Day 29 study evaluations will be done before antimalarial rescue treatment is provided).
												A thin blood smear should be reserved in the event of recrudescence, to confirm *P. falciparum*. The exact sampling timepoints during the hospitalization period are provided in Table 2.
[redacted]		CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CCCI [redacted] C I		[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Assessments & Procedures		Hospitalization				Out-patient Visits					Unscheduled Visit[a]	Notes
Visit Number	**SCR**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9/ EOS**	[a] An unscheduled visit can be required due to AEs, increase in ATs, or CNS events.	[b] Dosing within 6 hours of disease diagnosis (at a maximum of 12 hours).
Day	**Day 1 (-12h)[b]**	**Day 1 (Dosing)**	**Day 2**	**Day 3**	**Day 4 (72h post)[c]**	**Day 8**	**Day 15**	**Day 22**	**Day 29[d]**	**Day 43**		[c] Hospitalization for 4 continuous days (72 hours post first dose).
Visit Window	**-**	**-**	**-**	**-**	**-**	**± 1 day**	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**		[d] Day 29, or day at premature discontinuation (Note: All Day 29 study evaluations will be done before antimalarial rescue treatment is provided).
PK blood sampling for M5717		X	X	X	X	X	X	X	X	X		The exact sampling timepoints during the hospitalization period are provided in Table 2. Not applicable for Pyramax (Cohort B3).
PK blood sampling for pyronaridine		X	X	X	X	X	X	X	X	X		The exact sampling timepoints during the hospitalization period are provided in Table 2. Not applicable for Pyramax (Cohort B3).
CCI												

ACPR= adequate clinical and parasitological response, AE=adverse event, ALP= alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, AT=aminotransferase, CNS=central nervous system, DILI=drug-induced liver injury, ECG=electrocardiogram, EOS=end-of-study, PK=pharmacokinetic(s), RT-qPCR= reverse transcription quantitative real-time polymerase chain reaction, QTcF= corrected QT interval by Fridericia's formula, RT=reverse transcriptase, SCR=screening, TB=total bilirubin, ULN=upper limit of normal, WOCBP= woman of childbearing potential.

Table 2 Assessment and Sampling Timepoints During the Hospitalization Period: PK, Vital Signs, ECG, and Parasitemia

Assessment																	Notes
Visit	**SCR**	**Visit 1**							**Visit 2**				**Visit 3**				**Visit 4**	
Day	**Day 1 (-12h)**	**Day 1 (first dose)**							**Day 2**				**Day 3**				**Day 4**	
Hours after first dosing		**Pre**	**2**	**4**	**6**	**8**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**66**	**72**	
Window		**± 30 min**							**± 30 min**				**± 30 min**					
Vital signs	X	X	X	X		X	X	X	X		X		X		X		X	
Temperature	X	X			X		X	X	X	X	X	X	X	X	X	X	X	Any other timepoint at the discretion of the Investigator
ECG	X		X	X		X											X	
Blood films (microscopy)	X	X			X		X	X	X	X	X	X	X	X	X	X	X	
CCI [redacted]		[redacted]					[redacted]		[redacted]				[redacted]				[redacted]	
PK blood sampling for M5717		X	X	X	X	X	X		X	X	X		X				X	Not applicable for Cohort B3.
PK blood sampling for pyronaridine		X	X	X	X	X	X		X	X	X		X				X	Not applicable for Cohort B3.

ECG=electrocardiogram, PK=pharmacokinetic(s), Pre=predose, RT-qPCR= reverse transcription quantitative real-time polymerase chain reaction, Scr=screening (approximately 12 hours before dosing).

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).

Detailed information on the chemistry, pharmacology, efficacy, and safety of M5717 and pyronaridine is in the respective IBs.

CCI [redacted]

[redacted]

[redacted]

[redacted]

2.2 Background

Human malaria is an acute febrile illness caused by 5 *Plasmodium* parasite species (*P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi*). According to the latest estimates, released in 2021 by the WHO, there were about 241 million cases of malaria and an estimated 627,000 deaths due to malaria worldwide in 2020 (WHO Malaria Report, 2021). Most deaths (77%) occur among children below 5 years of age, most of whom live in Africa. In a non-immune individual, symptoms appear about 7 days after the infective mosquito bite and the subsequent asymptomatic liver stages.

The goal of drug combination therapy for parasitic diseases such as malaria is to prevent the emergence of resistance while providing additional benefit for the treatment by providing a higher cure rate than the individual compounds alone, which would reduce the risk of developing severe malaria as well as the mortality rate.

The standard of care according to the WHO 2021 guidelines (WHO Guidelines for Malaria, 2021) is artemisinin-based combination therapy. Artemisinin derivatives have a very rapid mode of action reducing the parasite biomass and thus reduce the probability to select resistance against the long-acting partner compound. Treatment with an artemisinin derivative alone (such as artesunate) requires a 7-day dosing due to its short half-life of about 1 hour and often results in incomplete clearance of the parasites, which may result in resistance. The combination with a long-acting partner synergizes the initial parasite killing rate, while providing prolonged antiparasitic protection and allowing reduction of the treatment course to 3 days. The 6 artemisinin-based combinations recommended by WHO have shown an efficacy superior to 90% to 95% evaluated through the efficacy outcome ACPR28.

The emergence of artemisinin resistance in Africa during the last years has increased the need for new non-artemisinin-based combination therapies that are effective against *P. falciparum* malaria. The need to provide supervised treatment to increase compliance and reduce resistance is a major objective for malaria elimination and as such TPP's favoring 1- or 2-day dosing have been prioritized for the development of new malaria combinations. M5717, a new chemical entity, plus pyronaridine a molecule already existing in the approved antimalarial product Pyramax (a combination of artesunate and pyronaridine) is a promising new combination.

M5717 is a first-in-class compound with a new mode of action (i.e., inhibition of plasmodial protein synthesis) and showed excellent activity against malaria blood stage (including clinical isolates and drug-resistant strains), liver-stage, and in transmission blocking assays in preclinical investigations. M5717 displayed a long half-life and an effective exposure with high potency against all forms of the parasite. This allows for administration of a single oral dose and maintaining protection over an extended period of time. A Phase I FIH study with an IBSM model demonstrated in laboratory isolates of *P. falciparum* that M5717 cured all 8 participants treated with a dose of 800 mg M5717 succinate (equivalent to 660 mg of the M5717), while lower doses were able to clear parasitemia, but recrudescence was observed in 3 out of 6 participants in the 150 mg cohort and in 2 out of 8 participants in the 400 mg cohort.

Pyronaridine was first used in China for the treatment of malaria as a single agent and later has been developed as a fixed-dose combination with artesunate which is currently registered in more than 25 countries and marketed in several countries as Pyramax: a fixed-dose combination of pyronaridine tetraphosphate and artesunate administered once a day for 3 consecutive days (180 mg/60 mg for the tablets and 60 mg/20 mg granules for oral suspension for the pediatric formulation) with a total daily dose depending on pre-defined weight bands with 720 mg/240 mg as maximum daily dose (Croft 2012). As of July 2021, more than 2 million patients have received Pyramax treatment worldwide. Pyronaridine is a molecule with blood stage activity that has to date shown no signs of resistance in the field.

Pyramax clinical efficacy and safety was demonstrated for acute uncomplicated *P. falciparum* malaria through 2 Phase II and 3 Phase III studies, as well as 1 Phase IIIB and 1 Phase IV study focused on the safety of the combination. A beneficial effect of Pyramax was established in the 2 pivotal Phase III studies (Africa, South-East Asia) in patients weighing > 20 kg and non-inferiority to established treatments could be shown. A single 3-day treatment course of Pyramax was generally well tolerated in the clinical studies. However, the clinical study data showed that a slightly higher number of patients experienced a transient mild to moderate increase in transaminases compared to the reference treatments.

In addition to matching CC half-life, CCI data have shown additive CC interactions between M5717 and pyronaridine with respect to PCT and elimination of M5717 resistant parasites. Both drugs have characteristics that meet the desired TPP for a new antimalarial treatment.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of M5717, pyronaridine, and pyronaridine-artesunate may be found in Section 4.2 and the respective IBs and SPC.

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

2.3.1 Risk Assessment

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) (M5717, Pyronaridine)		
Lack of efficacy (ETF) and progression to severe malaria	In Part A, in which intermediate doses of the M5717-pyronaridine combination are evaluated, an ETF in around 2.5% to 40% of the population depending on the model used for the efficacy prediction could occur.	Close parasitemia monitoring is implemented in the Schedules of Assessments and rescue medication with standard of care will be applied once the treatment failure is confirmed by microscopy.
Overlapping liver enzymes increase and hepatotoxicity	Pyronaridine has been shown to induce transaminases increase in around 2% to 3% of the population, while M5717-induced mild, transient, non-dose related increases of transaminases, but there is an unknown risk of potentiation of such undesirable effects.	Specific monitoring of LFT has been established, patients with abnormal LFT at Baseline have been excluded, specific stopping criteria have been established between the dose increase from Part A to Part B, and before opening the randomized phase of Part B.
Overlapping central nervous system events	M5717 at high doses produced mild and transient CNS events (blurred vision and paresthesia), while Pyronaridine has been related to some neurological events (paresthesia and dizziness)	Specific monitoring of neurological signs and symptoms included in the participants' follow-up; exclusion of patients with known history of neurological diseases. A maximum dose was established for Part B so that predicted exposures will remain below those observed in participants with CNS events during the FIH study.
Overlapping gastrointestinal events	Both compounds, M5717 and pyronaridine have been shown through the nonclinical and clinical studies to induce gastrointestinal events such as nausea, vomiting, and abdominal pain.	Specific monitoring of the severity and duration of gastrointestinal symptoms is included in the participants' follow-up.
Study Procedures		
Blood extraction (blood sampling for films, PK, hematology, and chemistry)	As adolescents are part of the target population, and malaria is associated with anemia due to hemolysis, excessive blood extraction can worsen the anemia.	Limits for blood sampling are established according to weight bands established by the University of Michigan guideline for blood draw. This is applicable for participants with a hematocrit ≥ 38%, corresponding to 10% of total blood volume for the entire study. For participants with a hematocrit value < 38%, the maximum total blood volume extracted for the entire study will not exceed 5% of the total blood volume, and in any case no more than 1% of total blood volume in a single day. Should hematocrit values be < 38%, the Investigator may determine whether PK samples will be collected.

<table>
<tr><th>Identified and Potential Risks of Clinical Significance</th><th>Summary of Data/Rationale for Risk</th><th>Mitigation Strategy</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><th>Weight Band (kg)</th><th>Maximum Blood Volume Extracted (mL) in Total During the Study</th><th>Maximum Blood Volume Extracted (mL) in Total During the Study for Participants with Hematocrit < 38%</th></tr>
<tr><td>24-25</td><td>150</td><td>75</td></tr>
<tr><td>26-30</td><td>200</td><td>100</td></tr>
<tr><td>31-35</td><td>250</td><td>125</td></tr>
<tr><td>36-40</td><td>300</td><td>150</td></tr>
<tr><td>41-45</td><td>350</td><td>175</td></tr>
<tr><td>46-50</td><td>400</td><td>200</td></tr>
<tr><td>>50</td><td>450</td><td>225</td></tr>
</table>
The overseeing physicians will have the ultimate authority to discontinue research blood draws.</td></tr>
<tr><th colspan="3">Other</th></tr>
<tr><td>SARS-CoV-2 infection for study participants as long as the COVID-19 pandemic situation is ongoing</td><td>As for the general population, there is a risk of a SARS-CoV-2 infection for study participants as long as the COVID-19 pandemic situation is ongoing.</td><td>During the entire study, all recommendations issued by WHO as well as local guidelines will be followed with respect to the minimization of the risk of disease spreading, e.g., social distancing, disinfection, hygiene, and wearing of appropriate mouth-nose masks. During the pandemic situation, further measures according to recommendations and requirements from local Health Authorities may become necessary and will be followed within the context of this study as far as applicable, in order to ensure full implementation of the principles of GCP with priority on participant safety in this study also during the COVID-19 pandemic situation. These measures are described in a preventive action plan implemented at the Investigator site.
In order to minimize the risk coming from a current infection and the risk of getting infected by other participants during the in-house periods of the study, the following measures are to be implemented: Only patients with a negative COVID-19 antigen test at screening will be included into the study. Furthermore, as part of the clinical study procedures, participants will be closely monitored (including for signs of COVID-19) during the entire study duration. The continuation of the study in the case of a SARS-CoV-2 infection in a study participant, in an identified contact to a SARS-CoV-2 positive participant, or COVID-19 patient will be decided at the Investigator’s discretion and in agreement with the medical monitoring</td></tr>
</table>

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		team. The Sponsor will monitor the events related to any SARS-CoV-2 infection reported following M5717-pyronaridine or Pyramax administration regularly and update the recommendations, if necessary.

