Protocol No.	QP17C19
Title:	A single-centre Phase 1b study to assess the safety, tolerability, pharmacokinetic profile, and antimalarial activity of single doses of co-administered artefenomel (OZ439) and piperaquine phosphate (PQP) against early *Plasmodium falciparum* blood stage infection in healthy adult volunteers
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The following statistical analysis plan has been prepared by Clinical Network Services (CNS) Pty Ltd, IntiQuan, and QIMR Berghofer for Medicines for Malaria Venture.

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Abbreviations and Definitions

ACPR28	Adjusted adequate clinical and parasitological response at day 28 post-dose
ACT	Artemisinin combination therapy
AE	Adverse Event/Adverse Experience
AESI	Adverse event of special interest
ATC	Anatomical Therapeutic Chemical
AUC	Area under the plasma concentration-time curve
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from 0 to infinity
BDI	Beck Depression Inventory
BMI	Body mass index
BLQ	Below limit of quantification
C_{max}	Maximum plasma concentration
CI	Confidence interval
CNS	Clinical Network Services Pty Ltd
eCRF	Electronic Case Report Form
CRA	Clinical Research Associate
CSR	Clinical study report
ECG	Electrocardiograph
EOS	End of Study
FBC	Full Blood Count
FSH	Follicle-stimulating hormone
G6PD	Glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
h	Hour
HREC	Human Research Ethics Committee
ICH	International Conference on Harmonisation
IBSM	Induced Blood Stage Malaria
IIV	inter-individual variability
IP	Investigational Product
IRB	Institutional Review Board
LFT	Liver function test

LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MMV	Medicines for Malaria Venture
NCA	Non-compartmental analysis
ND	Not detected
NLME	Nonlinear mixed effects (modelling)
PD	Pharmacodynamics(s)
Pf	*Plasmodium falciparum*
PI	Principal Investigator
PCR	Polymerase Chain Reaction
PK	Pharmacokinetic
PRR	Parasite reduction ratio
QIMR Berghofer	QIMR Berghofer Medical Research Institute
QT_c	QT interval corrected for heart rate
QT_cB	QT interval corrected with Bazett's formula
QTcF	QT interval corrected with Friderica's formula
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SD	Standard deviation
SDRT	Safety and Data Review Team
SE	Standard error
SOP	Standard Operating Procedure
t_{max}	Time at which C_{max} was achieved / time to reach maximum plasma concentration
TEAE	Treatment-emergent adverse event
WHO	World Health Organization
WOCBP	Women of Childbearing Potential
%CV	Coefficient of variation

SECTION 1: INTRODUCTION

1.1 SCOPE

This Statistical Analysis Plan (SAP) is an adjunct to the Medicines for Malaria Venture (MMV) Protocol Number QP17C19 Version 4.0 (dated 27 August 2018).

This SAP outlines the QP17C19 study and describes the methods for the analysis of the data arising from this clinical trial, namely the safety data, the non-compartmental analysis of pharmacokinetic (PK), the calculation of parasite reduction ratio (PRR), and the PKPD modelling.

This document is mainly based on the statistical section of the study protocol; therefore, some sections are described briefly, and references are made to the related sections in the protocol. The analyses outlined in this document, if different from the protocol, will supersede those specified in the protocol.

The structure and content of this SAP are designed to provide sufficient detail to meet the requirements described by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Statistical Principles For Clinical Trials.

1.2 STUDY BACKGROUND

Malaria is the second most prevalent infectious disease in the world and threatens half of the world's population. In accordance by the World Health Organisation (WHO), there were an estimated 216 million new cases of malaria worldwide and 445,000 deaths in 2016 [1]. Most of the malaria mortality has been reported in sub-Saharan Africa and in children under 5 years of age.

Malaria drug resistance is a major hurdle to achieving malaria eradication. Resistance has been developed not only to conventional monotherapies such as chloroquine, amodiaquine and sulfadoxine/pyrimethamine but also to the gold standard treatment for uncomplicated *P. falciparum* malaria, artemisinin combination therapy (ACT). Resistance to ACTs has been reported across the Greater Mekong Subregion in South-East Asia [2, 3] and the inevitable spread of artemisinin resistance to Africa is of great concern. Artemisinin resistance has been linked to mutations in the propeller domain of the *P. falciparum Kelch13* gene [4]. Artemisinin-resistant isolates are not completely resistant to artemisinin, but instead have a slow parasite clearance phenotype compared to artemisinin-sensitive isolates. This can lead to reduced clearance of young ring-stage parasites, and therefore further maturation and sequestration of parasites leading to increased morbidity and mortality. As such, a continual generation of new compounds and drug combinations are needed to avoid a dangerous shortage of potential future treatment options.

To achieve eradication of malaria, long-lasting, single-dose treatments that completely clear malaria parasites from the body and provide a period of protection following the treatment are required. These ideal types of medicines are referred to as single encounter radical cures (SERCs). The WHO and Medicines for Malaria Venture (MMV) have identified the key properties that a SERC must have. These properties are defined by Burrows *et al*. (2017) in the antimalarial target product profile (TPP) [5]. A key requirement of a target product is the inclusion of two or more active molecules with different mechanisms of action. The aim of including two or more active compounds is to achieve an increased barrier to resistance by using drugs with different mechanisms of action, forcing the parasite to develop multiple simultaneous mutations in order to become resistant. Furthermore, in a combination therapy, one of the two active compounds should have a rapid onset of action, killing most of the parasite load. Both active compounds should maintain plasma concentrations levels above the minimal parasiticidal concentration for approximately the same time and ensure complete elimination of all parasites [5].

Artefenomel (OZ439) is a novel trioxolane, and a front-runner candidate for inclusion in a new antimalarial combination. It is a synthetic ozonide with potency comparable to artemisinin, with a rapid parasite clearance rate of approximately 3.6 h in *P. falciparum*. Additionally, OZ439 has a substantially longer half-life than artemisinin (46–62 h as opposed to 1–3 h for artemisinin [6]). For these reasons, clinical studies in which artefenomel is combined with a companion drug with a different mechanism of action are being planned, or are currently in progress.

Piperaquine is a *bis* 4-aminoquinoline and was used mainly in China from the 1960s to the 1980s as an antimalarial monotherapy. In the 1980s, it became clear that parasite resistance had developed to piperaquine phosphate (PQP) monotherapy. PQP is characterised by slow absorption and a long elimination half-life (4–5 weeks) and is now widely used in combination with dihydroartemisinin as a fixed dose ACT. The successful pairing of PQP with an artemisinin, together with PQP's long biological half-life, means PQP is potentially a good drug partner for OZ439.

SECTION 2: STUDY OVERVIEW

2.1 STUDY DESIGN AND TREATMENTS

This is a single-centre, open-label, adaptive, randomised study using the *P. falciparum* induced blood stage malaria (IBSM) inoculum as a model to characterise the safety, tolerability, PK, pharmacodynamic (PD) activity, and PK/PD relationship of combined single dose administration of OZ439 and PQP.

The study was conducted in three cohorts of 8 subjects each using up to 4 different single doses of OZ439 and PQP in each cohort. Subjects were malaria naïve healthy males or females, aged between 18-55 years old, who met all of the inclusion criteria and none of the exclusion criteria.

The first cohort was composed of 4 groups of 2 subjects each. Subjects were randomised into one of 4 dose groups and administered single oral doses of OZ439 and PQP in combination. The combined dose of OZ439 and PQP was different for each of the 4 groups in this cohort as shown in Table 1.

Table 1. OZ439 and PQP Cohort 1 dose groups

Drug	Dose group			
	1A	1B	1C	1D
OZ439 (mg)	200	200	400	400
PQP (mg)	480	640	480	640

The OZ439 and PQP dose levels and the number of subjects per dose for Cohorts 2 and 3 were determined adaptively during the study.

After review of the PK/PD and safety data from Cohort 1 by the Safety and Data Review Team (SDRT) it was determined that cohort 2 would be composed of 2 dose groups of 4 subjects each. Subjects were randomised into one of 2 dose groups and administered single oral doses of OZ439 and PQP in combination. The combined dose of OZ439 and PQP will be different for each dose group in this cohort as shown in Table 2.

Table 2. OZ439 and PQP Cohort 2 dose groups

Drug	Dose group	
	2A	2B
OZ439 (mg)	800	200
PQP (mg)	960	320

A similar analysis was done at the end of Cohort 2 by combining data from cohorts 1 and 2 to decide the doses to be tested in Cohort 3. Two groups of 4 subjects each were considered. Subjects were randomised into one of 2 dose groups and administered single oral doses of OZ439 and PQP in combination as shown in Table 3.

Table 3. OZ439 and PQP Cohort 3 dose groups

Drug	Dose group	
	3A	3B
OZ439 (mg)	400	800
PQP (mg)	640	640

Each subject was inoculated on Day 0 with approximately 2,800 viable parasites of *P. falciparum*-infected human erythrocytes administered intravenously. Subjects were followed up daily via phone call or text message on Days 1 to 3 post-inoculation to solicit any AEs.

Subjects then came to the clinical unit once daily from Day 4 until presence of asexual parasites was established by quantitative polymerase chain reaction (qPCR) targeting the 18S rRNA gene (referred to hereafter as malaria 18S qPCR). Once malaria 18S qPCR became positive and until OZ439 and PQP administration, subjects came to the clinical unit twice-daily, separated by approximately 12 hours, for clinical evaluation and blood sampling.

On day 8, subjects were admitted to the clinical unit for single dose administration of OZ439 and PQP on Day 8. Subjects were followed up as inpatients for 72 hours to ensure tolerance of the investigational treatments (OZ439 and PQP) and clinical response.

After discharge from the clinical unit, subjects were followed up regularly for safety assessments, PK sampling, clinical evaluation, and malaria 18S qPCR blood sampling until Day 42±2 (34 days after OZ439 and PQP co-administration). All subjects received a standard course of Riamet® (artemether-lumefantrine) on Day 42±2, or earlier in the event of failure of clearance or recrudescence of parasitaemia or at Investigators discretion based on subject safety. For guidance, the definitions for failure of parasite clearance and recrudescence are provided.