2.3.2 Benefit Assessment

The M5717-pyronaridine combination has never been used in patients with acute uncomplicated *P. falciparum* malaria. There is already evidence supporting the efficacy and safety of pyronaridine, as it is a component of Pyramax (together with artesunate). Pyramax received a positive opinion in 2012 from EMA and is currently recommended by WHO as standard of care for the treatment of acute uncomplicated malaria. M5717 has been evaluated through an IBSM study in which volunteers were infected with *P. falciparum* strains, and the parasitemia was monitored. M5717 demonstrated the ability to clear parasites at a 640 mg dose, avoiding recrudescence (re-emergence of parasites), and was shown to be safe and tolerated up to 1440 mg dose in a FIH study.

The individual benefit to a particular participant cannot be guaranteed, but the prediction based on modeling and simulation activities is that > 60% to 98% of the participants will be cured depending on the dosing regimen (data on file). The patient's participation will help to contribute to the process of developing new therapies in an area of unmet need, in which resistance to the standard of care is returning malaria to being a life-threatening condition with a limited therapeutic arsenal.

As a mitigation strategy of the risks identified, all participants will be monitored in a close follow-up that exceeds the standard of care and their status will be checked for laboratory procedures (hematology, chemistry, and urinalysis) as well as medical tests (ECG).

2.3.3 Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to 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 participants with acute uncomplicated *P. falciparum* malaria.

3 Objectives and Estimands

Part A: Safety/Pharmacokinetics Run-in Cohort

Part A of the study will explore the safety and PK of a single dose of M5717 of 330 mg given in combination with pyronaridine tetraphosphate (360 mg) in adult participants with acute uncomplicated *P. falciparum* malaria. Efficacy will be evaluated as a secondary objective. Doses in Part B of the study may be adjusted based on the exposure and safety data collected in Part A.

Please note that if endpoints refer to specific timepoints, the timepoints given refer to days after treatment. Thereby, time of treatment start is defined to be on Day 1. Consequently, if an endpoint defines the measurement to be taken, e.g., 7 days after treatment, this means that the measurement is actually taken on Day 8.

Table 3 Objectives, Endpoints, and Estimands Part A

Objectives	Estimands/Endpoints	Ref. #
Primary		
To evaluate the safety and tolerability of the M5717-pyronaridine combination in adult participants with acute uncomplicated malaria due to *P. falciparum*	**Endpoint:** Incidence, severity, and seriousness of study intervention-related TEAEs, as per CTCAE v 5.0 Additional endpoints related to safety and tolerability up to Day 29 (± 2 days): laboratory assessments, ECGs, and vital signs.	1
Secondary		
To characterize the PK of M5717 and pyronaridine in adult participants with acute uncomplicated malaria due to *P. falciparum*	**Endpoint:** • PK profiles for M5717 and pyronaridine • PK parameters of M5717 and pyronaridine such as $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}24}$, C_{max}, $t_{½}$, t_{max}, CL/F, V_Z/F, when data permits	2
To describe the clinical efficacy of the M5717-pyronaridine combination in adult participants with acute uncomplicated malaria due to *P. falciparum*	**Endpoint:** ETF defined as meeting any of the following: • Danger signs or severe malaria 1, 2, or 3 days after treatment, in the presence of parasitemia • Parasitemia 2 days after treatment higher than on day of treatment, irrespective of axillary temperature • Parasitemia 3 days after treatment with axillary temperature ≥ 37.5°C • Parasitemia 3 days after treatment ≥ 25% of count on day of treatment **Target Population:** Adult patients with acute uncomplicated malaria due to *P. falciparum* **Treatment:** Single dose M5717 330 mg plus pyronaridine 360 mg **Intercurrent Event Strategy:** • Intake of rescue medication before or at Day 4: Composite variable strategy, i.e., endpoint is considered as failure (= presence of ETF) • Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity) before or at Day 4: Principal Stratum strategy, i.e., treatment effect is estimated within the principal stratum of participants that potentially don't experience the ICE • Experience of any event that affects absorption (i.e., vomiting within the study intervention absorptive period of 2 × median t_{max}) or immune response (severe immunocompromised participants): Treatment policy strategy, i.e., treatment effect is estimated regardless of intercurrent event or Principal Stratum strategy • Premature study discontinuation before or at Day 4 due to lack of efficacy: Composite variable strategy • Death due to malaria before or at Day 4: Composite variable strategy **Population-level Summary:** ETF rate, i.e. proportion of participants with ETF.	3

Objectives	Estimands/Endpoints	Ref. #
	Endpoint: LCF defined as: • Danger signs or severe malaria in the presence of parasitemia on any day between 4 and 28 days after treatment (i.e., between Days 5 and 29) in participants who did not previously meet any of the criteria of ETF • Presence of parasitemia on any day between 4 and 28 days after treatment with axillary temperature ≥ 37.5°C in participants who did not previously meet any of the criteria of ETF **Target Population:** See endpoint 3 **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** • Intake of rescue medication between 4 and 28 days after treatment: Composite variable strategy, i.e., endpoint is considered as failure (= presence of LCF) • Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity) between 4 and 28 days after treatment: Principal Stratum strategy, i.e., treatment effect is estimated within the principal stratum of participants that potentially don't experience the ICE • Experience of any event that affects absorption (i.e., vomiting within the study intervention absorptive period of 2 × median t_{max}) or immune response (severe immunocompromised participants): Treatment policy strategy, i.e., treatment effect is estimated regardless of intercurrent event or Principal Stratum strategy • Premature study discontinuation between 4 and 28 days after treatment due to lack of efficacy: Composite variable strategy • Death due to malaria between 4 and 28 days after treatment: Composite variable strategy **Population-level Summary:** LCF rate, i.e., proportion of participants with LCF	4
	Endpoint: LPF defined as: Presence of parasitemia on any day between 7 and 28 days after treatment (i.e., between Days 8 and 29) with axillary temperature < 37.5°C in participants who did not previously meet any of the criteria of ETF or LCF **Target Population:** See endpoint 3 **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** • Intake of rescue medication between 7 and 28 days after treatment: Composite variable strategy, i.e., endpoint is considered as failure (= presence of LPF) • Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity) between 7 and 28 days after treatment: Principal Stratum strategy, i.e., treatment effect is estimated within the principal stratum of participants that potentially don't experience the ICE	5

Objectives	Estimands/Endpoints	Ref. #
	• Experience of any event that affects absorption (i.e., vomiting within the study intervention absorptive period of 2 × median t_{max}) or immune response (severe immunocompromised participants): Treatment policy strategy, i.e., treatment effect is estimated regardless of intercurrent event • Premature study discontinuation between 7 and 28 days after treatment due to lack of efficacy: Composite variable strategy or Principal Stratum strategy • Death due to malaria between 7 and 28 days after treatment: Composite variable strategy **Population-level Summary:** LPF rate, i.e., proportion of participants with LPF	
	Endpoint: Crude (PCR-uncorrected) ACPR 14, 28, and 42 days after treatment defined as absence of parasitemia (thick smear/microscopy), irrespective of axillary temperature, in participants who did not previously meet any of the criteria of ETF, LCF, or LPF **Target Population:** See endpoint 3 **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** • Intake of rescue medication at any timepoint: Composite variable strategy, i.e., endpoint is considered as treatment failure • Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity) at any timepoint: Principal Stratum strategy, i.e., treatment effect is estimated within the principal stratum of participants that potentially don't experience the ICE • Experience of any event that affects absorption (i.e., vomiting within the study intervention absorptive period of 2 × median t_{max}) or immune response (severe immunocompromised participants): Treatment policy strategy, i.e., treatment effect is estimated regardless of intercurrent event or Principal Stratum strategy • Premature study discontinuation at any timepoint due to lack of efficacy: Composite variable strategy • Death due to malaria at any timepoint: Composite variable strategy **Population-level Summary:** Crude ACPR rate at each timepoint, i.e., proportion of participants with crude ACPR at each timepoint	6
	Endpoint: PCR-adjusted ACPR 14, 28, and 42 days after treatment defined as absence of parasitemia (thick smear/microscopy, after adjustment for parasitemia due to new infections as determined by genotyping using PCR techniques), irrespective of axillary temperature, in participants who did not previously meet any of the criteria of ETF, LCF, or LPF. **Target Population:** see endpoint 3 **Treatment:** see endpoint 3 **Intercurrent Event Strategy:** See endpoint 3 **Population-level Summary:** PCR-adjusted ACPR rate at each timepoint, i.e., proportion of participants with PCR-adjusted ACPR at each timepoint	7

Objectives	Estimands/Endpoints	Ref. #
	Endpoint: Crude (PCR-uncorrected) efficacy 8 days after treatment, defined as absence of parasitemia (thick smear/microscopy) in participants who did not previously meet any of the criteria of ETF or LCF **Target Population:** See endpoint 3 **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** See endpoint 3 **Population-level Summary:** Crude efficacy rate, i.e., proportion of participants with crude (PCR-uncorrected) efficacy 8 days after treatment (Day 9)	8
	Endpoint: PCR-adjusted efficacy 8 days after treatment as defined as absence of parasitemia (thick smear/microscopy, after adjustment for parasitemia due to new infections as determined by genotyping using PCR techniques) in participants who did not previously meet any of the criteria of ETF or LCF **Target Population:** See endpoint 3 **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** see endpoint 3 **Population-level Summary:** PCR-adjusted efficacy rate, i.e., proportion of participants with PCR-adjusted efficacy 8 days after treatment (Day 9)	9
	Endpoint: PRR defined as decrease in viable parasites over 48 hours, corresponding to 1 asexual parasite life cycle **Target Population:** See endpoint 3 **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** see endpoint 3 **Population-level Summary:** Geometric mean of the PRR	10
	Endpoint: Fever clearance time defined as the time from first dosing to the first measurement of an axillary temperature < 37.5°C for 2 consecutive temperature readings plus confirmed normal temperature 24 h after the first normal body temperature reading. **Target Population:** Adult patients with acute uncomplicated malaria due to *P. falciparum* with an increased axillary temperature (≥ 37.5°C) **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** • Intake of rescue medication: Composite variable strategy, i.e., time to fever clearance is censored at Day 29 • Intake of concomitant medications as a continuous treatment that have an impact on fever: Composite variable strategy, i.e., time to fever clearance is censored at Day 29 • Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity): Composite variable strategy, i.e., time to fever clearance is censored at Day 29	11

Objectives	Estimands/Endpoints	Ref. #
	• Experience of any event that affects absorption (i.e., vomiting within the study intervention absorptive period of 2 × median t_{max}) or immune response (severe immunocompromised participants): Treatment policy strategy, i.e., treatment effect is estimated regardless of intercurrent event or Principal Stratum strategy • Premature study discontinuation due to lack of efficacy: On-treatment strategy, i.e., time to fever clearance is censored at the day of the last available body temperature assessment • Death due to malaria: On-treatment strategy, i.e., time to fever clearance is censored at the day of the last available body temperature assessment **Population-level Summary:** Median fever clearance time as estimated by Kaplan-Meier method	
	Endpoint: Parasite clearance time defined as time from dosing to the first negative (no parasites) film (microscopy) **Target Population:** See endpoint 3 **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** see previous endpoint with the exception of intake of concomitant medications, which is not an ICE for parasite clearance time. Censoring will be done at the day of the last available microscopy assessment. **Population-level Summary:** Median parasite clearance time as estimated by Kaplan-Meier method	12
	Endpoint: Time to recrudescence, defined as the time from primary cure to the re-emergence of the same parasite strain that originated the primary infection **Target Population:** Adult patients with acute uncomplicated malaria due to *P. falciparum* who are primarily cured **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity) at any timepoint: Principal Stratum strategy, i.e., treatment effect is estimated within the principal stratum of participants that potentially don't experience the ICE **Population-level Summary:** Median time to recrudescence as estimated by Kaplan-Meier method	13
	Endpoint: Time to re-infection, defined as the time from primary cure to the re-emergence of a different parasite strain that originated the primary infection **Target Population:** See endpoint 3 **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** Intake of prohibited medication that impacts treatment effect (e.g. drug with antimalarial activity) at any timepoint: Principal Stratum strategy, i.e., treatment effect is estimated within the principal stratum of participants that potentially don't experience the ICE **Population-level Summary:** Median time to re-infection as estimated by Kaplan-Meier method	14

Objectives	Estimands/Endpoints	Ref. #
	Endpoint: Time to re-emergence, defined as the time from primary cure to having recrudescence or re-infection (the first one that occurs) **Target Population:** see endpoint 3 **Treatment:** See endpoint 3 **Intercurrent Event Strategy:** Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity) at any timepoint: Principal Stratum strategy, i.e., treatment effect is estimated within the principal stratum of participants that potentially don't experience the ICE **Population-level Summary:** Median time to re-emergence as estimated by Kaplan-Meier method	15
CCI		

Part B: Part B of the study will explore the efficacy, safety, tolerability, and PK of different regimens of M5717 in combination with pyronaridine in adolescent and adult participants with acute uncomplicated *P. falciparum* malaria. Randomization to either M5717-pyronaridine in a single day regimen (Cohort B1), or M5717-pyronaridine in a 2-day regimen (Cohort B2), or Pyramax (3-day regimen, Cohort B3) is planned to evaluate the efficacy and safety of the combination.

Table 4 Objectives, Endpoints, and Estimands Part B

Objectives	Estimands/Endpoints	Ref. #
Primary		
To describe clinical efficacy of the M5717-pyronaridine combination and of Pyramax in adult and adolescent participants with acute uncomplicated malaria due to *P. falciparum*	**Endpoint**: PCR-adjusted ACPR 28 days after first treatment (i.e., on Day 29) defined as absence of parasitemia (thick smear/microscopy, after adjustment for parasitemia due to new infections as determined by genotyping using PCR techniques), irrespective of axillary temperature, in participants who did not previously meet any of the criteria of ETF, LCF, or LPF	19
	Target Population: Adult and adolescent patients with acute uncomplicated malaria due to *P. falciparum* **Treatment:** • Single dose M5717 660/500 mg (adolescents < 45 kg) plus pyronaridine 720 mg (≥ 65 kg), 540 mg (≥ 45 to < 65 kg), or 360 mg (≥ 24 to < 45 kg) (Cohorts B0 and B1) • 2-day regimen of M5717 660/500 mg plus pyronaridine 720 mg (≥ 65 kg), 540 mg (≥ 45 to < 65 kg), or 360 mg (≥ 24 to < 45 kg) (Cohort B2) • 3-day regimen of Pyramax (pyronaridine-artesunate) 720/240 mg (≥ 65 kg), 540/180 mg (≥ 45 to < 65 kg), or 360/120 mg (≥ 24 to < 45 kg) (Cohort B3) **Intercurrent Event Strategy**: • Intake of rescue medication: Composite variable strategy, i.e., endpoint is considered as treatment failure (= presence of parasitemia) • Intake of prohibited medication that impacts treatment effect (e.g., drug with antimalarial activity) at any timepoint: Principal Stratum strategy, i.e., treatment effect is estimated within the principal stratum of participants that potentially don't experience the ICE • Experience of any event that affects absorption (i.e., vomiting within the study intervention absorptive period of 2 × median t_{max}) or immune response (severe immunocompromised participants): Treatment policy strategy, i.e., treatment effect is estimated regardless of intercurrent event or Principal Stratum strategy • Premature study discontinuation due to lack of efficacy: Composite variable strategy • Death due to malaria: Composite variable strategy **Population-level Summary:** PCR-adjusted ACPR rate, i.e., proportion of participants achieving PCR-adjusted ACPR at Day 29	

Objectives	Estimands/Endpoints	Ref. #
Secondary		
To describe the clinical and parasitological efficacy of the M5717-pyronaridine combination and of Pyramax in adult and adolescent participants with acute uncomplicated malaria due *to P. falciparum*	**Endpoint:** ETF **Target Population:** See endpoint 19 **Treatment:** See endpoint 19 **Intercurrent Event Strategy:** See endpoint 3 **Population-level Summary:** See endpoint 3	20
	Endpoint: LCF **Target Population:** See endpoint 19 **Treatment:** See endpoint 19 **Intercurrent Event Strategy:** See endpoint 4 **Population-level Summary:** See endpoint 4	21
	Endpoint: LPF **Target Population:** see endpoint 19 **Treatment:** see endpoint 19 **Intercurrent Event Strategy:** See endpoint 5 **Population-level Summary:** See endpoint 5	22
	Endpoint: Crude (PCR-uncorrected) ACPR 14, 28 and 42 days after treatment **Target Population:** See endpoint 19 **Treatment:** See endpoint 19 **Intercurrent Event Strategy:** See endpoint 6 **Population-level Summary:** See endpoint 6	23
	Endpoint: PCR-adjusted ACPR 14 and 42 days after treatment **Target Population:** see endpoint 19 **Treatment:** see endpoint 19 **Intercurrent Event Strategy:** see endpoint 7 **Population-level Summary:** see endpoint 7	24
	Endpoint: Crude (PCR-uncorrected) efficacy 8 days after treatment **Target Population:** See endpoint 19 **Treatment:** See endpoint 19 **Intercurrent Event Strategy:** See endpoint 8 **Population-level Summary:** See endpoint 8	25

Objectives	Estimands/Endpoints	Ref. #
	Endpoint: PCR-adjusted efficacy 8 days after treatment **Target Population:** See endpoint 19 **Treatment:** See endpoint 19 **Intercurrent Event Strategy:** See endpoint 9 **Population-level Summary:** See endpoint 9	26
	Endpoint: PRR **Target Population:** See endpoint 19 **Treatment:** See endpoint 19 **Intercurrent Event Strategy:** See endpoint 10 **Population-level Summary:** See endpoint 10	27
	Endpoints: Fever clearance time **Target Population:** Adult and adolescent patients with acute uncomplicated malaria due to *P. falciparum* with an increased axillary temperature (≥ 37.5°C) **Treatment:** See endpoint 19 **Intercurrent Event Strategy:** See endpoint 11 **Population-level Summary**: See endpoint 11	28
	Endpoint: Parasite clearance time **Target Population:** See endpoint 19 **Treatment:** See endpoint 19 **Intercurrent Event Strategy:** See endpoint 12 **Population-level Summary**: See endpoint 12	29
	Endpoint: Time to recrudescence **Target Population:** See endpoint 19 **Treatment:** See endpoint 19 **Intercurrent Event Strategy:** See endpoint 13 **Population-level Summary:** See endpoint 13	30
	Endpoint: Time to re-infection **Target Population:** See endpoint 19 **Treatment:** See endpoint 19 **Intercurrent Event Strategy:** See endpoint 14 **Population-level Summary:** See endpoint 14	31

Objectives	Estimands/Endpoints	Ref. #
	Endpoint: Time to re-emergence **Target Population:** See endpoint 19 **Treatment:** See endpoint 19 **Intercurrent Event Strategy:** See endpoint 15 **Population-level Summary:** See endpoint 15	32
To evaluate the safety and tolerability of the M5717-pyronaridine combination in adult and adolescent participants with acute uncomplicated malaria due to *P. falciparum*	**Endpoint**: Incidence, severity, and seriousness of study intervention-related TEAEs, as per CTCAE v 5.0 Additional endpoints related to safety and tolerability up to Day 29 (± 2 days): laboratory assessments, ECGs, and vital signs.	33
To characterize the PK of M5717 and pyronaridine in adult and adolescent participants with acute uncomplicated malaria due to *P. falciparum* in Cohorts B0, B1 and B2.	**Endpoint:** • PK profiles for M5717 and pyronaridine in Cohorts B0, B1 and B2. • PK parameters of M5717 and pyronaridine such as $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}24}$, C_{max}, $t_{½}$, t_{max}, CL/F, V_Z/F, when data permits	34

[redacted]

4 Study Design

4.1 Overall Design

Study Design:	Phase IIa, proof of concept, randomized, open-label study
Control Method:	Randomized and controlled (internal benchmark)
Single or Multicenter:	Multicenter
Control Group:	Pyronaridine-artesunate (Pyramax)
Study Population Type:	Adults and adolescent patients with acute uncomplicated malaria due to *P. falciparum*
Level and Method of Blinding:	Open label
Bias Minimalization Method(s):	Evaluators are blinded (parasitologists and laboratory personnel performing the microscopy and PCR)
Study Intervention Assignment Method:	Part B only – randomized, stratified. Randomization occurs immediately after Screening (after completion of Cohort B0 and second IDMC), as treatment should be provided within the first 6 hours after disease diagnosis.
Involvement of Special Committee(s):	Yes (see Appendix 2)
Total Duration of Study Participation per Participant:	Part A and Part B: 42 (± 2 days) (see Section 1.3)
Provisions for Study Extension or Entry into Roll-over Studies:	Not applicable
Adaptive Aspects of Study Design:	Safety stopping criteria established in the protocol, with an IDMC evaluating the TEAE imputation as well as dose cohort escalation (transition from Part A to Part B, Cohort B0, and after Cohort B0 to continue the 1-day dosing in Cohort B1, to include the 2-day dosing in Cohort B2, and to include the 3-day dosing of Pyramax in Cohort B3, see Section 1.2). 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 or more 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 or more 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 v 5.0. Lack of efficacy will be monitored in the first 16 participants recruited in Cohort B0. Lack of efficacy is defined as the requirement to administer rescue medication to ≥ 5 of the first 16 participants randomized and treated in Cohort B0 (if predicted exposure is observed) until 28 days after first dosing (Day 29). If this condition is met, the recruitment will not start for Cohort B1 without necessarily becoming a criterion for stopping the study if the safety is not of concern. The dose of the combination in Part B could be adapted by the IDMC after Part A based on safety findings as well as exposure of M5717 in 12 adult participants receiving an intermediate dose. In Cohort B0, 16 participants (approximately 8 adults and 8 adolescents) with a body weight ≥ 45 kg will be included first. If these 16 participants do not meet the safety stopping criteria, another 9 adolescent participants with a lower body weight (≥ 24 to < 45 kg) and an adapted dose for M5717 (500 mg) will be included. An increase or decrease in dose for subsequent cohorts will be based on observed safety, efficacy, and PK data from Cohort B0 as this is the first time M5717 is being administered in a malaria patient. Cohorts B1, B2, and B3 will be started in a 1:2:1 randomized ratio according to a stratification by site.

4.2 Scientific Rationale for Study Design

The intent is to develop a 1- or 2-day dosing regimen of the M5717-pyronaridine combination. The approach in this study to define the doses to be used is based on considerations of safety and efficacy for these 2 dosing regimens.

The highest chance to show whether this combination is efficacious requires evaluating the highest therapeutic monotherapy doses in combination for both compounds. For pyronaridine, the highest approved dose in patients ≥ 65 kg is 720 mg daily in a 3-day treatment regimen. Therefore, 720 mg is the highest daily dose and has been selected for the 1-day (total dose 720 mg) and the 2-day dosing regimens (total dose 1,440 mg). This permits maintaining a reasonable safety margin compared to the 3-day Pyramax dosing regimen (total dose 2,160 mg).

Considering that this drug combination is administered to humans for the first time, Part A will investigate the safety and exposure after a single-day administration of an intermediate dose of 330 mg M5717 and 360 mg pyronaridine tetraphosphate in a group of 12 adults with acute uncomplicated *P. falciparum* malaria. This dose has been derived from half of the dose that showed a clinically relevant therapeutic effect as a single dose in previous studies (Blood Stage VIS); the outcomes of this study part will help to confirm the assumptions in terms of safety and exposure and decide whether dose adaptations are required for Part B.

Only adults will be recruited in Part A of the study, permitting to collect PK data that will help to understand if the exposure is matching with the predictions. In addition, risk of progression to severe malaria due to the potential lower efficacy of intermediate doses is expected to be lower in an adult population than in adolescents, who are immunologically better prepared to manage the infection (Long 2017, Maurizio 2019).

Although no formal DDI studies have been conducted with M5717 in humans, available data on the metabolism of M5717 (predominantly metabolized by CYP3A4) and pyronaridine (mainly metabolized by CYP3A4 and CYP2D6) do not suggest any clinically relevant DDI alert between the two molecular entities regarding a CYP-mediated P450 interaction (data on file). The DDI risks are considered low for M5717 to inhibit CYP3A4 metabolism of pyronaridine and for pyronaridine as a perpetrator of transporter-mediated interactions with M5717 (data on file). MS5717 is a substrate of P-gp (IC_{50} of 4 µM). Alba (2019) indicated that although pyronaridine inhibits P-gp (IC_{50} of 32.7 µM), its DDI risk as a perpetrator of transporter-mediated interactions is low. There is, however, the theoretical potential for transporter mediated DDI perpetrated by M5717 on pyronaridine which might result in an increase in pyronaridine concentrations, although one cannot exclude that this pathway is already saturated by the individual compound themselves.