- **Failure of parasite clearance**: failure to clear parasitaemia by at least 10-fold at 72 hours post-IP administration
- **Recrudescence**: defined as participants who showed substantial increases in parasitaemia after the initial clearance and were treated with a standard course of Riamet® to clear parasites.

The clinical judgement was made based on serial samples to ensure participant safety. Guidelines for increasing parasitaemia following initial clearance were a 2-fold parasitaemia increase from previous sample and parasitaemia exceeding the

clinically safe threshold (e.g. ≥5 000 blood stage parasites/mL), or re-occurrence of malaria symptoms with a malaria clinical score >6. However clinical judgement and practicality were overriding criteria for rescue treatment.

2.2 STUDY OBJECTIVES

Primary objectives:

a) To characterise the PK/PD relationship between OZ439 and PQP plasma concentrations and blood stage asexual parasitaemia in healthy subjects following *P. falciparum* IBSM infection.
b) To evaluate the safety and tolerability of OZ439 and PQP when co-administered as single doses in healthy subjects following *P. falciparum* IBSM infection.

Secondary objectives:

a) To describe the PK of OZ439 and PQP when co-administered as single doses in healthy subjects under fasted conditions.
b) To characterise the PD effect of co-administered single doses of OZ439 and PQP on clearance of *P. falciparum* asexual blood stage parasites from the blood of healthy subjects in the IBSM model.

2.3 STUDY ENDPOINTS

Primary endpoints:

- The PK/PD relationship between OZ439 and PQP plasma concentrations and blood stage asexual parasitaemia will be determined by PK/PD modelling of:
  - OZ439 plasma concentration over time
  - PQP plasma concentration over time
  - Parasitaemia profile over time, following treatment administration

  The following parameters will be estimated from the PK/PD model:
  - Effect of OZ439 on Emax and EC50 of PQP
  - Effect of PQP on Emax and EC50 of OZ439

  The following PD endpoints will be predicted from the PK/PD model:
  - Time to recrudescence defined as the time at which parasite levels re-occur after being BLQ or the time for which parasitaemia levels are minimum, or, if not defined, the last observed time point without recrudescence.
  - ACPR28 defined as the fraction of patients for which no parasitaemia is observed at Day 28 after drug administration,
- The incidence, severity and relationship to OZ439 and PQP of observed and self-reported AEs after the co-administration of single doses of OZ439 and PQP to healthy subjects inoculated with IBSM.

Secondary endpoints:

- Estimation of OZ439 and PQP PK parameters after co-administration of single doses using non-compartmental methods: $AUC_{0\text{-}168h}$, AUC_{last}, $AUC_{0\text{-}inf}$, C_{max}, t_{max}, $t_{1/2}$, t_{lag}, C_{168h}, CL/F, Vz/F and λ_{inf}.
- The effect of co-administered single oral doses of OZ439 and PQP on clearance of *P. falciparum* blood stage parasites from the blood of inoculated subjects as measured by qPCR up to trial Day 42±2 after co-administration of OZ439 and PQP. Parasite clearance will be assessed by the following parameters:
    - Parasite clearance half-life ($PC_{t½}$).
    - Parasite reduction ratio (PRR).
    - Percentage of subjects with recrudescence of parasitaemia, defined as ≥5 000 blood stage parasites/mL and a 2-fold increase within 48 hours, or re-occurrence of malaria symptoms with a malaria clinical score >6).

Exploratory objectives for the study, including presentation of endpoints, analysis methods and results, will be addressed separately, outside of the main clinical study report (CSR).

2.4 SAMPLE SIZE

A total of 24 healthy subjects were enrolled in the study (3 cohorts of 8 subjects each). Subjects were malaria-naïve healthy males or females, aged between 18-55 years old, who met all of the inclusion criteria and none of the exclusion criteria. Sample size was not determined based on formal power calculation.

In each cohort, if more than 2 discontinuations due to non-safety related reasons had occurred; additional subjects could have been recruited to replace the discontinued subjects on agreement with the study sponsor.

Historically, 8 subjects per cohort have been manageable from a resourcing and logistics perspective. The selection of more than one dose level for each treatment should enable the effect of the drugs to be characterised and should provide dose/concentration-response information about malaria parasite kinetics following IBSM in healthy subjects.

2.5 STUDY SCHEDULE

The complete schedule of events with all procedures is presented in Table 4.

Table 4. Schedule of Events

Procedure	Screening D-28 to D-1	Eligibility visit[a] D-3 to D-1	Malaria inoculation day D0	Post-inoculation phone call or text message D1 to D3	Malaria monitoring[b] D4 to D7	OZ439 and PQP treatment and clinical unit confinement D8 to D11	Out-patient monitoring D12 to D42±2 (35 days after OZ439/PQP)	EOS visit D45±2
Informed consent & BDI	X							
Medical history, eligibility & prior medications	X		X					
Drug & alcohol screen	X		X			X		
Full physical examination	X							X
Symptom-directed physical examination[c]			X		X	X	X	
Vital sign assessment	X		X		X	X	X	X
ECG	X		X			X[j]		X
Urinalysis	X	X				X[k]	X	X
Haematology & biochemistry	X	X				X	X	X
CRP testing[f]		X				X	X	X
G6PD testing	X							
RBC alloantibody	X							X
Serology	X							X
Pregnancy test[d]	X		X			X		X
Safety serum storage			X					X
AEs & concomitant medications			X	X	X	X	X	X
Malaria clinical score			X		X	X	X[l]	X
Malaria 18S qPCR blood sampling			X		X	X	X	X
Parasite lifecycle stage qRT-PCR blood sampling[e]							X	X
OZ439 and PQP concentration blood sampling						X	X	
Drug treatment								

Procedure	Screening D-28 to D-1	Eligibility visit[a] D-3 to D-1	Malaria inoculation day D0	Post-inoculation phone call or text message D1 to D3	Malaria monitoring[b] D4 to D7	OZ439 and PQP treatment and clinical unit confinement D8 to D11	Out-patient monitoring D12 to D42±2 (35 days after OZ439/PQP)	EOS visit D45±2
Malaria inoculum			X[g]					
OZ439 and PQP treatment						X		
Riamet® treatment[h]							X	
Primacin™ treatment[i]							X	

PQP: piperaquine phosphate; EOS: End of Study, BDI: Beck Depression Inventory; ECG: electrocardiograph, CRP: C-reactive protein; G6PD: glucose-6-phosphate dehydrogenase, RBC: red blood cell, PK: pharmacokinetic, PD: pharmacodynamic, qPCR: quantitative polymerase chain reaction, qRT-PCR: reverse transcription qPCR.

[a] An additional safety visit will occur between Day -3 and Day -1 to collect samples for haematology, biochemistry and urinalysis, unless screening laboratory assessments were conducted within this period.

[b] Daily visits until qPCR positive, and then twice daily visits until OZ439 and PQP treatment.

[c] Symptom-directed physical examinations will be performed only if clinically indicated at the discretion of the Investigator (see Appendix 3 of protocol for a list of symptoms and signs of malaria).

[d] Serum β-hCG pregnancy test (all female subjects) and follicle stimulating hormone test (FSH) (post-menopausal females) at screening. Urine β-hCG pregnancy test for WOCBP at other indicated time points (Day 0 pre-malaria inoculation, Day 8 pre-OZ439 and PQP administration, EOS).

[e] If required, at the Investigator's discretion.

[f] May be performed at the Investigator's discretion.

[g] Cannulate subjects with an indwelling intravenous cannula for the malaria inoculum, and record which arm is utilised. Cannulate subjects with an indwelling intravenous cannula for the malaria inoculum, and record which arm is utilised. Administer the malaria inoculum of ~2 800 viable *P. falciparum* 3D7 infected human RBCs intravenously in the morning (approximately 9:00 AM). Observe for a minimum of 60 minutes after inoculation to evaluate for immediate adverse reactions. Educate subjects on signs and symptoms of malaria (Appendix 3 of protocol). Emphasise to subjects the importance of returning on the nominated day (approximately Day 8), or as advised by the clinical unit staff, for IP antimalarial treatment. Provide subjects with diary cards and thermometers to record any temperature readings during the study in the event of symptoms of fever. Subjects will also record symptoms and concomitant medications on the diary cards during the study.

[h] Riamet® treatment will occur on Day 42±2, or earlier if there is failure of clearance or recrudescence of parasitaemia, or at the Investigator's discretion.

[i] Primacin™ treatment if required (Section 6.1.5 of protocol).

[j] ECG to be performed in triplicate at 4, 6, 8, 12, 24 and 72 h post-OZ439 and PQP dosing, or at the Investigator's discretion

[k] At the time of admission to clinical unit only.

[l] Only if vital signs are abnormal, or at the Investigator's discretion.

SECTION 3: INTERIM ANALYSES

There are no formal interim analyses planned for this study.

3.1 SAFETY DATA REVIEW

A review by the SDRT of data from each cohort will be conducted prior to dosing the subsequent cohort. Safety and tolerability data up to Day 42±2 and PK/PD analysis outcomes (based on PD data up to Day 42±2 and PK data up to Day 35±2), from all subjects from Cohort 1 who received treatment with OZ439 and PQP will be required for the review. The SDRT will determine the OZ439 and PQP dose levels and the number of subjects per dose for Cohort 2 from that review. A similar analysis will be done at the end of cohort 2 combining cohorts 1 and 2 data to decide the dose(s) to be tested in cohort 3. This will be decided by the funding sponsor and the Principal Investigator following review of the data by the SDRT and scientific evaluation.

The doses used in all cohorts will not exceed the maximum acceptable doses predefined for this study (800 mg for OZ439 and 1440 mg for PQP) as determined in previous safety, pilot efficacy and phase 2 studies.

Currently, no formal interim analysis is planned. Additional interim analyses may be conducted to support decision making concerning the current clinical study, the sponsor's clinical development projects in general or in case of any safety concerns. In this case, the analyses as described in the sections below are conducted for the relevant endpoints.

SECTION 4: OVERARCHING SAP INFORMATION

This SAP document presents all pre-planned analyses, as approved prior to final database lock. Any major deviations from the final approved SAP or additional unplanned post-hoc analyses will be documented (with justification) in the CSR.

SECTION 5: ANALYSIS SETS

Data from **all enrolled subjects** will be listed. Listings will present data ordered by cohort, dose group, subject, and timepoint (as relevant).

In this study, dose group (e.g., 1A, 2B) is defined as the combination of OZ439 and PQP single dose levels. For subjects for which the actual treatment received does not match the randomised treatment the treatment actually received will be used for the analysis. Unless specified otherwise, summary outputs will be presented by dose group and timepoint (as relevant).

The **inoculation set** will include all subjects inoculated with the *P. falciparum* challenge agent.

The **safety analysis set** will include all subjects that received any study treatment.

The **PK analysis set** will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study treatment and experienced no protocol deviations with relevant impact on PK data.

The **PD analysis set** will include all subjects with any available PD data, who received any study treatment and experienced no protocol deviations with relevant impact on PD data.

The **PK/PD analysis set** will include all subjects from the PK set and all subjects from the PD set.

Protocol deviations will be reviewed and exclusion of subjects from the analysis sets will be decided during final data review prior to database lock.

SECTION 6: SAFETY STATISTICAL METHODOLOGY

6.1 GENERAL CONSIDERATIONS

The statistical analysis and reporting of safety data will be the responsibility of the study biostatistician at CNS. Data will be reported for the inoculation set and/or for the safety set as relevant.

For categorical/discrete variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Continuous variables will be summarised using descriptive statistics, including n, mean, standard deviation (SD), median, minimum, and maximum values.

Numeric safety variables (i.e. clinical laboratory values, vital signs, and key ECG parameters) will be reported to the same precision as the source data. Derived variables will be reported using the same precision to the value(s) from which they were derived. For the reporting of descriptive statistics, the minimum and maximum values will be presented to the same precision as the source data; mean and median will be reported to 1 decimal place greater than the source data and SD will be reported to 2 decimal places greater than the source data. The coefficient of variation (%CV) will always be reported as a percentage (i.e. ×100) to 1 decimal place.

Extra measurements (such as unscheduled or repeat assessments) will not generally be included in summary tables, but will be included in subject listings.

For safety data, unless specifically mentioned otherwise, baseline is defined as:

- the last scheduled observation prior to the administration of the inoculum [Inoculation Baseline],
- the last scheduled observation prior to the first administration of IP(s) [Treatment Baseline].

If a scheduled baseline reading is missing, then the last non-missing measurement (e.g. screen value or unscheduled) will be used.

6.2 SOURCES OF DATA

Analysis datasets will be generated from data extracted from the Clinical Study Database.

6.3 DATA HANDLING

Subject Identification Codes

For each cohort, all eligible subjects will be randomised to one of the dose groups on the morning of Day 8.

Randomisation and subject identification codes will be listed. Subject identification codes will be reported in all other listings.

Subjects who are inoculated but do not receive the IP will be included in all safety listing using their subject identification codes.

Assessment Time-Point Identifiers

In the data listings and summary tables presented as part of the CSR, scheduled assessments for Safety data will be identified by the study day name/number and/or protocol scheduled time points (Screening, Day -3 to -1, Day 0, Malaria Monitoring Visit, OZ439 and PQP treatment, and clinical unit confinement, Outpatient Monitoring, Rescue treatment with Riamet® and EOS visit and/or 4, 6, 8, 12, 24 and 72 hours post-OZ439 and PQP dosing), where relevant.

Derived Data

Derived data variables for inclusion in data listings will be calculated as follows:

- Age (in integer years) = (Screening Date – Date of Birth + 1) / 365.25)
- Body Mass Index (BMI) = Weight (kg) / (Height ^{2} (m))
- AE time since Inoculum (in hours, to one decimal place) = (Onset Date + Onset Time) – (Inoculum Date + Inoculum Time).
- AE time since study treatment administration (in hours, to one decimal place) = (Onset Date + Onset Time) – (Study Treatment Administration Date + Study Treatment Administration Time).
- Duration of AE (in hours, to one decimal place) = (Resolution Date + Resolution Time) - (Onset Date + Onset Time).

AE time since Inoculum/study treatment administration and duration of AE will be converted to days (to one decimal place) in the follow-up period.

Handling of Missing Data

Missing values will not be imputed and will be reported in the listings as either "missing" or as the justification for the value being missing e.g. "ND" (not detected), where appropriate.

For the current study the duration of historical medical conditions and prior and concomitant medication administration will not be calculated or summarised and as such missing start and end times/dates will not be imputed.

Descriptive statistics will be calculated from actual data only, with the number of actual data points used for the calculation of the summary statistics reported. Missing data will not be imputed.

For censored safety lab data (i.e. haematology, clinical biochemistry and urinalysis results that are outside the limit of quantification) the actual values reported by the lab (e.g. "<2" for bilirubin) will be presented in the data listings. For the calculation of summary statistics, safety lab data values below the lower limit of quantification (LLOQ) will be set to ½ the LLOQ. For the calculation of summary statistics, safety lab data values above the upper limit of quantification (ULOQ) will be set to the ULOQ.

6.4 DISPOSITION AND STUDY PARTICIPATION

A disposition listing will present date and time of informed consent, date of study completion or early withdrawal, and the reason for early discontinuation.
The number of subjects that completed, number of subjects that discontinued and the main reasons for early withdrawal will be summarised by dose group. Dose group assignment and IP administration will be presented for individual subjects in a data listing.

All available information concerning major protocol deviations, violations on eligibility criteria, exclusion from analysis sets and subjects not treated will be listed. The number of subjects in each analysis set will be tabulated.

6.5 DEMOGRAPHIC AND BASELINE DATA

Individual subject demographics at screening (age, sex, race, height, weight and BMI), serology and special tests, red cell alloantibody, urine drug screen results, alcohol breath test results, G6PD status, pregnancy and FSH test results, and the Beck Depression Inventory will be presented in data listings.

Subject age, height, weight, and BMI will be summarised by treatment using descriptive statistics. Sex and race will be summarised using frequency counts and percentages.

6.6 MEDICAL HISTORY

Medical history findings are coded using the Medical Dictionary for Regulatory Activities (MedDRA) into system organ classes and preferred terms. For each finding, a start and stop date or ongoing flag is collected.

Medical history will be tabulated as below:

- The number and percentage of subjects with and without findings

- The number and percentage of subjects with findings by system organ class and preferred term

All medical history data will be listed.

6.7 STUDY MEDICATION/COMPLIANCE

Individual records of drug name, dose levels, date and time of challenge agent administration, IP administration and rescue medication administration will be presented in data listings.

6.8 SAFETY DATA

Adverse events

Adverse events (AEs) and AESIs will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA®) available at CNS (21.0). Listings of AEs, as well as the severity, relationship, duration, outcome, actions taken, and whether the AE was treatment-emergent and/or an SAE will be presented for each subject. Treatment-emergent adverse events (TEAEs) will be defined as any AE with an onset after administration of study drug, or any AE that has worsened after administration of study drug.

An AESI (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or programme, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor could be appropriate. Any abnormalities listed below should be reported as AESI:

Hepatic:

- any ALT or AST above 5xULN
- an elevation in bilirubin 2xULN
- any AST or ALT above 2xULN and (TBL > 1.5x ULN or INR > 1.4)
- any AST or ALT above 2xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (eosinophil percent or count above the ULN)

Cardiac:

- QTcB or QTcF at any time >480 msec,
- bundle branch block (except right bundle branch block that was present prior to IP administration)

any arrhythmia, except:

- sinus bradycardia that is
  – clinically asymptomatic, and
  – not associated with any other relevant ECG abnormalities
- sinus tachycardia that is
  – clinically asymptomatic, and
  – associated with a body temperature >38.0 °C, and
  – not associated with any other relevant ECG abnormalities

respiratory sinus arrhythmia,

wandering atrial pacemaker,

isolated, single premature atrial/ventricular complex (i.e. no bigeminy, trigeminy, couplets, triplets or salvos) that does not occur more than once in a particular ECG tracing.

Haematological:
HB drop >2.0 g/dL from baseline prior to inoculation

Absolute neutrophil count <500/µl.

Platelet count <75,000 /mm3

Dermatological:
Clinical signs of possible cutaneous adverse reactions such as:

- dermatitis,
- rash,
- erythematous rash,
- macular rash,
- papular rash,
- maculopapular rash,
- pruritic rash,
- pustular rash,
- vesicular rash.

Data for AEs for each subject will be presented in data listings. A listing of deaths, other serious and significant AEs, as well as AESIs, will also be presented.

All AEs and AESIs will be summarised in tables. An overview table will show the number and percentage of subjects with at least one event and the number of events for the following:

- TEAEs
- Serious TEAEs
- Fatal TEAEs

- Treatment-related TEAEs
- TEAEs related to IBSM inoculum
- TEAEs related to procedure
- TEAEs related to rescue drug
- Serious treatment-related TEAEs
- TEAEs for which the study was discontinued
- TEAEs for which the study drug was discontinued
- TEAEs of special interest

Summary tables by MedDRA system organ class and preferred term will show the number and percentage of subjects with at least one event. The table of TEAEs will additionally show the number of events. Separate tables will be prepared for the following:

- TEAEs by phase (treatment/rescue) and overall
- TEAEs related to IBSM inoculum
- TEAEs related to treatment
- TEAEs related to rescue drug

Additionally, a summary table by MedDRA preferred term will show the number and percentage of subjects with at least one event, by descending order of frequency (number of subjects with events in the total group). This table will be shown by phase (treatment/rescue) and overall. Treatment phase is defined as Day 8 after dosing or earlier to Day 42±2 (OZ439 and PQP) and rescue phase from Day 42±2 after dosing (Rescue treatment) to (EOS visit).

Prior and concomitant medications

Prior and concomitant medications relative to inoculum and IP will be listed for each subject and coded using the WHO drug dictionary (latest version available to CNS) with the listing to include the verbatim term and WHO drug dictionary drug class and preferred term (anatomical therapeutic chemical (ATC) Level 2 and standardised medication name), where appropriate. Prior medications relative to inoculum will be defined as those medications started before the administration of Inoculum (Day 0) and prior medications relative to IP will be defined as those medications started before the administration of IP (Day 8).

Concomitant medications relative to inoculum will be defined as those medications started on or after the administration of inoculum (Day 0) up to the EOS visit or premature study withdrawal, whichever is earliest and concomitant medications

relative to IP will be defined as those medications started on or after the administration of IP (Day 8) up to the EOS visit or premature study withdrawal, whichever is earliest.