The second study part (Part B, see Section 1.2) is designed as a randomized, controlled, open-label study. It includes a specific interim analysis of the safety, efficacy, and PK data from Cohort B0 to decide whether the planned dosing regimens lead to the expected exposures, whether the escalation from 1-day to 2-day treatment is acceptable, and whether the data from Cohort B0 support investigation (evaluation) of the single day treatment regimen in Cohort B1. After the IDMC decision, Cohorts B1, B2, and B3 will be opened in a randomized setting with a 1:2:1 randomization ratio. Participants in Cohort B2 will be treated with 660 mg M5717 plus 720 mg pyronaridine (daily doses) in a 2-day dosing regimen. Cohort B3 will act as an internal

control in order to provide reference safety data leveraging that the pyronaridine moiety is part of all the Part B cohorts. At the same time, the internal control arm will provide a benchmark for the efficacy to put the efficacy endpoints achieved in Cohort B1 and B2 into perspective. The pyronaridine dose will be adjusted according to the participants' weight following the dosing recommendations (based on the Pyramax SmPC dosing recommendations), with 720 mg being the maximum daily dose for participants weighing ≥ 65 kg. Pyramax is used as an internal control for efficacy and monitoring of resistance against pyronaridine. As it is a well-established product, clinical procedures will be limited and there will be no blood sampling for PK.

The primary objective of Part B is to determine the efficacy of the M5717-pyronaridine combination in adult and adolescent participants. The endpoint selected for the assessment of the efficacy is PCR-adjusted ACPR defined as absence of parasitemia (thick smear/microscopy), irrespective of axillary temperature, in participants who did not previously meet any of the criteria of ETF, LCF, or LPF at Day 29 after adjustment for parasitemia due to new infections as determined by genotyping using PCR techniques. PCR-adjusted ACPR is the regulatory accepted endpoint for the assessment of antimalarials efficacy according to WHO and EMA and has been the basis for granting authorization for several ACT combinations recently (Eurartesim EMA/739355/2011). Additional endpoints such as fever clearance time and clinical signs and symptoms of malaria have been included, being endpoints traditionally evaluated in malaria clinical studies.

The population selection rationale in Part B that involves an extension to adolescents ≥ 12 years of age is based on:

- Demonstration of good tolerability in Part A in the adult population that permits a full dose in Part B.
- Good tolerability in 16 adult and adolescent participants with a body weight ≥ 45 kg in Cohort B0 with the higher dose before including adolescents on 500 mg dose of M5717 (body weight < 45 kg).
- Evaluation of whether the predicted exposure is reached in the first 9 adolescent participants treated with 500 mg dose of M5717 before including further adolescent participants at that dose.
- Higher incidence of acute uncomplicated *P. falciparum* malaria in this population subset. In addition, it is important to understand and collect data on the PK and PD behavior of the combination in the older pediatric population subset as a basis for further age de-escalation studies in younger children.

4.2.1 Participant Input into Design

Not applicable.

4.3 Justification for Dose

Based on data from a Phase I study (MS201618_0013), the M5717 monotherapy at doses up to 1,440 mg (1,800 mg succinate) were considered safe and well tolerated. The exposure observed

at that dose has been set as the maximum exposure for the study as a 1-day or 2-day dosing regimen.

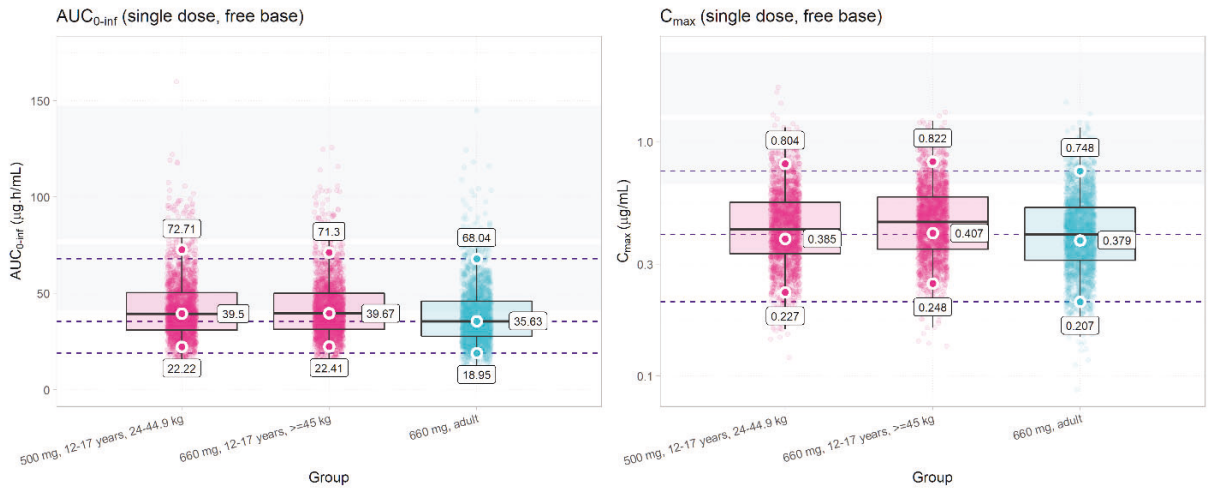
As this is the first administration of M5717 in combination with pyronaridine, a reduced dose was chosen for the safety run-in (Part A). From an ethical perspective it is important to ensure, a minimum efficacy for those participants treated with an intermediate dose of the M5717-pyronaridine combination. For this purpose, a preliminary PK/PD modeling was performed to assess the percentage of participants reaching 95% ACPR28 efficacy (data on file). This model suggests that with a single dose of 330 mg M5717 combined with 360 mg pyronaridine, the median ACPR28 efficacy is predicted to be between 59.1% and 92.2%. In addition, the dose selected is providing a large safety margin for individual compounds (M5717: 330 mg versus 1,440 mg, pyronaridine: single dose 360 mg versus 720 mg for 3 days) compared to the doses evaluated in the FIH/clinical studies. In particular, the AUC and C_{max} (90% prediction interval) associated with single and 2-day administration of M5717 is within the safe and tolerable 1,400 mg exposures. For pyronaridine, the dose selected for the safety run-in group was based on minimizing the risk of liver enzymes increase potentiation which remains the only relevant safety risk identified for this molecule.

Single doses of 660 mg M5717 (= 800 mg M5717 succinate) were shown to be efficacious in monotherapy in the FIH study. This dose was selected as the target dose for the pyronaridine combination in Part B. To account for the broad body weight range in the target population of adolescents and adults between 12 and 55 years, dose stratification by body weight was introduced. Exposure simulations based on the population PK model predict exposures for all body weight categories, and for both 1-day (Figure 1) and 2-day (Figure 2) regimens that are below the maximal exposure achieved in the FIH Study (ctr-ms201618-0013) after administration of the maximal dose of 1,400 mg, and that was found to be safe and well tolerated.

Based on population PK modeling and simulation, assuming allometric scaling, doses were adjusted for participants ≥ 24 to < 45 kg for 1 day (see Figure 1) and 2 days (see Figure 2). A dose of 500 mg M5717 in participants with a body weight of ≥ 24 to < 45 kg (left pink box plots) is expected to lead to exposure similar to that after administration of 660 mg in adults (right blue box plot). The 1-day and 2-day exposures (90% prediction interval) in the adult and adolescent population are within the 1,440 mg exposure (grey area).

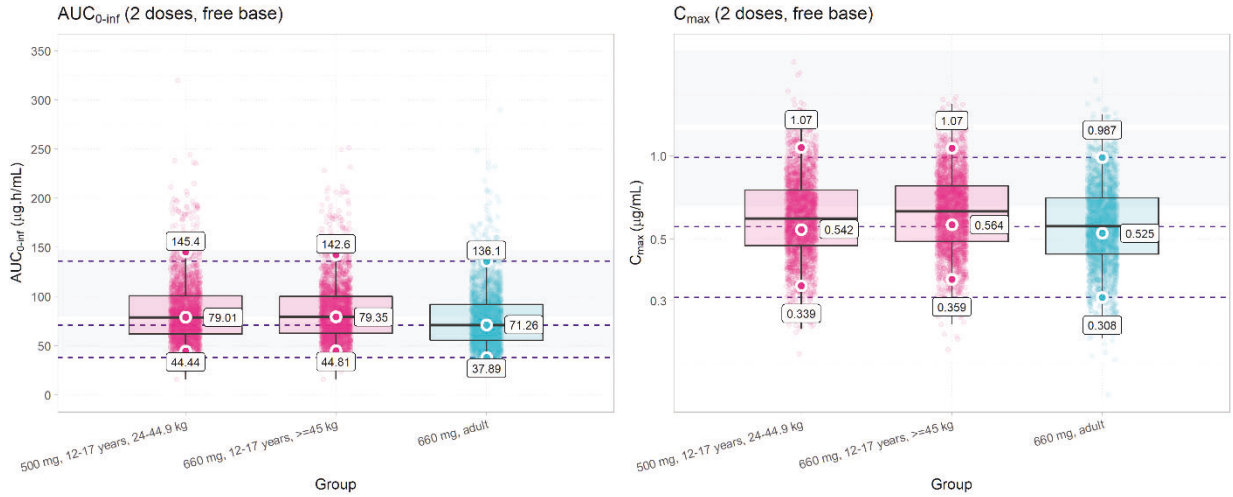
In addition, preliminary PK/PD modeling and simulation suggested that the median ACPR28 efficacy is predicted to between 69.7% to 98% for Cohorts B0 and B1 and 78.9% to 99.3% for Cohort B2 (data on file).

Figure 1 **Simulated Exposures in the Body Weight Categories for the Respective Recommended Single-dose Based on Population Pharmacokinetic Model**



Annotated points are geometric means and 90% prediction intervals.
White lines and grey area are median and 95% prediction interval for 1,440 mg single dose in adults.

Figure 2 **Simulated Exposures in the Body Weight Categories for the Respective Recommended 2-Day Dosing Based on Population Pharmacokinetic Model**



Annotated points are geometric means and 90% prediction intervals.
White lines and grey area are median and 95% prediction interval for 1,440 mg single dose in adults.

4.4 End-of-Study Definition

The end of the study is defined as the date of the last site closure in the study globally.

A participant has completed the study if he/she has completed all study parts, including the last visit or the last scheduled procedure shown in Section 1.3.

5 Study Population

The study population are African adults and adolescents ≥ 12 and ≤ 55 years of age, with a diagnosis of acute uncomplicated *P. falciparum* malaria. In Part A only adults are allowed to be recruited, while in Part B adults and adolescents can be recruited. Recruitment will be performed at hospitals, clinics, or health care facilities.

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

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

Before performing any study assessments that are not part of the participant's routine medical care, the Investigator will confirm that the participant or the participant's legal representative (where allowed by local laws and regulations) has provided written informed consent, as indicated in Appendix 2.

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 (≥ 18 and ≤ 55 years of age for Part A) at the time of signing the informed consent.
Type of Participant and Disease Characteristics:	2. Microscopic confirmation of acute uncomplicated *P. falciparum* using Giemsa-stained thick and thin film. 3. *P. falciparum* parasitemia of ≥ 1,000 to ≤ 50,000 asexual parasites/µL of blood in Part A and *P. falciparum* parasitemia of > 1,000 to ≤ 150,000 asexual parasites/µL of blood in Part B. 4. Axillary temperature ≥ 37.5ºC or tympanic temperature ≥ 38.0ºC (use as per COVID-19 protocols at the site [only at Screening]), or history of fever during the previous 24 hours (at least documented verbally).
Weight:	5. Have a body weight ≥ 24 kg.

Category	Criterion
Sex and Contraception/Barrier Requirements	6. "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 the 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 WOCBP. OR c. Use a male condom: o When having sexual intercourse with a WOCBP, who is **not** currently pregnant, and instruct her to use a highly effective contraceptive method with a failure rate of <1% per year, as described in Appendix 3, 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 study intervention). o Is not a WOCBP. OR o If a WOCBP, 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 3: 1. Before the first dose of the study intervention(s), 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 study intervention period.