Medications with a start date/time prior to administration of inoculum and an end date/time after administration of the inoculum will be assigned to both prior medication and concomitant medication categories relative to inoculum.

Medications with a start date/time prior to the administration of IP and an end date/time after administration of IP will be assigned to both prior medication and concomitant medication categories relative to IP.

Laboratory parameters

All individual laboratory results (haematology, biochemistry, and urinalysis) and change from baseline values will be presented in data listings. Values outside the laboratory reference range will be flagged (low-L, high-H). Classification will be done in standardised units, using non imputed values and limits. In addition, abnormal haematology, biochemistry and urinalysis laboratory parameters considered clinically significant will be presented in a listing with all parameters listed in a single column. All laboratory data will be listed. In addition, a listing will be provided showing only parameters for which abnormal values were reported.

Additionally, for liver enzymes, the following elevation categories will be defined:

- ALT: >3 x Upper Limit of Normal (ULN); >5 x ULN; >8 x ULN
- AST: >3 x Upper Limit of Normal (ULN); >5 x ULN; >8 x ULN
- ALT or AST >3 x ULN;
- Total bilirubin >2 x ULN;
- ALT or AST >3 x ULN and total bilirubin >2 x ULN at the same time point, together with a conjugated bilirubin fraction (direct bilirubin / total bilirubin) > 35% (Potential Hy's law cases).

The statistical analysis will present results in standardised units.

Continuous laboratory parameters will be summarised by means of descriptive statistics at each analysis visit. Actual values and changes from baseline will be tabulated separately. Categorical and semi-quantitative parameters will be listed only.

Laboratory abnormalities will be presented as cross-tabulations of the abnormality at each post-baseline analysis visit versus the baseline abnormality. Numbers of subjects with treatment-emergent abnormalities will also be shown.

Additionally, a frequency table showing the liver enzyme elevation categories for the highest post-dose values will be prepared.

Vital signs

The following vital signs parameters are collected: supine heart rate, supine systolic (SBP) and diastolic blood pressure (DBP) and body temperature.

Low, normal, and high ranges for vital signs are defined in Table 5 below.

Table 5. Low, normal, and high ranges for vital signs

	Heart rate (bpm)	SBP (mmHg)	DBP (mmHg)	Temperature (°C)
Low	<40	<90	<45	<35.0
Normal	40-100	90-150	45-90	35.0-37.5
High	>100	>150	>90	>37.5

Vital signs parameters will be summarised by means of descriptive statistics at each analysis visit. Actual values and changes from baseline will be tabulated separately.

Abnormalities will be presented as cross-tabulations of the abnormality at each post-baseline analysis visit versus the baseline abnormality. Numbers of subjects with treatment-emergent abnormalities will also be shown.

All vital signs data will be listed. In addition, a listing will be provided showing only abnormal values and their baseline.

Electrocardiograms

All individual ECG parameter results (heart rate, PR interval, RR interval, QRS duration, QT interval, QTcB interval, QTcF interval) and the clinical assessment of the ECG will be presented in a data listing. ECG parameter values and changes from baseline will be summarised, using descriptive statistics, by treatment and visit. Where triplicate ECG evaluations were performed, the mean value for each subject (for the protocol specified time-point) will be used for the calculation of summary statistics. In addition, individual abnormal ECG results will be presented in a separate data listing.

The clinical assessment of the ECG (RR, PR, QRS, QT and QTcF intervals) will be presented in subject data listings.

Clinical assessment of the ECG (Normal, Abnormal NCS, Abnormal CS, Not Evaluable and Not Done) will also be summarized, by treatment, using frequency tabulations (number and percentage of subjects under each category). The normal ECG ranges once on study are in Table 6.

Table 6. ECG normal ranges

Parameter	Range
PR interval	<= to 210 msec
QRS	>50 to < = to120 msec
QT interval	>200 to < 500 msec
QTcB/QTcF	Males: ≤ 450 msec
QTcB/QTcF	Females: ≤ 470s msec

Malaria clinical score

For each subject, malaria clinical score will be listed as individual score for each of the 14 symptoms. The total of all the scores obtained on the 14 symptoms will also be presented, per timepoint. The number (and percentage) of subjects scoring each symptom (0=absent; 1=mild; 2=moderate; 3=severe) will be tabulated per treatment and per protocol defined timepoint. In addition, the total malaria clinical score will be treated as a continuous outcome and summarised per treatment and over timepoint, as well as a change from baseline, using descriptive statistics.

Physical examinations

Abnormal physical examination assessment findings will be listed.

6.9 ANALYSIS SOFTWARE

Data manipulation and generation of listings and tables for all safety data and disposition and participation data will be performed using SAS Enterprise Guide Software version 7.12.

6.10 DATA CHECKING, MANAGEMENT AND SECURITY

Quality control review of listings and tables will be undertaken to ensure data contained in these documents correctly represent data recorded in the study databases. Where review by the Sponsor identifies erroneous values or the requirement for modification, the appropriate SAS program will be updated, and the document recreated. Updated documents will undergo a repeat of the quality control process. Where modification to electronic data files is required (e.g., SAS program, analysis data file), the old file will be retained.

All electronic data storage systems containing study data or analysis information will be password protected at all times, with access restricted to authorised CNS staff. Multisite backup of all electronic data and files will be performed daily.

6.11 ARCHIVING

All statistical analysis documents and records are to be retained for a minimum of fifteen years after trial completion. Written agreement from the Sponsor must precede destruction of the same.

SECTION 7: STATISTICAL METHODOLOGY FOR PHARMACOKINETIC DATA

7.1 GENERAL CONSIDERATIONS

Listings of pharmacokinetic data will be generated by CNS. Summary statistics, non-compartmental analysis (NCA), and graphical representation of PK data and their statistics will be performed by IntiQuan.

NCA of PK data will be performed to determine the $AUC_{0\text{-}168h}$, AUC_{last}, $AUC_{0\text{-}inf}$, C_{max}, t_{max}, $t_{1/2}$, t_{lag}, CL/F, V_z/F and λ_{inf} for OZ439 and PQP for the subjects in QP17C19.

7.2 SOURCE OF DATA

Plasma concentration of OZ439 and PQP, treatment and blood sampling information will be recorded and merged to produce source PK concentration data for analysis.

7.3 DATA HANDLING

Data Imputation for Pharmacokinetic Concentration Data Reporting

No imputations will be done for missing concentration values or missing time information, i.e., records with missing concentrations or times will be discarded. Concentrations that are below the lower limit of quantification (LLOQ) are defined as being below limit of quantification (BLQ) and will be reported as "BLQ" in data listings. For calculation of geometric means, geometric standard deviation (SD) and geometric coefficient of variation (CV%) concentration values reported as BLQ will be set to ½ × LLOQ and for all other summary statistics concentration values reported as BLQ will be set to zero.

Data used for Pharmacokinetic Estimation

In general, only concentration values above the LLOQ are used, hence, BLQ values are discarded with the following exceptions:

- Individual BLQ concentration values between the first dosing time and the first time point above LLOQ (i.e. during lag-time) are set to 0 and included in the PK evaluation.
- Pharmacokinetically plausible concentration value(s) below LLOQ at time points between two measurable concentration values are replaced by the LLOQ/2 value, flagged and included in the PK evaluation.

Actual time from dose administration will be used for parameter estimation except for the pre-(first) dose data point which will be set to the nominal time of 0 hour. Data with missing time information will be discarded.

7.4 METHODS

Data Listings

Individual data listings containing the drug concentrations of OZ439 and PQP will be represented with same number of decimal places or significant digits as the source data.

Calculation of descriptive statistics

The CV% is calculated as

$$CV\% = 100 \cdot \frac{SD}{mean}$$

The geometric SD is calculated as

$$SD_{geometric} = e^{SD(\ln(datavalues))}$$

The geometric CV% is calculated as

$$CV\%_{geometric} = 100 \cdot \sqrt{e^{SD(\ln(datavalues))^2} - 1}$$

Summary Tables

The concentration time courses will be represented in tables stratified by dose group. Descriptive statistics will be reported for each scheduled time-point with the precision as given in Table 7.

Table 7. Number of decimal places for PK concentration summary statistics

Descriptive statistic	Number of decimal places
Number of subjects	none
Geometric mean	i + 1
Median	i + 1
Minimum	i
Maximum	i
Arithmetic mean	i + 1
SD	i + 1
CV%	1
i = number of decimal places in source	

Figures

The concentration-time courses will be represented graphically based on following plots.

1. Individual profiles (one panel per subject) with concentrations of OZ439 and PQP on linear scale
2. Individual profiles (one panel per subject) with concentrations of OZ439 and PQP on $\log_{10}$ scale
3. Spaghetti plots of individual profiles stratified by dose group with concentrations on linear scale, separately for OZ439 and PQP.
4. Spaghetti plots of individual profiles stratified by dose group with concentrations on $\log_{10}$ scale, separately for OZ439 and PQP.
5. Summary plots of arithmetic means per scheduled timepoint presenting all dose groups in one panel, separately for OZ439 and PQP. Subjects are summarized per

dose group. Plots on both linear and on log_{10} scale for the concentrations will be produced. Error bars representing +/- 1 arithmetic SD will be included.

6. Summary plots of geometric means per scheduled timepoint presenting all dose groups in one panel, separately for OZ439 and PQP. Plots on both linear and on log_{10} scale for the concentrations will be produced. Error bars representing +/- 1 geometric SD will be included. If the (geometric mean – geometric SD) value is zero or negative, then only the value for (geometric mean + geometric SD) will be displayed as error bars on the plot.

Pharmacokinetic Parameter Estimation (NCA)

Definition and calculation of Pharmacokinetic Parameters

Table 8 provides a list of definitions for PK parameters that will be calculated in this study.

Table 8. Definitions and calculation of PK Parameters

Parameter	Description
AUC_{last}	Area under the plasma concentration-time curve, calculated using linear-up logarithmic down trapezoidal summation from time zero to the last measurable concentration.
$AUC_{0\text{-}inf}$	Area under the plasma concentration-time curve from time zero to infinity, $AUC_{0\text{-}inf}$ is calculated as the sum of AUClast plus the last measurable plasma concentration divided by elimination rate constant [λ_{inf}].
C_{max}	Maximum observed drug concentration in observed individual concentration time profile.
t_{max}	Time to maximum observed drug concentration within a dose interval. If the maximum value occurs at more than one time point, t_{max} is defined as the first time point with this value.
$t_{1/2}$	Apparent elimination half-life, calculated as ln[2]/λ_{inf}.
t_{lag}	Elapsed time from dosing at which drug concentration was first quantifiable.
CL/F	Apparent total body clearance after extravascular administration, calculated as Dose/$AUC_{0\text{-}inf}$.
Vz/F	Apparent total volume of distribution at the terminal phase after extravascular administration, calculated as Dose/[λ_{inf} × $AUC_{0\text{-}inf}$].
λ_{inf}	Apparent terminal elimination rate constant, calculated by linear regression of the terminal linear portion of the log concentration vs. time curve. The terminal slope is calculated using the Best slope algorithm that sequentially fits (log(y) ~ x) from the last point of x to the previous points with at least 3 points. It chooses a slope with the highest adjusted R-square. If the difference is less then 1e-4, it picks a longer slope. x here represents the times of PK samples and y their observed concentrations.

Tabular and graphical presentation of NCA results

Values for λinf, t1/2, CL/F and Vz/F, AUC0-inf for a subject will only be reported if the following criteria for the log-linear phase for the concentration-time data are met:

- A minimum of 3 measurable concentration-timepoints during the log-linear portion of the terminal elimination phase, excluding Cmax.
- r^2 > 0.80 for the regression of the log-concentration time data during the terminal elimination phase.
- Negative slope for log regression fit.
- Extrapolated portion of AUC0-inf < 20% of total AUC0-inf.

Individual PK parameters will be reported as a table grouped by dose level with stratification for dose of the second treatment and overall. Individual and dose-normalized PK parameters (Cmax and AUCs) will be visualized by dose level for PQP and OZ493, separately.

7.5 SOFTWARE AND WORKING DIRECTORY

All data processing, summary statistics, and NCA will be performed in R 3.5.1 using the IQRtools package 1.0.0 [IQR18].

7.6 REPORTING IN MAIN BODY OF CSR

The NCA results and key figures of the PK profiles will be reported in the main text of the CSR.

SECTION 8: STATISTICAL METHODOLOGY FOR PHARMACODYNAMIC DATA

8.1 GENERAL CONSIDERATIONS

Data listings and summary tables will be generated by CNS for the following,

- Parasitaemia data
- PD endpoints:
    - Parasite reduction ratio at 48 h (PRR_{48}) and parasite clearance half-life ($PC_{t1/2}$)
    - Percentage of subjects with recrudescence of parasitaemia

Unless specifically mentioned otherwise, baseline is defined as the last observation prior to first treatment administration. If a baseline reading is missing, then an earlier measurement will be used.

8.2 SOURCES OF DATA

All parasitaemia data will be generated by the Queensland Paediatric Infectious Diseases (QPID) laboratory and transferred electronically to QIMR Berghofer, who will process the data and provide to CNS for the parastiaemia listing.

All PD data will be generated from processed parasitaemia data. Please refer to CTM QIMR SOP 87 for details regarding the processing of the parasitaemia data.

The contents of the Clinical Study Database and the processes that will be used for reconciliation and locking are described in more detail in the QP17C19 Data Management Plan.

8.3 DATA HANDLING

Handling of Replicates

The data will be recorded as triplicate parasitaemia values for each subject at each timepoint. These data will be summarised by calculating the arithmetic mean of the replicate $\log_{10}$ parasitaemia to obtain the geometric mean per subject and timepoint.

Handling of Missing Data

For any replicates that were ND, the value was substituted with 1 prior to calculating the geometric mean. For calculation of the PRR_{48} and parasite clearance half-life, if all replicates within a timepoint for a participant were ND, the first timepoint with all ND was included in model fitting, and all other timepoints were set to missing. All regression analyses were performed using the mean $\log_{10}$ parasitaemia. If no samples were all ND for a subject within 5 days post treatment, the last timepoint included was either 5 days post treatment or three timepoints after the minimum observed mean $\log_{10}$ parasitemia.

8.4 DATA ANALYSIS

Parasitaemia data will be listed for all enrolled subjects and summarised for the PD population. Parasitaemia and PD parameters will be presented for all subjects included in the PD population.

Parasitaemia profiles

Individual parasitaemia values (parasites/mL), nominal timepoints and actual sampling times post-inoculation will be presented in a data listing. ND and BLQ values will be flagged.

The data will be presented as average of triplicate parasitaemia values for each subject at each timepoint. These data are summarised by calculating the arithmetic mean of the replicate $\log_{10}$ parasitaemia to obtain the geometric mean.

Parasitaemia data will be summarised on the log_{10} scale by dose group with descriptive statistics at each scheduled timepoint.

The following descriptive statistics will be calculated: N, mean, SD, CV%, median, minimum, and maximum.

Individual parasitaemia data as well as the mean (by dose group) across time will be presented graphically on a log_{10} scale. Actual sampling times post inoculation will be used for the graphical presentation of data and scheduled timepoints for means.

PD Parameters Determination

PRR_{48} and parasite clearance half-life ($PC_{t1/2}$)

Processed parasitaemia data (refer to CTM QIMR SOP 87) is used to determine PD parameters.

The data used for all model selection and fitting calculations is comprised of the geometric mean of parasitaemia per timepoint per subject up to the first time all replicates are ND. All subsequent timepoints are set to 'missing', regardless of whether parasitaemia values increased afterwards due to potential recrudescence of malaria infection.

The PD responses will be estimated by calculating the optimal parasite clearance rate (slope coefficient from the log-linear decay regression of qPCR data) for each individual, as detailed in CTM QIMRB SOP 41, and Marquart et al. [7].

A regression modelling method, to incorporate both left and right censoring to remove potential lag and tail phases of the parasitaemia decay curve in a systematic way, will be used to determine the optimal number of data-points required to calculate the slope (β_1) of the log-linear parasitemia decay. A minimum number of 4 timepoints will be required for regression modelling. If fewer than 4 timepoints are used or if the adequacy of the fit to the data is not sufficient (based on the overall model R^2 p value ≥0.001), the slope and derived parameters will be reported as missing.

The individual PRR_{48} standardised to 48 hours will be derived from the regression modelling versus time in hours as

$$PRR_{48} = 10^{-48 \times \beta_1} \qquad (1)$$

The parasite clearance half-life is the transformation of the slope coefficient (per time, equivalent to PRR_{48}) into a time period. The relationship between PRR_{48} and parasite clearance half-life is a simple transformation of the PRR_{48}, as shown in Equation (2):

$$t_{½} = log_{10}(2) \times \left(\frac{48\ hours}{log_{10}(PRR_{48})}\right) = \frac{\log_{10}(2)}{-\beta_1} \qquad (2)$$

where the PRR_{48} is the parasitaemia ratio estimated over a 48 h interval that is subsequently transformed into a per hour clearance rate.

Individual regression plots of parasitaemia over time after treatment will be produced. Data listings of PRR_{48} and $PC_{t1/2}$ will show the first, last time point and the number of time points used in the regression model.

Weighted mean of regression coefficient (95% CI) of PD endpoints (log_{10}-(Parasitemia) and $PC_{t1/2}$ by dose group) will be plotted by dose group.

Estimating dose group specific PRR (PRR_{48}, D)

Of the s subjects with appropriate overall fit (p<0.001), the average PRR_{48} and corresponding 95% CI for each dose group is estimated by using the inverse variance method [9] to calculate the weighted average linear regression slope ($\overline{\beta_1}$) and corresponding SE. The weighted average slope for s subjects in the dose with appropriate overall fit is given by Equation (3):

$$\overline{\beta_1} = \frac{\sum_{i=1}^{s}(w_i \times \beta_{1,i})}{\sum_{i=1}^{n} w_i},\ i = 1, \ldots, \quad (3)$$

where the weight is the inverse of the squared SE, $w_i = \frac{1}{SE(\beta_{1,i})^2}$. The SE of $\overline{\beta_1}$ is estimated as, $SE(\overline{\beta_1}) = \sqrt{\frac{1}{\sum_{i=1}^{s} w_i}}$.

Therefore, the dose group specific PRR (PRR_{48}, D) and corresponding 95% CI is estimated as shown in Equation (4) and (5), respectively:

$$PRR_{48,D} = 10^{-48 \times \overline{\beta_1}} \quad (4)$$

$$95\%\ CI:\ 10^{-48 \times \left(\overline{\beta_1} \pm 1.96 \times SE(\overline{\beta_1})\right)} \quad (5)$$

Comparison of dose group specific PRR_{48}s

To determine whether there are differences between dose group specific PRR_{48}s, an omnibus test for between dose group differences is used [10]. The test is used to assess whether there are differences in the weighted mean slope of the J doses, using the test statistic shown in Equation (6) at the 5% significance level,

$$Q_B = \sum_{j=1}^{J} w_{j\cdot}\left(\bar{\beta}_{j\cdot} - \bar{\beta}_{\cdot\cdot}\right)^2 \sim \chi^2_{J-1} \qquad j = 1, \ldots, J \quad (6)$$

The weight for the j^{th} dose is denoted by $w_{j\cdot} = \sum_{i=1}^{s_j} w_{ij}$ for subject i with appropriate overall fit in dose j. The $\bar{\beta}_{j\cdot}$ is the weighted average slope for dose j as defined in Equation (7), and $\bar{\beta}_{\cdot\cdot}$ is the weighted grand mean given by:

$$\bar{\beta}.. = \frac{\sum_{j=1}^{J} w_{j\cdot}\bar{\beta}_{j\cdot}}{\sum_{j=1}^{J} w_{j\cdot}} \qquad (7)$$

Interim analyses of comparisons between dose-group specific PRR_{48}s will first be performed for all dose groups within each cohort. Final analyses will include the comparison between the dose groups 1D vs. 3A, each receiving the same dose combination (OZ439 400 mg, PQP 640 mg). Final analyses will be performed based on the factorial design of the study, for the following dose groups to assess differences in increasing PQP dose with constant 200 mg dose of OZ439 (1A vs. 1B vs. 2B), 400 mg dose of OZ439 (1C vs. 1D/3A) and 800 mg dose of OZ439 (2A vs. 3B). Similarly, comparisons will be made to assess differences between dose groups with increasing OZ439 dose with constant 480 mg dose of PQP (1A vs. 1C) and 640 mg dose of PQP (1B vs. 1D/3A vs. 3B). Type 1 error corrections will not be performed as analyses was implicit by the study design.