Category	Criterion
	3. After the study intervention period (i.e., after the last dose of study intervention is administered) for ≥ 62 days, corresponding to the time needed to eliminate any study intervention(s) (5 terminal half-lives of 155 hours) plus 30 days (a menstrual cycle) after the last dose of study intervention (and agree not to donate eggs [ova, oocytes] for reproduction during this period). The Investigator evaluates the effectiveness of the contraceptive method in relationship to the first dose of study intervention. The Investigator reviews the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy.
Informed Consent	7. Capable of giving signed informed consent, as indicated in Appendix 2, 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. Mixed *Plasmodium* infections as per thin film microscopy results. 2. Signs and symptoms of severe malaria according to WHO 2021 criteria (WHO 2021). 3. 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 severe liver disease, known gallbladder or bile duct disease, acute or chronic pancreatitis, or severe malnutrition.
	4. 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).
Prior/Concomitant Therapy:	5. Previous treatment with pyronaridine as part of a combination therapy during the last 3 months. 6. 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.

Category	Criterion
	7. 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). 8. Patients taking medications prohibited by the protocol.
Prior/Concurrent Clinical Study Experience:	9. Previous participation in any malaria vaccine study or received malaria vaccine in any other circumstance during the last 3 months. 10. Participation in any clinical study within 3 months or 5 half-lives prior to Screening or during participation in this study.
Diagnostic Assessments:	11. Serum creatinine levels ≥ 2 × ULN. 12. AST and/or ALT > 1.5 × ULN, regardless of the level of TB. 13. AST/ALT > 1.0 and ≤ 1.5 × ULN and TB is > 1.5 × ULN. 14. TB > 2 × ULN, regardless of the level of AST/ALT. 15. A marked Baseline prolongation of QTc interval > 450 msec applying the Fridericia's correction. 16. Known disturbances of electrolyte balance, ≥ Grade 2 according to the CTCAE v5.0, e.g., hypokalemia, hypocalcemia, or hypomagnesemia. 17. Moderate to severe anemia (hemoglobin level < 8 g/dL). 18. Severe malnutrition as a mid-upper arm circumference < 18 cm for adolescents (Hadush 2021) or as a BMI < 18.5 kg/m^2 for adults. 19. 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	20. Known history of hypersensitivity, allergic or adverse reactions to pyronaridine, M5717, and/or artesunate. 21. 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

Abstain from consumption of the following from 14 days before the start of study intervention until after the final dose: 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).

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 and cannabinoid-containing products for 24 hours before the start of dosing until after collection of the final PK and/or PD sample.
- 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 for the same malaria event. Should malaria be confirmed (Rapid Diagnostic Test or blood smear), individuals will receive standard of care treatment. In the case an individual develops a new episode of acute uncomplicated malaria due to *P. falciparum* and does not take any prohibited prior or concomitant medicines (see Section 6.8.3), rescreening is acceptable, but assessment of all eligibility criteria and parameters need to be repeated.

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

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

Arm Name:	1-Day M5717 plus Pyronaridine Safety/PK Assessment Run-in Cohort (Part A)	1-Day M5717 plus Pyronaridine Safety/PK Assessment Run-in Cohort (Part A)	1-Day M5717 plus Pyronaridine (Part B: Cohort B0 and B1)	1-Day M5717 plus Pyronaridine (Part B: Cohort B0 and B1)	2-Day M5717 plus Pyronaridine (Part B: Cohort B2)	2-Day M5717 plus Pyronaridine (Part B: Cohort B2)	3-Day Pyronaridine-artesunate (Pyramax) (Part B: Cohort B3)
Arm Type:	Experimental	Experimental	Experimental	Experimental	Experimental	Experimental	Active Comparator
Arm Description:	M5717 plus pyronaridine once daily in a single day treatment regimen	M5717 plus pyronaridine once daily in a single day treatment regimen	M5717 plus pyronaridine once daily in a single day treatment regimen	M5717 plus pyronaridine once daily in a single day treatment regimen	M5717 plus pyronaridine once daily in a 2-day treatment regimen	M5717 plus pyronaridine once daily in a 2-day treatment regimen	Pyronaridine-artesunate (Pyramax) once daily in a 3-day treatment regimen
Intervention Name:	M5717	Pyronaridine	M5717	Pyronaridine	M5717	Pyronaridine	Pyronaridine-artesunate (Pyramax)
Type:	Drug	Drug	Drug	Drug	Drug	Drug	Drug
Dose Formulation:	Granule to be dispersed in water	Tablet	Granule to be dispersed in water	Tablet	Granule to be dispersed in water	Tablet	Tablet
Unit Dose Strength(s):	100 mg capsules, 30 mg capsules	180 mg tablets	100 mg capsules, 30 mg capsules	180 mg tablets	100 mg capsules, 30 mg capsules	180 mg tablets	180/60 mg fixed-dose combination
Dose Amount:	330 mg	360 mg	Adults and adolescents ≥ 45 kg: 660 mg, Adolescents < 45 kg: 500 mg	≥ 24 to < 45 kg: 360 mg, ≥ 45 to < 65 kg: 540 mg, ≥ 65 kg: 720 mg	Adults and adolescents ≥ 45 kg: 660 mg, Adolescents < 45 kg: 500 mg	≥ 24 to < 45 kg: 360 mg, ≥ 45 to < 65 kg: 540 mg, ≥ 65 kg: 720 mg	≥ 24 to < 45 kg: 360/120 mg, ≥ 45 to < 65 kg: 540/180 mg, ≥ 65 kg: 720/240 mg
Frequency:	1-day treatment regimen	1-day treatment regimen	1-day treatment regimen	1-day treatment regimen	2-day treatment regimen	2-day treatment regimen	3-day treatment regimen
Route of Administration:	Oral, fasting conditions	Oral, fasting conditions	Oral, fasting condition	Oral, fasting conditions	Oral, fasting condition	Oral, fasting conditions	Oral, fasting conditions
IMP/NIMP:	IMP	IMP	IMP	IMP	IMP	IMP	IMP
Sourcing	M5717 will be provided by the Sponsor	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Packaging and Labeling	Study intervention M5717 will be provided in study-specific, uniquely labelled Alu/Alu blisters, respectively. Each blister will be labeled per country requirement.	Study intervention pyronaridine will be provided in study-specific, uniquely labelled Alu/Alu blisters, respectively. Each blister will be labeled per country requirement.	Study intervention M5717 will be provided in study-specific, uniquely labelled Alu/Alu blisters, respectively. Each blister will be labeled per country requirement.	Study intervention pyronaridine will be provided in study-specific, uniquely labelled Alu/Alu blisters, respectively. Each blister will be labeled per country requirement.	Study intervention M5717 will be provided in study-specific, uniquely labelled Alu/Alu blisters, respectively. Each blister will be labeled per country requirement.	Study intervention pyronaridine will be provided in study-specific, uniquely labelled Alu/Alu blisters, respectively. Each blister will be labeled per country requirement.	Pyramax will be provided in study-specific, uniquely labeled Alu/Alu blisters. Each blister will be labeled per country requirement.
Current/Former Name(s) or Alias(es)	M5717: MSC2576186A		M5717: MSC2576186A		M5717: MSC2576186A		

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.
- 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 re-dispensed to a different participant.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.

Further guidance and information for the final disposition of unused study intervention(s) are provided in the Study Reference Manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

In Part B, after completion of Cohort B0 and evaluation by the IDMC, participants will be randomly assigned to Cohorts B1, B2, and B3. Randomization to the cohorts will be stratified by site with a ratio of 1:2:1 to Cohorts B1, B2, and B3 using a computer-generated randomization list integrated in the electronic data capturing system.

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 one of the 3 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

The study will be open-label.

Parasitologists and laboratory personnel performing the microscopy and PCR will be blinded in order to minimize bias.

6.4 Study Intervention Compliance

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

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. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site staff will examine each participant's mouth to ensure that the study intervention was ingested.

6.5 Dose Modification

A single daily dose 660 or 500 mg M5717 is selected as the dose to be evaluated in Cohort B0/B1 and a daily dose of 660 or 500 mg will be administered daily for 2 days in Cohort B2 (see Table 5). After completion of Part A, and after completion of Cohort B0, the IDMC will have the option to recommend a dose adjustment for M5717 based on the exposure deviation from the predicted exposure, that will be supported by internal PK/PD analysis. This is planned to avoid unnecessary under or overexposures in any of the doses assigned across the two weight bands established.

Table 5 M5717 Free Base Dosage for Part A and B (Cohorts B0/B1 and B2)

	Part A		Part B			
			Cohort B0/B1		Cohort B2	
Body Weight	Equivalent Dose	Treatment Regimen	Equivalent Dose	Treatment Regimen	Equivalent Dose	Treatment Regimen
Adolescents ≥ 24 to < 45 kg	NA	NA	500 mg	Daily for 1 day	500 mg	Daily for 2 days
Adolescents ≥ 45 kg	NA	NA	660 mg	Daily for 1 day	660 mg	Daily for 2 days
Adults	330 mg	Daily for 1 day	660 mg	Daily for 1 day	660 mg	Daily for 2 days

NA=not applicable.

The pyronaridine dose in Cohorts B0/B1 and B2 will be a maximum daily dose of 720 mg pyronaridine for participants with body weight ≥ 65 kg and will be adjusted to the weight bands as specified for Pyramax in the SmPC (Pyramax SmPC, see Table 6). This dose of pyronaridine will be given together with M5717 on a daily basis for a single day (Cohort B0/B1, in total 720 mg) or for 2 days (Cohort B2, in total 1,440 mg).

Table 6 Pyronaridine Tetraphosphate Dosage for Part A and B (Cohorts B0/B1 and B2)

	Part A		Part B			
			Cohort B0/B1		Cohort B2	
Body weight	Number of Tablets and Dose	Treatment Regimen	Number of Tablets and Dose	Treatment Regimen	Number of Tablets and Dose	Treatment Regimen
≥ 24 to < 45 kg	2 tablets = 360 mg/day	Daily for 1 day	2 tablets = 360 mg/day	Daily for 1 day	2 tablets = 360 mg/day	Daily for 2 days
≥ 45 to < 65 kg	2 tablets = 360 mg/day	Daily for 1 day	3 tablets = 540 mg/day	Daily for 1 day	3 tablets = 540 mg/day	Daily for 2 days
≥ 65 kg	2 tablets = 360 mg/day	Daily for 1 day	4 tablets = 720 mg/day	Daily for 1 day	4 tablets = 720 mg/day	Daily for 2 days

A daily dose of Pyramax of a maximum of 720 mg pyronaridine and 240 mg artesunate will be given in Cohort B3 for 3 consecutive days according to the SmPC (Pyramax SmPC, see Table 7).

Table 7 Pyronaridine-artesunate (Pyramax) Dosage for Part B (Cohort B3)

Body weight	Number of Tablets and Dose of Pyronaridine-artesunate	Treatment Regimen
≥ 24 to < 45 kg	2 tablets = 360 mg-120 mg/day	Daily for 3 days
≥ 45 to < 65 kg	3 tablets = 540 mg-180 mg/day	Daily for 3 days
≥ 65 kg	4 tablets = 720 mg-240 mg/day	Daily for 3 days

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

This protocol allows some alteration from the outlined dosing schedule, but for M5717 the maximum daily dose will not exceed exposure achieved with the 1,440 mg dose in the FIH study. For pyronaridine the maximum daily dose specified in Section 6.1 will not be modified for each weight band.

No dose modifications are permitted at the participant level due to safety or tolerability reasons. If a participant in Cohorts B2 or B3 experiences a severe AE at the first or second day of treatment, the second and/or third day of treatment can be omitted according to Section 7.1 or judgment of the Investigator, but the dose cannot be reduced or delayed.

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 significantly from what is normally expected for patients with acute uncomplicated malaria due to *P. falciparum* infection. They will receive rescue treatment if the intervention fails to cure the disease and resolve the clinical event.

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 a SAE and Overdose Report Form, following the procedure in Appendix 4.

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

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.

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 time the participant signs the informed consent until completion of the study, 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.

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 5 half-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.

Paracetamol, at doses of ≤ 2 g/24 hours, is permitted for use across 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 of study intervention or withdrawal from the study and the implementation of rescue medication:

1. Development of danger signs or signs of severe malaria in the presence of parasitemia on Days 1, 2, or 3, or a clinical requirement for parenteral treatment (WHO definition).
2. Parasitemia on Day 2 (48 hours) higher than Baseline count, irrespective of axillary temperature (WHO definition).
3. Parasitemia on Day 3 with axillary temperature ≥ 37.5°C (WHO definition).
4. Parasitemia on Day 3 ≥ 25% of count at Baseline (WHO definition).
5. Parasitemia present on Day 8 (irrespective of the clinical state or temperature).
6. 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. For each participant, a maximum of 2 doses may be replaced throughout the treatment schedule).