Post-hoc pair-wise comparisons can be calculated using the test statistic $Z_G = \frac{G}{\sqrt{v_G}}$, where G is the contrast ($G = c_1\bar{\beta}_1. + \cdots + c_J\bar{\beta}_J$) and v_G is the variance of the contrast ($v_G = \frac{c_1^2}{w_{1\cdot}} + \ ... + \frac{c_J^2}{w_{J\cdot}}$). The p-value of the L pair-wise comparisons will be calculated using the Scheffe method, by comparing Z_G^2 to a chi-squared distribution with $L - 1$ degrees of freedom.

Recrudescence

Recrudescence will be defined as subjects who show substantial increases in parasitaemia after the initial clearance and are treated with a standard course of Riamet® prior to the compulsory scheduled timepoint for Riamet® treatment.

PD Parameters Analysis

All PD parameters will be listed. Summary statistics will be produced by dose group. For continuous data, the number of observations, mean, SD, median, minimum and maximum values will be reported. The number and percentage of subjects will be reported for incidence data.

8.5 ANALYSIS SOFTWARE

R version 3.5.0, RStudio version 1.1.447, and SAS Enterprise Guide Software version 7.12 or more recently updated versions will be used for all data processing and analyses.

8.6 REPORTING

The PD and parasitaemia results will be reported in the main text of the CSR, and will also be presented in listings, tables, and figures.

SECTION 9: PK/PD ANALYSIS

9.1 OVERVIEW

A population PKPD model will be derived from the concentrations and parasitaemia observed in the challenge volunteers. It is achieved by sequentially developing a population PK model to describe the observed individual PK profiles and a population PD model for quantifying the relationship of plasma concentrations and the parasite clearance. The model building is supported by PK/PD data from studies QP12C10 and QP13C05 for OZ439 and PQP mono treatment in healthy volunteers.
The final model will be employed to simulate patients of the OZ439 mono study 12_006 and the OZ439/PQP combo study 13_003. Predictions of the ACPR28 will be used to evaluate the predictive power of the human challenge model by comparing the simulations with the observed ACPR28 in clinical trials 12_006 and 13_003.

9.2 SOURCES OF DATA

9.3 DATA HANDLING

Data from studies QP12C10, QP13C05 and QP17C19 will be pooled. The data set will contain information on the individual OZ439/PQP doses, OZ439 PK concentrations, PQP PK concentrations, the triplicated parasitemia levels and typical covariates such as age, height, weight, sex and race.

Data assembly

First a master dataset will be assembled formatted according to the MMV dataset standard (cf., "*MS_IQdataset_V1.docx*"). Plasma concentrations will be in µg/mL, total parasite levels in counts/mL, and doses in mg. Parasite data after the first administration of rescue medication is flagged by setting the IGNORE column to "*Observations after rescue medication*". The time in hours is relative to the OZ439/PQP administration time. Total counts of parasites for which counts of gametocytes exceeded 10% of total counts are flagged to be ignored (by setting the column IGNORE to "gametocytes") If the lab providing the parasitemia data marks records as (mainly) gametocytes the values are set to half of the LLOQ.

A general analysis dataset is derived from the master dataset. The general analysis dataset will contain the following observations: OZ439 plasma concentrations, PQP plasma concentrations, and total counts of parasites. Values of replicate measurement and their geometric means are contained for the parasite counts. In addition, dosing records for *P. falciparum* inoculation, OZ439/PQP administration, and rescue medication administration will be defined. It is advised to define additional columns DOSELEVEL1 and DOSELEVEL2 to indicate the dose amounts of OZ439 and PQP a subject received as covariate columns.

Nonlinear mixed effects (NLME) datasets for the PK and PD modelling will be derived from the general dataset.

PK modelling data set

Observations below the lower limit of quantification (LLOQ) will be censored by setting the CENS column for these observation records to 1 and setting the corresponding dependent variable (DV) column to the LLOQ (→ M3 method). Observation records with missing values and records with missing times will be ignored. Records flagged to be ignored will be removed from the dataset. Observations not analysed in the PK modelling (i.e., all parasite count records) will be removed.

As a result, the PK modelling dataset only contains OZ439/PQP dosing records and OZ439/PQP plasma concentration records.

PD modelling data set

Observations below the LLOQ will be censored by setting the CENS column for these observation records to 1 and the corresponding DV value to the LLOQ, i.e., 10 p/mL (→ M3 method). Total counts of parasites for which counts of gametocytes exceeded 10% of total counts are flagged to be ignored (by setting the column IGNORE to "gametocytes"). If the lab providing the parasitaemia data marks records as (mainly) gametocytes the values are set to half of the LLOQ. Observation records with missing values and records with missing times will be ignored. Records flagged to be ignored will be removed from the dataset. Observations not analysed in the PD modelling analysis (i.e., concentration records) will be removed.

As a result, the PD modelling dataset only contains only OZ439/PQP dosing records and total parasite counts (i.e., cleaned replicate means). The total parasite counts will be log-transformed for the PD modelling and estimated individual PK model parameters will be added to the dataset as regressors. For a correct estimation of the model baseline parasitaemia value that is defined as the value at the first observation for each subject, the first observation time needs to be similar across the subject to ensure that the baseline values are at similar values. Hence, the first modelled observation time is a timepoint at which the observed parasitaemia value is available for all subjects. All previous timepoints will be removed.

9.4 METHODS

Model building

General PKPD model building approach

Population models of the PK and PD will be developed in step-wise manner.

1. An NLME model for the PK (OZ439, PQP and combinations) will be developed to obtain individual PK parameter estimates based on which the individual PK profiles are described well.
2. The PKPD population model for OZ439 mono treatment will be built sequentially. That is, a PK model will be developed first. Second, using the individual PK parameter estimates as regression parameters and estimating the PD part of the model only. Estimation of typical and individual PD parameters will first be performed with IQRtools SysFit to investigate model identifiability and second with Monolix to additionally estimate inter-individual variability (IIV).
3. The PKPD population model for PQP mono treatment will be built using the individual PK parameter estimates as regression parameters and estimating the PD part of the model only. Estimation of typical and individual PD parameters will first be performed with IQRtools SysFit to investigate model identifiability and second with Monolix to additionally estimate IIV.
4. The parasitaemia base line levels and parasite growth rate (PD parameters) in the absence of the drug will be estimated from the total parasite counts of the OZ439/PQP combo study QP17C19 before treatment. Estimation of typical and individual PD parameters will be performed with IQRtools SysFit.
5. The PKPD model for the OZ439/PQP combo study will be built using the
   - individual PK parameter estimates as regression parameters,
   - individual growth rate and base line parasitaemia values as regression parameters,
   - typical E_{max}, EC50 and Hill parameter values of OZ439 and PQP as fixed parameters from the mono PD models (Monolix),
   - IIV values for and E_{max}, EC50 of OZ439 and PQP as fixed parameters from the mono PD models (Monolix).
   - Individual PD parameters and drug-drug interaction parameters will first be estimated using IQRtools SysFit to investigate identifiability of multiple drug-drug interaction models. Second, considering the identifiability analysis, Monolix will be used to estimate individual parameters for selected models.

For both PK (NLME with Monolix) and PD (IQRtools SysFit), IIV is implemented for normally distributed parameters using the following equation with θ_0 as population average parameter, θ_i as individual parameter, and η_i as random effect that is distributed normally around zero ($\eta_i \sim N(0, \omega^2)$):

$$\Theta_i = \Theta_0 + \eta_i.$$

The following equation is used for log-normally distributed parameters:

$$\ln(\Theta_i) = \ln(\Theta_0) + \eta_i.$$

Continuous covariates on log-normally distributed parameters will be implemented as follows:

$$\Theta_i = \Theta_0 \cdot \left(\frac{COV_i}{COV_{median}}\right)^{\beta} \cdot \eta_i.$$

Θ_i represents the individual parameter, Θ_0 the population mean value, COV_i the individual covariate value, COV_{median}, the population median covariate value, β the covariate coefficient, and η_i the individual random effect.

Categorical covariates on log-normally distributed parameters will be implemented as follows.

$$\Theta_i = \Theta_0 \cdot \sum_j \left(e^{\beta_j \cdot COV_{ij}}\right) \cdot \eta_i$$

The individual covariate values COV_{ij} are 1 if subject i belongs to the jth category of the covariate and 0 otherwise. β_j is the covariate value for the jth category. For one category, i.e. the reference, β_j is 0.

For the NLME PK modelling, the log-likelihood and the Fisher information matrix will be approximated by linearization. The number of iterations in the burn-in and the accumulation phase will be 500 and 200 respectively, but might be adjusted if required based on inspection of parameter estimate and objective function traces along estimation iterations. Individual parameters will be determined as conditional modes.

For PD modelling, the IQRtools SysFit implementation using a non-linear fixed-effects modelling approach is employed. Typical and individual parameters are both treated as fixed effects. The parameterization of individual parameters and covariates is fully consistent with the NLME parameterization above. The variances ω^2 of NLME random effects are accounted for by quadratic priors, $l_{prior}(\eta) = \frac{1}{2}\frac{\eta^2}{\omega^2}$, added to the log-likelihood function, where the values for ω^2 are fixed and the η parameters are estimated.

The profile-likelihood method [RAU09, KAS16] is used to compute confidence intervals of the parameters estimated with the SysFit approach.

Model evaluation

Assessment of model adequacy and decisions about increasing model complexity will be driven by the data and guided by goodness-of-fit criteria, including

1. visual inspection of diagnostic scatter plots (observed vs. predicted concentration, residual/weighted residual vs. predicted concentration or time and histograms of individual random effects, for example),
2. successful convergence of the minimization routine with at least 2 significant digits in parameter estimates,
3. plausibility of parameter estimates,
4. precision of parameter estimates,
5. correlation between model parameter estimation errors<0.95, and
6. the Bayesian information criterion, given the minimum objective function value and number of estimated parameters.

For the nonlinear fixed effects models, additional diagnostic plots will be produced:

7. objective function values across multiple fits from randomised initial guesses, and

8. profile likelihood plots

All parameter estimates will be reported with a measure of estimation uncertainty, such as the standard error of the estimates. The individual PK fits will be used to evaluate the adequacy to use the individual PK parameter estimates as regression parameters for PD modelling.

The adequacy of simulation with the final models will be evaluated by visual predictive checks. Visual predictive checks for each dose level will be performed by simulation of the study 200 times taking parameter estimation uncertainty into account. 95%-confidence intervals for the 5th percentile, the median, and the 95th percentile will be derived and compared to the corresponding values based on the data.

To compare simulations of the final model with patient data, both, the data and the simulation will be transformed into a life table format indicating for each individual the time of recrudescence, i.e., the time at which parasite levels re-occur after being BLQ or the time for which parasitaemia levels are minimum, or, if not defined, the last observed time point without recrudescence. The Kaplan-Meier estimator [KAP58, THE15, TER00] will be used to compare model and data.

PK modelling

The PK of OZ439/PQP will be modelled using compartmental models describing the absorption after oral administration, distribution between central and peripheral compartments, and the elimination from the central compartment. The visual data analysis will guide the selection of models that will be tested (e.g., with respect to number of compartments, linear or saturable elimination, absorption kinetics and error model).

The allometric function will be used to include the impact of weight (WGT) on the clearance rate (CL) and central compartment volume (Vc):

$$CL_i = CL \cdot \left(\frac{WGT_i}{WGT_{median}}\right)^{0.75}$$

$$Vc_i = Vc \cdot \left(\frac{WGT_i}{WGT_{median}}\right)^{1.00}.$$

The same relation as for CL will be used for the inter-compartmental clearance rate $Q1$ and, if a third compartment is required, $Q2$. The same relation as for Vc will be used for the peripheral volume $Vp1$ and, if a third compartment is required, $Vp2$. The previous analysis of the OZ439 mono study QP12C10 (human challenge) has revealed that the dose amount might be a significant covariate for the clearance rate. The PK model is supposed to be used in simulations of patients, including children. Therefore, dose amount as covariate might not be appropriate, because the same dose

amount could lead to significantly different drug exposure, depending on the clearance that relates to weight. To correctly account for exposure, a new covariate

$$AUC = \frac{Doseamount}{Weight^{0.75}}$$

is derived from the base covariates and will be included when testing covariates. More covariates will be included if appropriate. It will be tested whether including interaction terms for the impact of one compound on the clearance of the other leads to a better description of the data.

PD modelling

As a general concept, the changes in living parasite P are modeled as the effect of a net exponential growth rate GR and a killing or clearance rate $Kill$ due to OZ439/PQP with an initial parasitemia level P_{base} at time t_0 (time of first observation). The equations are expressed on the log-scale such as

$$\begin{aligned} \frac{dPL}{dt} &= GR - Kill \\ PL(t_0) &= PL_{base}, \end{aligned}$$

where $PL = \ln(P)$ is the log-transformed parasite counts. The killing rate $Kill = Kill_1 + Kill_2$ is composed of contribution from OZ439 (index 1) and PQP (index 2). The killing rate of each drug is described by an Emax model. The Emax model assumes a direct effect of concentrations on parasite killing/clearance, such as:

$$\begin{aligned} Kill_1 &= EMAX_1 \cdot \frac{Cc_1^{Hill_1}}{Cc_1^{Hill_1} + EC50_1^{Hill_1}} \\ Kill_2 &= EMAX_2 \cdot \frac{Cc_2^{Hill_2}}{Cc_2^{Hill_2} + EC50_2^{Hill_2}} \end{aligned}$$

Here, Cc is the concentration in the central compartment, $EMAX$ is the maximum effect of the drug, $EC50$ is the concentration that results in 50% of the maximum effect and $Hill$ is the Hill coefficient.

Two alternative models to combine the killing effect of each drug are considered. First, a so-called empirical Bliss independence approach is applied. The kill is modelled as sum of the single effects and an interaction term that is the scaled product of the single effect and an interaction coefficient γ.

$$Kill = Kill_1 + Kill_2 + \gamma \cdot \frac{Cc_1^{Hill_1}}{Cc_1^{Hill_1} + EC50_1^{Hill_1}} \frac{Cc_2^{Hill_2}}{Cc_2^{Hill_2} + EC50_2^{Hill_2}} \min(Kill_1, Kill_2)$$

Second, an additive effect of both drugs on the killing rate is assured, $Kill = Kill_1 + Kill_2$. However, the Emax and EC50 values employed in the killing contributions can be affected by the other drug. In the analysis, two drug-drug interaction models will be used to describe the effect one drug exerts on the EC50 and Emax of the other drug: a mutual and a non-mutual model.

The non-mutual model states that

$$EC50_1^* = EC50_1\left(1+(e^{-\alpha_{21}}-1)\frac{Cc_2^{Hill_2}}{EC50_2^{Hill_2}+Cc_2^{Hill_2}}\right)$$
$$EC50_2^* = EC50_2\left(1+(e^{-\alpha_{12}}-1)\frac{Cc_1^{Hill_1}}{EC50_1^{Hill_1}+Cc_1^{Hill_1}}\right)$$
$$EMAX_1^* = EMAX_1\left(1+(e^{\beta_{21}}-1)\frac{Cc_2^{Hill_2}}{EC50_2^{Hill_2}+Cc_2^{Hill_2}}\right)$$
$$EMAX_2^* = EMAX_2\left(1+(e^{\beta_{12}}-1)\frac{Cc_1^{Hill_1}}{EC50_1^{Hill_1}+Cc_1^{Hill_1}}\right).$$

Hence, the modified EC50 or E_{max} for one drug is the original value scaled by a factor that is modulated by the other drug concentration. In short, $\alpha \geq 0$ decreases the EC50 and $\beta \geq 0$ increases the E_{max}.

The mutual model assumes that $\alpha_{12} = \alpha = \alpha_{21}$ and $\beta_{12} = \beta = \beta_{21}$. Thereby, the number of interaction parameters is reduced from 4 to 2 in the mutual model.

IIV will be assumed on all parameters except the Hill coefficient and the interaction parameters. Parameters are assumed to be log-normally distributed besides the log-transformed parasite baseline value for which the normal distribution was assumed. The standard deviation of the IIV will be fixed to 0.2 for the SysFit approach. When parameters are estimated with Monolix, standard deviations of the IIV will be estimated.

Using the SysFit approach for PD modelling, parameter estimation will be started from 24 initial guesses. Identifiability of the best fit will be analysed using the profile likelihood method. In case, several local optima with similar objective value are found, those local optima will be investigated and it will be checked using modelling, if additional cohorts could help to reduce the number of local optima.

Using Monolix, optimization will be initialized with the estimated values obtained with SysFit. If optimization with Monolix poorly converges for some of the parameters as being assessed by the Monolix convergence traces, these values will be fixed to the value obtained with SysFit.

Simulations to predict ACPR28 in patients

Simulations of patients will build on the patient characteristics found in the 12_006 and 13_003 studies. Simulations will be performed as if patient PK and PD information was completely missing. Only covariates such as weight, actual dose, expected exposure and parasitaemia levels at $t = 0$ (shortly before treatment) will be used.

For each dose group, n = 200 patients will be randomly drawn with replacement. Individual parameters will be sampled from the IIV estimated by Monolix, taking covariates of the randomly chosen patients into account.

Individuals in each dose group will be simulated at densely sampled time points between 0 and 1600 hours. Initial values for the parasitaemia simulation will be fixed to the parasitaemia level of the selected patient.

The simulated time-course will be translated to a life table containing the information about the time to recrudescence. The Kaplan-Meier estimator will be used to derive the recrudescence rate at every time point and the probability of recrudescence as (1-recrudescence rate)x100%.

9.5 ANALYSIS SOFTWARE AND WORKING DIRECTORY

All data processing, analysis, model setup and modelling result analysis including goodness-of-fit plots will be performed in R 3.5.1 using the IQRtools package 1.0.0 [IQR18].

NLME modelling will be performed with Monolix 2018R2 [MLX18] using Stochastic Approximation Expectation Maximization (SAEM) for parameter estimation. For PD modelling where typically the variance of random-effects cannot be estimated from the data, the IQRtools SysFit approach [KAS16] will be used to estimate typical and individual PD parameters.

A library of functions related to the analysis of PKPD studies of antimalarials may be used (available at https://github.com/IntiQuan/iqrmalaria).

9.6 REPORTING

The analysis results will be reported in the main body of the CSR and technical details will be reported as an appendix (referred to here as the 'technical appendix'). The technical appendix will include the clinical data used in the analysis, data assembly, modelling methods, all results, discussions, and conclusions.

Key results will include description and interpretation of the final model, parameter estimates, and diagnostic plots of goodness-of-fit and simulations and will be included in the main text. Limitations of the model prediction will be discussed in the Discussion section of the technical appendix and mentioned in the main text of the CSR.

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APPENDIX 1: PLANNED LISTINGS

The following listings are planned to be generated for the QP17C19 study (note: Numbering is indicative only and may be updated based on CSR requirements):

	Listing Number	Listing Title	Population
16.2.1 Subject Disposition			
	Listing16.2.1.1	Study Enrolment and Completion/Discontinuation	All Enrolled
	Listing16.2.1.2	Visit Dates	All Enrolled
	Listing 16.2.1.3	Dose Group Assignment	All Enrolled
16.2.2 Protocol Deviations			
	Listing16.2.2.1	Protocol Deviations	All Enrolled
16.2.3 Subject Excluded from Analyses			
	Listing16.2.3.1	Analysis Population Assignment	All Enrolled
	Listing16.2.3.2	Subjects Excluded from Any Analysis Set(s)	All Enrolled
16.2.4 Demographic and Other Baseline Data			
	Listing16.2.4.1	Demography	All Enrolled
	Listing16.2.4.2	Inclusion and Exclusion Criteria	All subjects
	Listing16.2.4.3	Medical History	All Enrolled
	Listing16.2.4.4	Pregnancy Test	All Enrolled
	Listing16.2.4.5	Follicle Stimulating Hormone (FSH) Test	All Enrolled
	Listing16.2.4.6	RBC Alloantibody	All Enrolled
	Listing16.2.4.7	Serology and Special Tests	All Enrolled
	Listing16.2.4.8	Urine Drug Screen and Alcohol Breath Test	All Enrolled
	Listing 16.2.4.9	Glucose-6-Phosphate Dehydrogenase (G6PD)	All Enrolled
	Listing 16.2.4.10	Beck Depression Inventory (BDI)	All Enrolled
	Listing 16.2.4.11	Body Weight, Height and Body Mass Index (BMI)	All Enrolled
	Listing 16.2.4.12.1	Prior Medications	All Enrolled

	Listing Number	Listing Title	Population
	Listing 16.2.4.12.2	Concomitant Medications	All Enrolled
16.2.5 Compliance and Drug Concentration Data			
	Listing16.2.5.1	Malaria Inoculum Administration	All Enrolled
	Listing16.2.5.2	IMP Administration	All Enrolled
	Listing16.2.5.3	Rescue Medication Administration	All Enrolled
	Listing16.2.5.4	Blood Collection for PK Assessments, and measured OZ439 and PQP plasma concentrations	All Enrolled
	Listing16.2.5.5	Pharmacokinetic (PK) Parameters	PK
16.2.6 Individual Parasitaemia and Pharmacodynamic Data			
	Listing16.2.6.1	qPCR 18S Daily	All Enrolled
	Listing16.2.6.2	qRT-PCR pfs25 Daily	All Enrolled
	Listing16.2.6.3	qRT-PCR pfs25 Retrospective	All Enrolled
	Listing16.2.6.4	Pharmacodynamic (PD) endpoints (log_{10}PRR48, PCt1/2, subject recrudescence)	PD
16.2.7 Adverse Event Data			
	Listing16.2.7.1	All Adverse Events	All Enrolled
	Listing16.2.7.2	Serious Adverse Events	All Enrolled
	Listing16.2.7.3	Adverse Events of Special Interest (AESIs)	All Enrolled
	Listing16.2.7.4	Deaths	All Enrolled
16.2.8 Laboratory Data			
	Listing16.2.8.1.1	Individual Haematology Results	All Enrolled
	Listing16.2.8.1.2	Individual Abnormal Haematology Results	All Enrolled
	Listing16.2.8.2.1	Individual Biochemistry Results	All Enrolled
	Listing16.2.8.2.2	Individual Abnormal Biochemistry Results	All Enrolled
	Listing16.2.8.3.1	Individual Urinalysis Results (Dipstick)	All Enrolled
	Listing16.2.8.3.2	Individual Abnormal Urinalysis Results (Dipstick)	All Enrolled

	Listing Number	Listing Title	Population
	Listing16.2.8.4.1	Individual Urine Microscopy Results	All Enrolled
	Listing16.2.8.4.2	Individual Abnormal Urine Microscopy Results	All Enrolled
16.4 Other Safety Data			
	Listing16.4.1	Vital Signs	All Enrolled
	Listing16.4.2	Individual Abnormal Vital Signs	All Enrolled
	Listing16.4.3	ECG Parameters and Changes from Baseline	All Enrolled
	Listing16.4.4	Abnormal ECG Findings	All Enrolled
	Listing16.4.5	Physical Examination	All Enrolled
	Listing16.4.6	Malaria Clinical Score	All Enrolled
	Listing16.4.7	Additional Comments	All Enrolled

APPENDIX 2: PLANNED SUMMARY TABLES

The following tables are planned to be generated for the QP17C19 study (note: Numbering is indicative only and may be updated based on CSR requirements):

	Table Number	Table Title	Population
14.1 Demographic Data			
	Table14.1.1	Study Participation and Disposition	All Enrolled
	Table14.1.2	Demographics and Baseline Characteristics	All enrolled
	Table14.1.3	IMP Administration	All Enrolled
	Table14.1.4	Analysis Population	All Enrolled
14.2 Pharmacokinetic, Parasitaemia, and Pharmacodynamic Data			
	Table14.2.1	Summary of OZ439 and PQP concentrations in plasma by timepoint and by dose group	PK
	Table14.2.2	Summary of PK endpoints by dose group	PK
	Table14.2.3	Summary of qPCR 18S Daily measurements by timepoint and by dose group	PD
	Table14.2.4	Summary of PD endpoints by dose group	PD
	Table 14.2.5	Treatment comparison across dose groups based on QB test for between-treatment differences of weighted slope	PD
	Table14.2.6	Final PK parameter estimates	PK
	Table14.2.7	Final PD parameter estimates	PKPD
14.3 Safety Data			
	Table14.3.1.1a	Overall Summary of Inoculum-Emergent Adverse Events	Inoculum
	Table14.3.1.1b	Overall Summary of Treatment-Emergent Adverse Events	Safety
	Table14.3.1.2a	Inoculum-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Inoculum

	Table Number	Table Title	Population
	Table14.3.1.2b	Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
	Table14.3.1.3a	Inoculum-Related Inoculum-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Inoculum
	Table14.3.1.3b	IMP-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
	Table14.3.1.4a	Inoculum-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term and Maximum Severity	Inoculum
	Table14.3.1.4b	Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term and Maximum Severity	Safety
	Table14.3.1.5a	Overall Summary of Inoculum-Emergent AESIs	Inoculum
	Table14.3.1.5b	Overall Summary of Treatment-Emergent AESIs	Safety
	Table14.3.1.6a	Inoculum-Emergent Adverse Events by MedDRA Preferred Term	Inoculum
	Table14.3.1.6b	Treatment-Emergent Adverse Events by MedDRA Preferred Term	Safety
	Table14.3.2a	Malaria Clinical Score and Change from Baseline	Inoculum
	Table14.3.2b	Malaria Clinical Score and Change from Baseline	Safety
14.3.4 Clinical Laboratory Data			
	Table14.3.4.1a	Haematology Results and Change from Baseline (Inoculum)	Inoculum
	Table14.3.4.1b	Haematology Results and Change from Baseline (IMP)	Safety
	Table14.3.4.2a	Biochemistry Results and Change from Baseline (Inoculum)	Inoculum
	Table14.3.4.2b	Biochemistry Results and Change from Baseline (IMP)	Safety
	Table14.3.4.3a	Cross-Tabulation of Haematology Abnormalities Versus Baseline (Inoculum)	Inoculum

	Table Number	Table Title	Population
	Table14.3.4.3b	Cross-Tabulation of Haematology Abnormalities Versus Baseline (IMP)	Safety
	Table14.3.4.4a	Cross-Tabulation of Biochemistry Abnormalities Versus Baseline (Inoculum)	Inoculum
	Table14.3.4.4b	Cross-Tabulation of Biochemistry Abnormalities Versus Baseline (IMP)	Safety
14.3.5 Vital Signs			
	Table14.3.5.1a	Vital Signs Results and Change from Baseline (Inoculum)	Inoculum
	Table14.3.5.1b	Vital Signs Results and Change from Baseline (IMP)	Safety
	Table14.3.5.2a	Abnormal Vital Signs Results (Inoculum)	Inoculum
	Table14.3.5.2b	Abnormal Vital Signs Results (IMP)	Safety
14.3.6 ECG Findings			
	Table14.3.6.1a	ECG parameters and Change from Baseline (Inoculum)	Inoculum
	Table14.3.6.1b	ECG parameters and Change from Baseline (IMP)	Safety
	Table14.3.6.2a	Abnormal ECG Results (Inoculum)	Inoculum
	Table14.3.6.2b	Abnormal ECG Results (IMP)	Safety
	Table14.3.6.3a	ECG Clinical Assessment (Inoculum)	Inoculum
	Table14.3.6.3b	ECG Clinical Assessment (IMP)	Safety

APPENDIX 3: PLANNED SUMMARY FIGURES

The following figures are planned to be generated for the QP17C19 study (note: Numbering is indicative only and may be updated based on CSR requirements):

Figure Number	Figure Title	Population
14.2 PK and PK Data		
Figure 14.2.1.1	Arithmetic mean (SD) concentration time-profiles by dose group	PK
Figure 14.2.1.2	Geometric mean (SD) concentration time-profiles by dose group	PK
Figure 14.2.1.3.1	Overlaying individual concentration-time profiles (Linear)	PK
Figure 14.2.1.3.2	Overlaying individual concentration-time profiles (Semi-log)	PK
Figure 14.2.1.4.1	Individual concentration-time profiles (Linear)	PK
Figure 14.2.1.4.2	Individual concentration-time profiles (Semi-log)	PK
Figure 14.2.1.5.1	Individual PQP AUC/C_{max} by dose group	PK
Figure 14.2.1.5.2	Individual Dose-Normalized PQP AUC/C_{max} by Dose Group	PK
Figure 14.2.1.6.1	Individual OZ493 AUC/C_{max} by dose group	PK
Figure 14.2.1.6.2	Individual Dose-Normalized OZ493 AUC/C_{max} by dose group	PK
Figure 14.2.2.1	Geometric Mean (SD) log_{10}-parasitaemia time profiles	PD
Figure 14.2.2.2	Individual log_{10}-parasitemia time profiles	PD
Figure 14.2.2.3	Individual log_{10}-parasitemia regression fit	PD
Figure 14.2.2.4	Weighted mean of regression coefficient (95% CI) PD endpoints by dose group	PD
Figure 14.2.3.1	Scatter plot of observations versus predictions of log_{10}(parasitemia)	PKPD

Figure Number	Figure Title	Population
Figure 14.2.3.2	Distribution of weighted residuals [log_{10}(parasitemia)]	PKPD
Figure 14.2.3.3	Scatter plot of weighted residuals over time [log_{10}(parasitemia)]	PKPD
Figure 14.2.3.4	Scatter plot of weighted residuals over predicted value [log_{10}(parasitemia)]	PKPD
Figure 14.2.3.5	Time courses of individual predictions and observations of log_{10}(parasitemia) stratified by dose group	PKPD
Figure 14.2.3.6	Kaplan-Meier plots of time to recrudescence for simulated Phase 2 trials	NA
Figure 14.2.3.7	Kaplan-Meier plots of Probability of recrudescence for simulated Phase 2 trials	NA