Rescue treatment involves therapy with an effective antimalarial available locally, preferably artemether-lumefantrine. 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:

- Antimalarial compounds or products with antimalarial activity (macrolides, trimethoprim sulfamethoxazole, dapsone, rifampin, and cyclins) except for ophthalmic use (see Appendix 7).
- Medicines with mitochondrial toxicity, such as valproate and antiretroviral medicines should be avoided due to risk of overlap toxicity (see Appendix 8; Will 2019).
- Medicines with photosensitivity risk such as tetracycline, doxycycline, nalidixic acid, voriconazole, amiodarone, hydrochlorothiazide, naproxen, piroxicam, chlorpromazine, and thioridazine (see Appendix 9; Drucker 2011).
- 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

7.1 Discontinuation of Study Intervention

If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for end of follow-up. The Schedule of Assessments 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 (see Section 1.3).

A participant will be discontinued from a study intervention (only applicable for Cohorts B2 and B3, in which 2- or 3-day treatment regimens are planned) if any of the following situations occur:

- LFT changes: study intervention will be discontinued on the second (Cohorts B2 and B3) and/or third day (Cohort B3) in a participant who develops jaundice or if a non-scheduled laboratory test shows an increase in transaminases and/or TB of ≥ 3-folds compared to the Baseline value.
- CNS events: study intervention will be discontinued on the second (Cohorts B2 and B3) and/or third day (Cohort B3) in a participant who develops study intervention-related (according to Investigator's judgment) neurological TEAE.
- Pregnancy: pregnancy tests will be performed at Screening and Day 1, and the maximum study intervention will last 3 days in Cohort B3, making it extremely unlikely for a pregnancy to occur in this time period. Details are provided in Section 8.3.4.
- ETF as specified in Table 3 (Ref #3) warrants the discontinuation of study intervention and the administration of rescue medication (see Section 6.8.1).

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may discontinue from the study at any time, at his/her own request or at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- At the time of study discontinuation, if possible, a discontinuation visit will be conducted, as listed in the Schedule of Assessments. The Schedule of Assessments specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed.
- If withdrawal from the study occurs for any reason, the Investigator must determine the primary reason for a participant's withdrawal from the study and record this information on the Study Completion CRF.
- Protocol violations should not lead to participant withdrawal unless they indicate a significant risk to the participant's safety.
- 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.
- A participant has the right at any time to request destruction of any biological samples taken. The Investigator will document this in the site study records and the CRF and inform the Sponsor. The samples will be destroyed.
- In case LFT derangements are observed, the IDMC would need to review the data; the participants who have been treated with M5717 will be followed up and might remain on the study, rather than being withdrawn, unless a decision is made otherwise by the Investigator or the IDMC.

  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 should 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 Schedule of Assessments (see Section 1.3).
- **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 should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the Schedule of Assessments, 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 2.
- Procedures conducted as part of the participant's routine medical care (e.g., blood count) and obtained before signing of the ICF may be used for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Assessments.
  - No more than 3 mL/kg of blood may be drawn in a 24-hour period, and no more than 9 mL/kg of blood in a 4-week period. Maximum blood volumes to be withdrawn are detailed in Section 2.3.1, according to the bodyweight and hematocrit value.
- 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 Part B of the study is defined by PCR-adjusted ACPR 28 days after first treatment (note that the primary endpoint of Part A is related to safety). ACPR is defined as absence of parasitemia (thick smear/microscopy, after adjustment for parasitemia due to new infections as determined by genotyping using PCR techniques), irrespective of axillary temperature, in participants who did not previously meet any of the criteria of ETF, LCF or LPF. ETF, LCF and LPF are defined according to WHO guidelines (WHO 2021, see also Table 3). PCR-adjusted ACPR is defined as clearance of asexual parasitemia within 7 days of initiation of study treatment and without recrudescence within 28 days of initiation of study treatment. New infection (with a different parasite stem as compared to primary infection) as evidenced by PCR genotyping studies will not be considered a treatment failure.

Assessment of Secondary Efficacy Endpoints

For the definitions of secondary efficacy endpoints please refer to Table 3.

Recrudescence is defined as reappearance of parasites of the same isolate as initial infection, with or without clinical signs, after initial clearance of parasites from the peripheral blood, with positive blood smear and PCR genotyping confirmation of the same isolate.

The time to fever clearance is defined as the time from first dosing to the first normal reading of temperature (< 37.5°C) for 2 consecutive normal temperature readings plus confirmed normal temperature 24 hours after the first normal body temperature reading. The method of temperature measurement must be the same (axillary) for all measures in the same patient. Those participants who are initially included on documented history of fever and who do not subsequently have a documented temperature reading of > 37.5°C during the 24 hours following initial dosing, will not be included in this endpoint analysis.

The parasite clearance time represents the time from first dosing to time of first blood draw with parasite clearance. Parasite clearance is defined as zero presence of parasites for 2 consecutive negative readings at least 6 hours apart.

The PRR index is defined as $\frac{C_{48}}{C_0} - 1$, where C_{48} is the parasite count at 48 hour and C_0 is the count at pre-dose on Day 1 (Baseline).

CCI

Parasitological Assessments

Parasite density expressed as the number of asexual parasites per µL will be measured serially to determine PCT. Blood sampling for genotyping will be done by extracting specific blood samples for this purpose.

Blood smears preparation, staining, examination, and interpretation should be in accordance with the current WHO 2003 protocol (WHO 2003: Assessment and monitoring of antimalarial drug efficacy for the treatment of acute uncomplicated *P. falciparum* malaria; Chapter 8: Technical Considerations and Quality Assurance). Should a clinical study site have established procedures deviating from the WHO 2003 protocol, the nature and the reason of the deviations must be discussed and approved by the Sponsor before the study commences.

Thick and thin blood films for parasite count should be obtained and examined at Screening to confirm inclusion/exclusion criteria. Thick blood films will be examined every 6 hours (± 0.5 hours) for the first 72 hours (Days 1 to 4): 2 negative readings taken 6 hours apart. Thick blood films will be also examined on Days 8, 15, 22, 29, and 43 or at any unscheduled visit (specific details provided in Table 1 and Table 2).

Additionally, blood films should be obtained whenever parasitological reassessment and genotyping is required. A thin blood smear will also be taken in case of reappearing parasitemia, to confirm *Plasmodium* species. The method of counting parasites will be described in a Laboratory Manual including gametocyte counts. Local quality control of slides is to be assured by reading of slides by 2 different qualified microscopists, reporting independently, with the arithmetic mean of the 2 counts being recorded in the patient record and CRF. In the case of discrepancy, a third microscopist will review the slides and the Site Principal Investigator will make the final classification to be reported in the CRF. An external quality control of slide reading may be established by an independent laboratory.

PCR

PCR genotyping will be used to differentiate recrudescence from re-infections of *P. falciparum* or different Plasmodium species (new infection).

A common technical protocol will be used for PCR sampling and analysis. PCR samples will be shipped by courier for centralized third party blinded review at a central laboratory and reporting of PCR data conducted for patients classified as treatment failure. Recommendations for sampling and storing blood samples for molecular marker studies will be provided in a Laboratory Manual.

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, ECGs, 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 43 [± 2 days]). At other time points an abbreviated physical examination can be performed. Additional physical examinations may be performed as deemed necessary, per the Investigator's discretion.

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

A 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 Baseline (or Day 2 if participant cannot collaborate due to the malaria symptoms), Days 2, 3, 4, 8, 15, and the end-of-study for all the participants enrolled, and if abnormalities are detected it should be repeated in the next visit to the one in which abnormalities are detected until resolution.

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 performed in the supine position at timepoints indicated in the Schedule of Assessments (Table 1) with detailed timepoints during hospitalization in Table 2.

Blood pressure and participant's position; 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 ECGs will be performed at timepoints indicated in the Schedule of Assessments (Table 1) with detailed timepoints during hospitalization in Table 2.

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

At visits where multiple assessments and procedures are to be done at the same timepoint, the ECG should be done after vital sign assessment and before blood sampling.

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 10 at the timepoints indicated in the Schedule of Assessments (Table 1). 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. If there is a clinical suspicion of acidosis related to a possible severe malaria, a venous blood gas testing should be performed to evaluate at least pH, bicarbonate, and bases excess.

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 4. The laboratory reports will be filed with the source documents.

Pregnancy testing (serum or highly sensitive urine, as required by local regulations) will be conducted at the end of the relevant systemic exposure of the study intervention at Day 43.

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.

8.2.5 Suicidal Ideation and Behavior Risk Monitoring

Not applicable.

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

- The definitions of an AE, SAE, and AESI are in Appendix 4.

- The Investigator and any qualified designees (e.g., Sub-Investigators) 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 4.
- All AEs, SAEs, and AESIs will be collected from the signing of the ICF until the End-of-Study Visit at the time points specified in the Schedule of Assessments (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 4. 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 if reported by the participant or observed by the Investigator.

Care will be taken not to introduce bias when detecting AEs, SAEs, and/or AESIs. Open-ended and non-leading 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 4.

All SAEs must be additionally documented and reported using the appropriate Report Form as specified in Appendix 4.

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 4.

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 towards 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, as necessary.

An Investigator 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 review and file it in the Investigator's Site File and will notify the IRB/IEC, if appropriate according to local requirements.

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 malaria clinical score is defined in Appendix 6 and needs to be assessed in case any malaria-related symptoms are seen.

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 signals (AT increase, TB increase) and CNS signals 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 signals will be monitored through LFTs that will include the two 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 5.
- Neurological signals will be monitored through specific neurological clinical examinations, detailed in Section 8.2.1. This neurological physical examination will be done at Baseline (or Day 2 if participant cannot collaborate due to the malaria symptoms), Days 2, 3, 4, 8, 15, and the end of the study for all the participants enrolled, and if abnormalities are detected it should be repeated in the following visits until resolution. If additional tests or assessments (such as CT, MRI, lumbar punction) are required to further evaluate neurological abnormalities detected, those will be done at discretion of the Investigator.

8.4 Pharmacokinetics

For details on PK blood sampling, see the Schedule of Assessments in Section 1.3, and Table 2. Note that there will be no PK blood sampling for Pyramax (Cohort B3). Metabolite concentrations, as applicable, may also be measured in blood samples.

The following PK parameters in Cohorts B0, B1 and B2 will be calculated, when appropriate, for M5717 and pyronaridine:

Symbol	Definition
$AUC_{0-\infty}$	The area under the concentration-time curve (AUC) from time zero (dosing time) extrapolated to infinity, based on the predicted value for the concentration at $t_{last,}$ as estimated using the linear regression from λ_z determination. $AUC_{0-\infty} = AUC_{0-tlast} + C_{last\ pred}/\lambda_z$
AUC_{0-24}	The AUC from time zero (dosing time) to 24 hours post dose. Calculated using the mixed log linear trapezoidal rule (linear up, log down) using the nominal dosing interval. The actual dosing interval calculated from CRF time data should not be used.
CL/F	The apparent total body clearance of study intervention following extravascular administration. $CL/F = Dose_{p.o.}/AUC_{0-\infty}$.
C_{max}	Maximum observed concentration
$t_{½}$	Apparent terminal half-life. $t_{½} = \ln(2)/\lambda_z$
t_{max}	The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, take the 1st occurrence in case of multiple/identical C_{max} values)
V_Z/F	The apparent volume of distribution during the terminal phase following extravascular administration. $V_z/F = Dose/(AUC_{0-\infty}*\lambda_z)$ following single dose. $V_z/F = Dose/(AUC_t*\lambda_z)$ following multiple dose.
λ_z	Terminal first order (elimination) rate constant. Determined from the terminal slope of the log-transformed concentration curve using linear regression on terminal data points of the curve
AUC_{0-24}/Dose	The dose normalized AUC from time zero to 24 hours post dose. Normalized using the actual dose, using the formula AUC_{0-24}/Dose.
$AUC_{0-tlast}$	The AUC from time zero (= dosing time) to the time of the last quantifiable concentration (t_{last}), calculated using the mixed log-linear trapezoidal rule (linear up, log down).
$AUC_{0-tlast}$/Dose	The dose normalized AUC from time zero to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification. Normalized using the actual dose, using the formula $AUC_{0-tlast}$ /Dose.
$AUC_{0-\infty}$/Dose	The dose normalized AUC from time zero extrapolated to infinity. Normalized using actual dose, using the formula $AUC_{0-\infty}$ /Dose.
C_{max}/Dose	The dose normalized maximum concentration. Normalized using the actual dose, and the formula C_{max} /Dose.

Additional PK parameters might be added based on emerging data and detailed in the IAP.

PK Sampling for M5717 and pyronaridine:

- Blood samples for measurement of whole blood concentrations of M5717 and pyronaridine, respectively. Collection times are specified in the Schedule of Assessments. Additional samples may be collected during the study if warranted and agreed upon between the Investigator and the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded to calculate actual time elapsed since the prior dose administration. The 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 a validated assay method. Concentrations will be used to evaluate the PK of M5717 and pyronaridine.
- Remaining samples collected for analyses of M5717 and pyronaridine concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Details on processes for collection and 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.

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

8.7 Immunogenicity Assessments

Not applicable.

9 Statistical Considerations

CCI [redacted]

CCI [redacted]

CCI

9.3 Analyses Sets

The Analysis Sets are specified in Table 8. The final decision to exclude participants from any analysis set will be made during a data review meeting prior to database lock.

Table 8 Analysis Sets

Analysis Set	Description
FAS	The FAS will include all enrolled participants. Participants will be analyzed according to the treatment assigned at enrollment as per the Intention-to-Treat 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 post-dose 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, standard deviation, median, lower and upper quartiles and minimum and maximum values. Where applicable, 95% confidence intervals 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 9 only main analyses are described for the primary and secondary efficacy endpoints. Additional sensitivity and subgroup analyses will be planned in the IAP. The description of the primary endpoint refers to Part B of the study. The primary endpoint of Part A is a safety-related endpoint for which no estimand attributes are defined and which will be analyzed as described in Section 9.4.2. The definitions of the efficacy endpoints are the same for Parts A and B.

Table 9 Summary of Main Statistical Analyses

	Statistical Analysis	Ref. #
Primary		
PCR-adjusted ACPR 28 days after first treatment defined as absence of parasitemia (thick smear/microscopy, after adjustment for parasitemia due to new infections as determined by genotyping using PCR techniques), irrespective of axillary temperature, in participants who did not previously meet any of the criteria of ETF, LCF, or LPF	ACPR rates will be estimated separately for participants of the single dose, the 2-day regimen and the Pyramax treatment arm together with 95% CIs. CIs will be derived by use of Wilson's score method. In order to investigate the impact of possible factors and covariates like, e.g., age, body weight and baseline parasitemia on ACPR, logistic regression models will be used.	19
Secondary		
ETF defined as • Danger signs or severe malaria 1,2 or 3 days after treatment, in the presence of parasitemia • Parasitemia 2 days after treatment higher than on day of treatment, irrespective of axillary temperature • Parasitemia 3 days after treatment with axillary temperature ≥ 37.5 °C • Parasitemia 3 days after treatment ≥ 25% of count on day of treatment	ETF rates will be estimated separately for participants of the single dose, the 2-day regimen and the Pyramax treatment arm together with 95% confidence intervals. Confidence intervals will be derived by use of Wilson's score method. In order to investigate the impact of possible factors and covariates on ETF, logistic regression models will be used.	3, 20
LCF defined as • Danger signs or severe malaria in the presence of parasitemia on any day between 4 and 28 days after first treatment (i.e., Day 5 and Day 29) in participants who did not previously meet any of the criteria of ETF • Presence of parasitemia on any day between 4 and 28 days after first treatment with axillary temperature ≥ 37.5 °C in participants who did not previously meet any of the criteria of ETF	Same as ETF	4, 21
LPF defined as • Presence of parasitemia on any day between 7 and 28 days after first treatment with axillary temperature < 37.5°C in participants who did not previously meet any of the criteria of ETF or LCF	Same as ETF	5, 22

	Statistical Analysis	Ref. #
PCR-adjusted efficacy 8 days after treatment as defined as absence of parasitemia (thick smear/microscopy, after adjustment for parasitemia due to new infections as determined by genotyping using PCR techniques) in participants who did not previously meet any of the criteria of ETF or LCF	Same as primary endpoint	9, 26
Crude (PCR-uncorrected) ACPR 14, 28 and 42 days after treatment defined as absence of parasitemia (thick smear/microscopy), irrespective of axillary temperature, in participants who did not previously meet any of the criteria of ETF, LCF or LPF	Same as primary endpoint.	6, 23
PCR-adjusted ACPR 14 and 42 days after treatment defined as absence of parasitemia (thick smear/microscopy, after adjustment for parasitemia due to new infections as determined by genotyping using PCR techniques), irrespective of axillary temperature, in participants who did not previously meet any of the criteria of ETF, LCF or LPF	Same as primary endpoint	7, 24
Crude (PCR-uncorrected) efficacy 8 days after treatment as defined as absence of parasitemia (thick smear/microscopy) in participants who did not previously meet any of the criteria of ETF or LCF	Same as PCR-adjusted efficacy rate 8 days after treatment	8, 25
Fever clearance time defined as the time from first dosing to the first measurement of an axillary temperature < 37.5°C for 2 consecutive temperature readings plus confirmed normal temperature 24 hours after the first normal body temperature reading	Median fever clearance time will be estimated by use of the Kaplan-Meier method separately for the one dose, the 2-day regimen, and the Pyramax treatment groups. A log-rank test will be applied to descriptively investigate differences between both treatment arms. In order to explore whether there is an impact of other covariates and factors, like, e.g., age, body weight, and baseline parasitemia on time to fever clearance a Cox Proportional Hazards model will be applied.	11, 28
PCT defined as time from dosing to the first negative (no parasites) film (microscopy)	Same as fever clearance time	12, 29
PRR defined as decrease in viable parasites over 48 hours, corresponding to one asexual parasite life cycle.	Geometric means of PRR will be estimated separately for participants of the single dose, the 2-day regimen and the Pyramax treatment arm together with 95% CIs. In order to investigate the impact of possible factors and covariates on PRR, a linear regression model will be used.	10, 27
Time to recrudescence, defined as the time from primary cure to the re-emergence of the same parasite strain that originated the primary infection.	Same as fever clearance time	13, 30

	Statistical Analysis	Ref. #
Time to re-infection, defined as the time from primary cure to the re-emergence of a different parasite strain that originated the primary infection.	Same as fever clearance time	14, 31
Time to re-emergence, defined as the time from primary cure to having recrudescence or re-infection (the first one that occurs).	Same as fever clearance time	15, 32

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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 PCR-adjusted ACPR 28 days after first dose, defined as absence of parasitemia (thick smear/microscopy, after adjustment for parasitemia due to new infections as determined by genotyping using PCR techniques), irrespective of axillary temperature, in participants who did not previously meet any of the criteria of ETF, LCF, or LPF.
- **Treatment**: Intervention of interest is either a **1-day (once daily)** or a **2-day regimen (once daily)** with M5717 660/500 mg plus pyronaridine 720 mg (≥ 65 kg), 540 mg (≥ 45 to < 65 kg), or 360 mg (≥ 24 to < 45 kg). A 3-day regimen (once daily) of Pyramax (pyronaridine-artesunate) 720/240 mg (≥ 65 kg), 540/180 mg (≥ 45 to < 65 kg), or 360/120 mg (≥ 24 to < 45 kg) is used as internal control arm mainly for safety analyses.
- **Target Population**: The target population is defined as the population of patients targeted by the clinical question. CCI
- **Strategies for handling ICEs**: A composite variable strategy, i.e. the primary endpoint is considered as failure (no ACPR) is applied if participants take rescue medication after intake of study intervention or if they discontinue the study due to lack of efficacy or 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}) or any event of immune response, a treatment policy strategy is applied as to which the treatment effect is estimated regardless of the ICE. A Principal Stratum strategy is

considered for participants with documented intake of prohibited medication that impacts the treatment effect (e.g., drug with antimalarial activity) at any timepoint.

- **Population-level summary**: The population-level summary of the primary endpoint is the proportion of participants achieving PCR-adjusted ACPR 28 days after first treatment (ACPR rate). ACPR rates will be estimated separately for participants of the single dose, the 2-day regimen and the Pyramax treatment arm together with 95% confidence intervals. Confidence intervals will be derived by use of Wilson's score method. ACPR rates and confidence intervals of the treatment groups will be compared descriptively. In order to investigate the impact of possible factors and covariates (e.g., age and baseline parasitemia) on ACPR, logistic regression models will be used. Details of these models and the factors and covariates to be used will be documented in the IAP.

9.4.1.2 Efficacy Analyses Related to Secondary and CCI Objectives

Most of the estimands targeting the secondary objectives of this study (refer to Section 3) share the attributes of the primary estimand as described in Section 9.4.1.1. Distinct attributes of each estimand are described below for each secondary endpoint.

For the secondary efficacy endpoint fever clearance time, defined as the time from first dosing to the first measurement of an axillary temperature < 37.5°C for 2 consecutive temperature readings plus confirmed normal temperature 24 hours after the first normal body temperature reading, the target population is defined as adult and adolescent patient with acute uncomplicated malaria due to *P. falciparum* with an increased axillary temperature (≥ 37.5°C). For this endpoint, the composite variable strategy that is applied to handle ICEs like intake of rescue medication and intake of concomitant medications with an impact on fever (as a continuous treatment) or intake of prohibited medication that impacts the treatment effect (e.g., drug with antimalarial activity) consists of a censoring strategy. If such ICEs are observed, those patients will be censored at Day 29. Premature study discontinuation due to lack of efficacy or malaria induced death will be handled according to an on-treatment strategy, i.e., the respective patients will be censored at the day of their last available body temperature assessment. With respect to the population-level summary, the median fever clearance time will be estimated by the Kaplan-Meier method separately for the one dose and 2-day regimen treatment groups. A log-rank test will be applied to descriptively investigate differences between both treatment arms. In order to explore whether there is an impact of other covariates and factors on time to fever clearance a Cox Proportional Hazard model will be applied. Details of the models will be described in the IAP.

The same approaches as described for fever clearance time are applicable also to PCT (note that for the target population for PCT the prerequisite of showing an increased axillary temperature does not hold).

For the endpoints time to recrudescence, time to re-infection and time to re-mergence, the target population are adult and adolescent patients with acute uncomplicated malaria due to *P. falciparum* who are primarily cured. The ICE intake of prohibited medication that impacts the treatment effect (e.g., drug with antimalarial activity) will be handled according to a Principal

Stratum strategy, i.e., the treatment effect will be estimated within the principal stratum of participants that potentially don't experience the ICE. Analyses and population-level summaries for these endpoints are the same as described for fever and PCT. The same holds also for the detection of mutations against M5717 or pyronaridine and presence of gametocytes as measured by microscopy and qRT-PCR.

For PK parameters no estimand attributes have been defined. Detailed descriptions of PK analyses will be part of an annex to the IAP.

9.4.2 Safety Analyses

The primary endpoint of Part A and a secondary endpoint of Part B is defined as incidence, severity, and seriousness of study intervention-related TEAEs, as per CTCAE v5.0.

Generally, AEs will be analyzed with frequency tables displaying number of participants with ≥ 1 AE by SOC and PT coded with MedDRA dictionary current at the time of database lock. Additionally, for the analysis of any safety endpoint the following definitions apply:

- TEAEs are defined as AEs which started at or after the administration of study intervention (study treatment) or which started prior to the first administration of study intervention 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. All AEs will be documented, and will include the Investigator term, the preferred term, start and end date of AE, duration (days), severity, study intervention relationship, action taken and outcome.
- Liver signals (AT increase, TB increase) and CNS signals will be considered AESIs and specifically followed-up 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 any study intervention).

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

Safety endpoints will primarily be analyzed on the SAF.

9.4.3 Other Analyses

Not applicable.

9.4.4 Sequence of Analyses

Two interim analyses will be performed by the IDMC. The IDMC will evaluate the interim efficacy and safety results after completion of Part A (first interim analysis) and after 25 participants have been enrolled and treated in Cohort B0 of Part B (second interim analysis). Cohort B0 will include 16 participants (approximately 8 adults and 8 adolescents) with a body weight ≥ 45 kg. Should these participants not meet the safety stopping criteria, another 9 adolescent participants with a body weight < 45 kg (with adapted dose) for M5717 (500 mg) will be included. Lack of efficacy will be monitored in the first 16 participants recruited in Cohort B0. Lack of efficacy is defined as the requirement to administer rescue medication to ≥ 5 of the first 16 participants randomized and treated in Cohort B0 (if predicted exposure is observed) until Day 29.

The scope of the analyses by IDMC will be evaluation of safety, efficacy, and PK, and assessment for potential dose adaptations.

10 References

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11 Appendices

Appendix 1 Abbreviations

ACPR	adequate clinical and parasitological response
ACPR28	ACPR on Day 28
ACT	artemisinin-based combination therapy
ADME	absorption, distribution, metabolism and excretion
AE	adverse event
AESI	adverse events of special interest
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	aminotransferase
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organizations of Medical Sciences
CNS	central nervous system
COVID-19	Corona Virus Disease 2019
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
DDI	drug-drug interaction
DILI	drug-induced liver injury
DRE	disease-related event
DRO	disease-related outcome
ECG	electrocardiogram
EMA	European Medicines Agency
ETF	early treatment failure
FAS	Full analysis set
FIH	first-in-human
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
IAP	Integrated Analysis Plan
IB	Investigator's Brochure

IBSM	induced blood-stage malaria
ICE	intercurrent event
ICF	Informed Consent Form
IC_{50}	half maximal inhibition concentration
ICH	International Council for Harmonisation
IDMC	Internal Data Monitoring Committee
IMP	investigational medicinal product
INR	international normalized ratio
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LAM	lactational amenorrhea method
LCF	late clinical failure
LPF	late parasitological failure
LFT	liver function test
NASH	non-alcoholic fatty liver disease
NCE	New Chemical Entity
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NRTI	nucleoside reverse transcriptase inhibitor
PD	pharmacodynamic(s)
PCR	polymerase chain reaction
PCT	parasite clearance time
PeEF2	plasmodium eukaryotic translation elongation factor 2
P-gp	p-glycoprotein
CCI [redacted]	
PK	pharmacokinetic(s)
PoC	proof of concept
PRR	parasite reduction rate
PT	preferred term
RT-qPCR	reverse transcription quantitative real-time polymerase chain reaction
QTcF	corrected QT interval by Fridericia' formula
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class

SUSAR	suspected unexpected serious adverse reaction
TB	total bilirubin
TEAE	treatment-emergent adverse event
TPP	target product profile
TT	thrombin time
ULN	upper limit of normal
WHO	World Health Organization
WOCBP	woman of childbearing potential

Appendix 2 Study Governance

Financial Disclosure

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

Informed Consent Process

Informed consent

- The Investigator or his/her representative will explain the nature of the study 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; HIPAA requirements, where applicable; and the IRB/IEC or study center.
- 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.
- In case a participant is not eligible at the screening activities ("screening failure"), he/she can be re-assessed at Investigator discretion. If the reassessment is performed later than 7 days after the initial Screening Visit, a new ICF should be obtained.

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 in separate manuals: Study Reference Manual, Safety Management Plan, IAP, Laboratory Manual, Pharmacy Manual, CRF Completion Guidelines, Monitoring Plan, and IDMC Charter.

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

An IDMC will be charged with reviewing safety and exposure data of M5717. In addition, it will review safety and efficacy data for all cohorts at the end of the study. The IDMC will be chaired by a person with experience in clinical studies and with participation in IDMCs. IDMC membership will comprise at least Sponsor Senior Experts (independent from study team) and SP representatives, Head of GPS, Head of TA Development Unit, Head of GBS.

Further details on the IDMC composition, processes, and decision criteria will be provided in the IDMC 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 non-serious 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.

Clinical Study Insurance and Compensation to Participants

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

One of the parents or guardian/legally authorized representatives of the children participating in the study will be compensated. The compensation will include reimbursement of transport to/from the hospital, food during the hospital visits, and a monetary compensation for the income loss due to the visits to the hospital. Prior to their implementation, the details of the proposed compensation will be reviewed by the applicable IEC/IRB.

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 pre-defined in the Study Reference Manual to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the 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 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 ICF.

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.
- 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 3 Contraception and Barrier Requirements

Definitions:

WOCBP:

A woman 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 study intervention, consider additional evaluation.

Postmenopause:

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

- A female on HRT and whose menopausal status are in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

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 WOCBP and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days. 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 the study intervention. 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 (male or female 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. Male condom and female condom cannot be used together (due to risk of failure from friction).

Appendix 4 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 (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 are considered clinically significant in the medical and scientific judgment of the Investigator (i.e., 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 a 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).

A 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 fulfils 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 a 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 postmortem 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 the SAE data into the electronic system 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 non-serious 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.
- Fax or email will be used, as per preferred method at the sites, and will be done within 24 hours. Facsimile transmission (fax to mail) of the paper form or any follow-up information or email is the preferred method for transmission and will be done within 24 hours to the Sponsor or its designee.

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

The DILI will be defined as following:

- 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 four 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 6 Malaria Clinical Score for Treatment Initiation

Symptoms	Clinical Score			
	Absent	Mild (1)	Moderate (2)	Severe (3)
Headache				
Myalgia (muscle ache)				
Arthralgia (joint ache)				
Fatigue/lethargy				
Malaise (general discomfort/uneasiness)				
Sweating/hot spells				
Anorexia				
Nausea				
Vomiting				
Abdominal discomfort				
Signs				
Fever (axillary temperature of ≥ 37.5°C)				
Chills/shivering/rigors				
Tachycardia				
Hypotension				
Total Score	XX			

Maximum Score: 3 × 14 = 42

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%.

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 Toxicity

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

Drug Class	Rank Order of Toxicity Observed (High to Low)	Target Organ
Anti-diabetic (thiazolidinediones)	Rosiglitazone Pioglitazone	Liver
Cholesterol lowering (statins)	Simvastatin Atorvastatin Fluvastatin	Muscle
Anti-diabetic (biguanides)	Metformin	Lactic acidosis
Anti-depressant/anxiety (SARIs)	Trazodone Buspirone	Liver
Anti-lipidemic (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
Anti-cancer (topoisomerase inhibitors)	Doxorubicin	Heart

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:

Laboratory Assessments	Parameters
Hematology	Hemoglobin Hematocrit Platelet count Red blood cell count Reticulocytes MCH MCHC MCV White Blood Cell Count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Biochemistry[1]	Blood Urea Nitrogen, Creatinine, Glucose, Lactate[3], Potassium, Sodium, Calcium, AST, ALT, ALP[2], Total Bilirubin, Protein
Coagulation	Prothrombin time aPTT TT INR
Notes: [1] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix 5. [2] If ALP is elevated, consider measuring the ALP isoenzymes. [3] If there is a clinical suspicion of acidosis related to a possible severe malaria, a venous blood gas testing should be performed to evaluate at least pH, bicarbonate and bases excess.	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, nitrite, leukocytes by dipstick
Other Screening Tests	Serum hCG pregnancy test (as needed for a WOCBP). All study-required laboratory assessments will be performed by local laboratories.

ALP=alkaline phosphatase, ALT=alanine aminotransferase, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, HBsAg=hepatitis B surface antigen, hCG=human chorionic gonadotropin, INR=international normalized ratio, MCV=mean corpuscular volume, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, TT=thrombin time, WOCBP=women of childbearing potential.


CCI

Appendix 12 Protocol Amendment History

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

Protocol Version 2.0, (27 July 2022)

Overall Rationale for the Amendment

The overall rationale for this amendment was to decrease the burden for the participants and to reduce operational complexity.

The following elements of the protocol were revised:

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 1.3 Schedule of Activities (Table1 and 2 – PK blood sampling) Section 3 Objectives and Estimands Section 4.2 Scientific Rationale for Study Design Section 8.4 Pharmacokinetics	The description of the PK objective and the related endpoint for Part B of the study was amended to clarify that PK will be characterized in Cohorts B0, B1, and B2. A note was added to the Schedule of Activities and to Section 8.4 to clarify that PK blood sampling is not applicable for Cohort B3 (Pyramax). . A rationale was added to explain why there will be no PK blood sampling for Pyramax (Cohort B3).	To clarify that PK blood samples will be taken for M5717 and pyronaridine (Cohorts A, B0, B1, and B2). No PK blood samples will be taken for Pyramax in Cohort B3 since it is a well- established product.
Section 1.3 Schedule of Activities (Table 1and Table 2 qPCR [parasitemia]); Section 8.1 Efficacy Assessments and Procedures	The qPCR test for confirming negative microscopy readings was removed.	Blood film microscopy is the standard method for assessing negative parasitemia (2 consecutive negative readings). Adding qPCR tests to confirm negative parasitemia would add operational complexity including additional visits. Therefore, this assessment was removed.
Section 1.3 Schedule of Activities (Table 1 – parasite genotyping)	Sampling timepoints for parasite genotyping were adjusted.	To clarify that the first sampling should occur prior to the dosing and not at Screening and that samples should be taken at every visit to reduce operational complexity.
Section 1.3 Schedule of Activities (Table 1 and 2 – PK blood sampling)	PK sampling timepoints during the hospitalization period were reduced. The sampling timepoints at 0.5 h, 1 h, 1.5 h, 3 h, 26 h, 28 h, 32 h and 60 h postdose were removed. PK sampling timepoints were added at 36 h and at the End-of-Study Visit.	To reduce the burden for participants and the probability of withdrawals from the study.
Section 1.3 Schedule of Activities (Table 2 - vital signs and temperature)	Timepoints for measuring the participants' temperature and vital signs during the hospitalization period were adapted in order to	To make sure that the timepoints are better aligned with the timepoints for blood films to reduce operational complexity.

Section # and Name	Description of Change	Brief Rationale
	better align with the sampling timepoints for blood films.	
Section 1.3 Schedule of Activities (Table 2 – blood films [microscopy])	Sampling timepoints for blood films were adjusted: 3 additional timepoints 42 h, 54 h, and 66 h postdose were added.	To specify that blood films will be collected every 6 hours during the hospitalization period to reduce operational complexity.
CCI [redacted]	[redacted]	[redacted]
Section 6.1 Study Intervention(s) Administration	Description of M5717 dose formulation and unit dose strengths was updated. Conditions of drug administration were updated.	To align the M5717 unit dose strength with the IMPD (“sprinkle” was removed) and to clarify that M5717 granules are not oro-dispersible, but the granule must be dispersed in water prior to administration. To clarify that all drugs will be administered under fasting conditions.
Section 8.1 Efficacy Assessments and Procedures	Finger prick blood testing was removed.	Removed since the exact methodology will be defined in the laboratory manual.
Section 8.4 Pharmacokinetics CCI [redacted]	Blood sample volumes for M5717 and pyronaridine PK sampling and for CCI [redacted] were adapted.	To reflect the practice at the sites and to align with the volumes provided in the Informed Consent Form.
Appendix 10 Clinical Laboratory Tests	Serology for HBsAg and hepatitis C virus antibody was removed from the table.	To clarify that serology assessments will not be done at Screening.
Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Assessment of intensity was updated.	To clarify that NCI-CTCAE will be used for assessing the intensity of adverse events.
Appendix 13 Sponsor Signature Page	The signatory was updated.	To clarify that there was a change in the Merck representative.
Throughout	Minor editorial and document formatting revisions	Minor; therefore, have not been summarized.

Appendix 13 Sponsor Signature Page

Study Title:	Phase IIa Proof of Concept, Multicenter, Randomized, Open-label Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of the Combination M5717 plus Pyronaridine Administered once Daily for 1 or 2 Days to Adults and Adolescents with Acute Uncomplicated *Plasmodium falciparum* Malaria
Regulatory Agency Identifying Numbers:	To be determined
Clinical Study Protocol Version:	02 November 2022/Version 3.0

I approve the design of the clinical study:

PPD

Signature

PPD

Date of Signature

Name, academic degree:	PPD
Function/Title:	Medical Responsible
Institution:	Merck Healthcare KGaA
Address:	Frankfurter Str. 250, 64293 Darmstadt, Germany
General Merck Phone Number:	+06151 720
General Merck Fax Number:	NA
E-mail address:	PPD

Appendix 14 Coordinating Investigator Signature Page

Study Title:	Phase IIa Proof of Concept, Multicenter, Randomized, Open-label Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of the Combination M5717 plus Pyronaridine Administered once Daily for 1 or 2 Days to Adults and Adolescents with Acute Uncomplicated *Plasmodium falciparum* Malaria
Regulatory Agency Identifying Numbers:	To be determined
Clinical Study Protocol Version:	02 November 2022/Version 3.0
Site Number:	

I approve the design of the clinical study, am responsible for the conduct of the study, 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 _____ 15 November 2022

Signature Date of Signature

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

Appendix 15 Principal Investigator Signature Page

Study Title:	Phase IIa Proof of Concept, Multicenter, Randomized, Open-label Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of the Combination M5717 plus Pyronaridine Administered once Daily for 1 or 2 Days to Adults and Adolescents with Acute Uncomplicated *Plasmodium falciparum* Malaria
Regulatory Agency Identifying Numbers:	To be determined
Clinical Study Protocol Version:	02 November 2022/Version 3.0
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: