STATISTICAL ANALYSIS PLAN

Protocol title: A randomized, open label, two-part, parallel-group phase I study to evaluate the pharmacokinetics of Piperaquine oral dispersible granules formulation compared to Piperaquine hard tablets administered as a single dose in fasting condition (Part 1) and of Piperaquine oral dispersible granules formulation administered as a single dose in various fed states (Part 2) in healthy adult participants.	
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Glossary of abbreviations

ABBREVIATION	DESCRIPTION
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
$AUC_{0\text{-}24h}$	Area under the plasma concentration curve from time zero to 24 hours
$AUC_{0\text{-}72h}$	Area under the plasma concentration curve from time zero to 72 hours
$AUC_{0\text{-}t}$	Area under the plasma concentration curve from time zero up to the last quantifiable concentration
$AUC_{0\text{-}168h}$	Area under the plasma concentration curve from time zero to 168 hours
$AUC_{0\text{-}\infty}$	Area under the plasma concentration-time curve from time 0 extrapolated to infinite time
$\%AUC_{extrap}$	Percentage of AUC that is due to extrapolation from tlast to infinity
BA/FE	Bioavailability/Food Effect
BPM	Beats Per Minute
CI	Confidence Interval
CV	Coefficient of Variation
$\frac{CL}{F}$	Apparent total plasma clearance
C_{max}	Maximal plasma concentration
DBL	Database Lock
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
F_{rel}	Relative Bioavailability
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
MedDRA	Medical Dictionary for Regulatory Activities
N	Sample size
ODS	Output Delivery System
PK	Pharmacokinetics
PT	Preferred Term
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SEM	Standard Error of Mean

SOC	System Organ Class
TEAEs	Treatment-Emergent Adverse Events
TLFs	Tables, data listings, and figures
T_{max}	Time at which the maximum plasma concentration occurs
$t_{1/2}$	Terminal elimination half-life
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary
ENRL	Enrolled Population Set
SAF	Safety Analysis Set
PK	PK Analysis Set
PQP	Piperaquine phosphate
LOQ	Limit of Quantification
Vz/F	Apparent volume of distribution during the terminal phase
λ_z	Terminal rate constant

1. Overview

1.1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within Protocol MMV_SMC_22_01 version 3.0 dated 08 Nov 2023. The scope of this plan includes the final analysis, which will be executed by the Biostatistics department unless otherwise specified.

The present pilot BA/FE study aims to assess the relative bioavailability and food effect on the systemic exposure of a new child-friendly, taste-masked dispersible granule formulation of PQP among healthy adults. In addition, PK and safety/tolerability profiles will be further evaluated and documented.

2. Trial objectives

The following objectives are those stated in the protocol.

2.1 Primary objective

- To determine the relative bioavailability of a single oral dose of PQP dispersible granule formulation (Test) as compared to PQP hard tablet formulation (Reference) in the fasted state.

2.2 Secondary objectives

- To assess the effect of different types of meal composition on the PK of single doses of PQP dispersible granule formulation in healthy adult participants.
- To further evaluate the PK of a single oral dose of PQP granule formulation in the fasted state and different fed states in healthy adult participants.
- To further document the safety/tolerability of PQP in healthy adult participants.

2.3 Exploratory objectives

- To further document PQP metabolite profiling and PK depending on the results of a former study (optional objective) as well as the results of genetic testing of CYP450s polymorphism (optional).
- To evaluate the palatability of the new PQP granule formulation in healthy adult participants.

3. Endpoints

3.1 Primary endpoint

- Relative bioavailability (F_{rel}) using the ratio of the geometric means for the dispersible granule (test) over the hard tablet (reference) in a fasted state for the area under the plasma concentration-time curve from time zero to 72 hours (AUC_{0-72h}), area under the plasma concentration-time curve from time zero to last detectable plasma concentration (AUC_{0-t}), area under the plasma concentration-time curve from time zero to 168 hours (AUC_{0-168h}), area under the plasma concentration-time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$), and maximum plasma concentration (C_{max}).

3.2 Secondary endpoints

- PK parameters for the hard tablet (fasted) and the dispersible granule formulations (fasted and fed); C_{max}, AUC_{0-24h}, AUC_{0-72h}, AUC_{0-t}, AUC_{0-168h}, $AUC_{0-\infty}$, time to maximum plasma concentration T_{max}, terminal elimination rate constant (λ_z), terminal elimination half-life ($t_{1/2}$), apparent volume of distribution during the terminal phase (V_z/F), apparent total plasma clearance (Cl/F), and percentage of AUC that is due to extrapolation from tlast to infinity ($\%AUC_{extrap}$).
- Occurrence of AEs including serious adverse events (SAEs) from the IMP administration throughout the entire study period (up to Day 30).
- Findings at different time points:
    - Physical examination, vital signs, clinical laboratory safety parameters, 12-lead ECG parameters.

4. Trial design

4.1 Design overview

This is a randomized, open-label, parallel-design study to evaluate the PK profile and relative bioavailability of a single dose of a PQP oral granule formulation dispersed in water (test) as compared to the PQP hard tablet formulation (reference) in fasting conditions (Part 1) and to assess the BA/FE of the PQP dispersible granules formulation when administered with different food restrictions (Part 2) among African participants residing in Tanzania, in Bagamoyo Town and surrounding areas. A total of sixty (60) healthy adult participants (male and female) will be enrolled in Part 1 and Part 2.

- **Part 1:** PQP tablet / dispersible granule administered in fasting condition of at least 10 hours.
    - Group 1: PQP hard tablet, 320 mg (N=12)
    - Group 2: PQP dispersible granule, 320 mg (N=12)
- **Transition to Part 2:**
    - To minimize the risk to healthy participants, a decision on transitioning from Part 1 to Part 2, will be taken by the Safety Review Committee (SRC) see protocol section 13.7, based on the safety and preliminary PK interim report of the granule formulation, compared to the PQP hard tablet, with safety data obtained up to Day 15 and PK data obtained up to Day 8. If necessary, doses may be readjusted for Part 2 to assess the food effect. A description of the rationale and oversight related to the potential for dose adjustment is provided in protocol section 2.2.
- **Part 2:** PQP dispersible granule administered in fed conditions (planned as 320 mg)
    - Group 3: High-fat meal (N=12)
    - Group 4: Low-fat meal representative of African diet (N=12)
    - Group 5: Whole milk 250 ml (N=12)

Participants will be screened within a window of ≤ 45 days before in-house admission on Day -1. Each participant will be admitted to the trial unit on Day -1, and after a new eligibility check, will receive a single dose of PQP on Day 1 and will be discharged on Day 3 (a total of 4 in-house days). Participants will attend the trial unit clinic for outpatient visits on Days 8, 15, 22, and 30.

4.2 Randomization

Healthy adult participants (male and female) will be randomly allocated to one of the 5 following treatment groups, dosing will be carried out in the fasted or fed state:

- During the study part 1, participants for fasted conditions will be randomly allocated to either group 1 (n=12) or group 2 (n=12), in order to assess the relative bioavailability of the dispersible granules formulation as compared to the hard tablet formulation.
    - Randomization will occur in blocks of 2 (each block contains 1 assignment from each of the groups 1 and 2).
- During study part 2, participants for fed conditions will be randomly allocated to either group 3 (n=12), 4 (n=12), or 5 (n=12), in order to assess the food effect after dosing of PQP dispersible granules formulation.

- Randomization will occur in blocks of 3 (each block contains 1 assignment from each of the groups 3, 4, and 5).

A computer-generated randomization schedule will be used and will be accessible only to the site-delegated study staff who will prepare the treatment for each participant according to the randomization allocation.

4.3 Determination of sample size

This is an exploratory trial to evaluate the PK and safety of each treatment group and the sample size is not based on formal statistical power. The number assigned to each treatment arm (n=12) is considered adequate to assess the trial objectives.

4.4 Schedule of Events

Refer to section 4.4 schedule of events of the protocol.

5. Changes/deviations from the planned analysis

The statistical analysis/methods as described in the protocol were adopted. There are no changes to the planned analyses. Any deviation from the original statistical analysis plan will be described and justified in the SAP or final clinical study report.

6. Analysis of populations

Protocol deviations will be reviewed, and exclusion of participants from each analysis sets will be decided during data review meeting prior to the final database hard lock. A list of all participants to be excluded from the relevant analysis populations, including the reason(s) for exclusion from the analysis populations will be provided.

The following sets will be used for the statistical analyses:

6.1 Enrolled Analysis Set (ENRL)

This population will include all participants who signed the informed consent form (ICF).

6.2 Safety Analysis Set (SAF)

This population will include all randomized participants who received at least one dose of the IMP.

6.3 PK Analysis Set (PK)

The PK analysis set will include those participants in the safety set who have sufficient blood samples taken for at least one of the PK variables to be calculated and experienced no protocol deviations with relevant impact on PK data.

7. General considerations

7.1 Baseline

Baseline is defined as the last non-missing observation made before the study treatment administration.

7.2 Data consideration

Not Applicable

7.3 End of study

Day 30 is the end of study day.

7.4 Stratifications

For analysis purposes, trial participants may be sub-classified into the following stratification levels, where applicable:

- **Groups for Part-1 (Fasting):**
  - Group 1 (PQP Hard Tablet)
  - Group 2 (PQP Dispersible Granules)
- **Groups for Part-2 (PQP Dispersible Granules - Fed):**
  - Group 3 (High-fat Meal)
  - Group 4 (Low-fat Meal)
  - Group 5 (Whole Milk 250ml)

7.5 Statistical tests

No formal tests will be applicable for the safety analysis.

7.6 Interim analysis

No formal interim analysis is planned for this study, other than the safety/PK report that will be performed for the SRC review during the transition from Part 1 to Part 2.

7.7 Common calculations

For quantitative measurements, change from baseline will be calculated as: (Test value at Visit Day X – Baseline value), where the baseline value is defined as the last non-missing observation made before first study treatment administration.

7.8 Software

All statistical analyses will be conducted using SAS® Version 9.4 or higher.

8. Statistical considerations

8.1 Multicenter studies

Not applicable.

8.2 Missing data

All data will be inspected for potential errors and a summary of missing data will be generated including the percentages of those with non-missing data, dropouts, and replacement of participants. Unrecorded values will be treated as missing. 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 adverse event, prior and concomitant medication data, partial date imputations will be performed where at least the year is provided.

9. Output presentations

The templates provided in the separate output templates document describe the format and content for the presentation of tables, listings, and figures (TLFs).

For continuous measures, summary statistics will include the number of participants (n), number of missing values, mean, standard deviation (SD), median, minimum, and maximum for both the actual and the change from baseline measurements. For categorical measures, summary statistics will include the number of participants (n), number of missing values and percentages.

All percentages (%) for a specific summary are calculated using the total number of participants included in the relevant analysis population as the denominator unless otherwise specified.

10. Participant disposition and withdrawal

The following analysis will be applicable to both, part-1, and part-2 of the study.

10.1 Variables and derivations

The following parameters will be summarized for the participant's disposition table as per eCRF:

- Number of screened participants
- Number of screening failure participants
- Number of enrolled participants
- Number of participants screened but discontinued before randomization.
- Number of randomized participants*
- Number of study completed participants.
- Number of study discontinued participants.
- Reasons for study discontinuation
- Number of participants in the Safety analysis set.
- Number of participants in the PK analysis set.

*Randomized: Participants who are screen positive and assigned to the treatment.

Screening Failure: Participants who did not meet any Inclusion/ Exclusion Criteria or Are not eligible for the trial.

10.2 Analysis

Population:	ENRL
Stratification:	Table: By part and group
	Listing: By part, group and participant
Statistics:	All above mentioned participant's disposition parameters, will be summarised (frequency & percentage) and participants listing for all participants by participant number will be provided.
	The reasons for study discontinuation will be summarized as per eCRF end of study form.
	The summary for safety and PK analysis set will be presented with their exclusion reason from respective analysis set and listing with population assignment and exclusion reason will be provided.
	Summary for protocol deviation will be presented by category (i.e., Major/Minor) and participant data listing will be provided by participant number.

11. Participant demographics and other baseline characteristics

The following analysis will be applicable to both, part-1, and part-2 of the study.

11.1 Variables and derivations

The following demographic and other baseline characteristics will be summarized:

- Age (Years)
- Sex
- Race
- Ethnicity
- Height
- Weight
- BMI

11.2 Analysis

Population:	Table: SAF and PK
	Listing: ENRL
Stratification:	Table: By part and group
	Listing: By part, group and participant
Statistics:	Baseline and Demographic variables will be summarized for each stratification factor and overall, also listed by participant number. The summaries will include descriptive statistics for continuous measures (number of participants, number of missing values, mean, SD, median, minimum & maximum) and for categorical measures (frequency, percentages, and number of missing values).

12. Exposure to IMP

12.1 Analysis

Population:	SAF
Stratification:	Table: By part and group Listing: By group and participant
Statistics:	Planned dose and actual dose will be summarized descriptively (number of participants, number of missing values, mean, SD, median, minimum & maximum). Study drug administration information will be listed by participant number.

13. Medical history summary

The following analysis will be applicable to both, part-1, and part-2 of the study.

13.1 Analysis

Population:	SAF
Stratification:	Table: NA
	Listing: By group and participant
Statistics:	Medical history data will be listed by participant number.

14. Prior, concomitant, and other medications

The following analysis will be applicable to both, part-1, and part-2 of the study.

14.1 Variables and derivations

Concomitant medications will be coded using the WHO-DD, dated 1 March 2023, or higher.

Prior medications are defined as any medication taken before the first administration of the study treatment.

'Concomitant medications' are defined as any medication taken after the first administration of the study treatment.

In section 23 of Appendix 1, the algorithm is given for the calculation of partial date imputation for prior and concomitant medications, and it will be used for partially missing prior and concomitant medications, start and end date imputation.

The following parameters will be summarised for concomitant medications:

- Number of participants with at least one prior and concomitant medication
- Number of participants for each prior and concomitant medication by ATC and PT.

14.2 Analysis

Population:	Table: SAF
	Listing: ENRL
Stratification:	Table: By part and group
	Listing: By part, group and participant
Statistics:	Prior and Concomitant medication will be summarized (frequency, percentages) by group and a listing will be presented.

15. Adverse events

The following analysis will be applicable to both, part-1, and part-2 of the study.

15.1 Variables and derivations

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, version 26.0 or higher.

For the definition of Adverse events (AE) and Serious adverse events (SAE) refer to the protocol sections 8.1.2 & 8.4.

Pre- treatment adverse-events are defined as AEs between informed consent and IMP administration.

Treatment-emergent adverse events (TEAEs) are defined as an event that emerges during treatment, have been absent pre-treatment or worsens relative to the pre-treatment state.

The following parameters will be summarised for the participant's adverse events as mentioned in eCRF:

- All Adverse Events
- Number of participants with at least one Pre-Treatment AE
- Number of participants with at least one TEAE
- Number of participants with at least one study drug-related TEAE
- Number of participants with at least one serious TEAE
- Number of participants with at least one study drug-related serious TEAE
- Ongoing AEs
- TEAEs by Toxicity Grade
- TEAEs by Outcome
- TEAEs by Action Taken with Study Treatment
- TEAEs by Relationship
- TEAEs leading to Death.
- TEAEs leading to withdrawn or discontinued the study.

Derivations:

- The question on eCRF page Adverse Events "Relationship to investigational product" is answered "Related/Suspected", then respective AEs will be considered as drug-related AEs.
- If The question on eCRF page Adverse Events "Was the adverse event serious" is answered as "YES" then the respective AE will be considered as serious AE.
- The question on eCRF page Adverse Events "Was the adverse event serious" is answered as "YES" and answered as "Related/Suspected" then respective AEs will be considered drug-related SAEs.

- If the seriousness criteria are “RESULTS IN DEATH” then we will consider it as AE leading to death.
- participant’s primary reason for discontinuation is “ADVERSE EVENT” then we will consider it as AE leading to withdrawal/discontinued from the study.

Imputations will only be performed where at least the year is provided. The imputations derived for partial dates will be as per appendix 1.

15.2 Analysis

Population:	Table: SAF Listing: ENRL
Stratification:	Table: By part and group Listing: By part, group and participant
Statistics:	An overall summary will be presented as the number of participants within each of the event type categories described in the sub-sections below, including the incidence of AEs by system organ class (SOC) and preferred term (PT) sorted by decreasing frequency within the SOC and PT. The number of participants with AEs will be presented. Both number of participants, number of events (One participant may be counted more than once) and percentage will be provided. The Adverse Event will be summarized and presented in data listings with all AEs (including coding details SOC and PT) and participants with SAEs, death, and events resulting in study discontinuation will be listed separately by participant number. Treatment-emergent AEs (TEAE) will be summarized for all participants by SOC and PT. Each TEAE will be counted only once for a given participant. If the same TEAE occurs on multiple occasions, the highest severity and relationship will be assumed. A summary of serious TEAE will be presented separately. All other TEAEs will be summarized similarly. Note: If there are uncoded adverse events, then the uncoded category will be added to the AEs by SOC/PT summary tables.

15.2.1 Incidence of Pre-Treatment AEs

The incidence of all AEs by SOC and PT will be presented.

15.2.2 Incidence of TEAEs (all causalities)

The incidence of all TEAEs by SOC and PT will be presented.

15.2.3 TEAEs by Toxicity Grade

The incidence of all AEs by SOC, PT, and toxicity grade will be presented.

15.2.4 TEAEs by Outcome

The incidence of all AEs will be presented by SOC, PT, and outcome.

15.2.5 TEAEs by Action Taken

The incidence of all TEAEs will be presented by SOC, PT, and action taken.

15.2.6 Drug-Related TEAEs

The incidence of all drug-related TEAEs will be presented by SOC and PT.

15.2.7 Drug-Related TEAEs by Severity

The incidence of all drug-related TEAEs will be presented by SOC, PT and severity.

15.2.8 Serious AEs and Serious TEAEs

The incidence of all serious AEs and TEAEs will be presented by SOC and PT.

15.2.9 TEAEs and SAEs leading to withdrawal/discontinuation from the study

The incidence of all TEAEs and SAEs leading to withdrawal/discontinuation will be presented by SOC and PT. A data listing of TEAEs and SAEs leading to withdrawal/discontinuation from the study will be presented.

15.2.10 TEAEs leading to death

The incidence of all TEAEs leading to death will be presented by SOC and PT. A data listing of all TEAEs for death participants will be presented.

16. Safety laboratory tests

The following analysis will be applicable to both, part-1, and part-2 of the study.

16.1 Variables and derivations

All the reported lab parameters will be presented for the below categories as per protocol:

- Biochemistry
- Hematology
- Thick blood smear – Malaria
- Urinalysis
- Urine for drugs of abuse
- Pregnancy test
- FSH
- Coagulation
- Serology
- Alcohol breath test

Quantitative laboratory measurements reported as "< X", i.e., below the limit of quantitation, or "> X", i.e., above the upper limit of quantification, will be converted to X for quantitative summaries but will be presented as recorded, i.e., as "< X" or "> X" in the data listings.

16.2 Analysis

Population:	Table: SAF Listing: ENRL
Stratification:	Table: By part and group Listing: By part, group, participant, timepoint & parameter
Statistics:	Summaries of all the laboratory tests will include descriptive statistics at each assessment of the following: • Actual and change from baseline (number of participants, mean, SD, median, minimum & maximum) (for quantitative measurements) for which baseline data is collected. i.e., Biochemistry, Hematology. • Frequencies and percentages (n and %) (for qualitative measurements). i.e., Thick blood smear – Malaria, Pregnancy test, Urinalysis, Urine for drugs of abuse, Alcohol breath test.) Qualitative laboratory measurements will be compared with the relevant laboratory reference ranges and summarized as: • Normal: Within the laboratory reference range (upper and lower limit included) • Abnormal NCS: Abnormal not clinically significant • Abnormal CS: Abnormal clinically significant • High: Higher than the upper limit of the reference range • Low: Lower than the lower limit of the reference range

Above categorizations and abnormal laboratory data will be flagged and presented in data listings.

The qualitative urinalysis data will be listed only. Those above lab parameters that will only be done in screening will be listed only.

17. 12-Lead ECG & Vital signs

The following analysis will be applicable to both, part-1, and part-2 of the study.

17.1 Variables and derivations

For ECG and vital signs, a baseline is defined as the last observation made before the first administration of study treatment.

The following vital signs parameters will be reported for this study:

- Blood pressure (Systolic and Diastolic)
- Heart rate
- Axillary temperature
- respiratory rate

All recorded in supine position.

The following 12-lead ECG parameters will be reported for this study:

- PR
- QRS
- QT
- QTcB
- QTcF
- HR

17.2 Analysis

Population:	Table: SAF
	Listing: ENRL
Stratification:	Table: By part and group
	Listing: By part, group, participant, timepoint & parameter
Statistics:	Summaries of all 12-Lead ECG & vital parameters will include descriptive statistics at each assessment of the following: • Actual and change from baseline (number of patients, mean, SD, median, minimum & maximum) (for quantitative measurements) • Frequencies and percentages (n and %) (for qualitative measurements) "Any Clinically Significant Abnormality Found in Vital Signs" will be found as "Yes" on the eCRF page of Vital signs, it will be summarized as Frequencies and percentages (n and%). In ECG analysis, if triplicate ECG performed then the average of three repetitions will be calculated and used for the further evaluation. The qualitative measurements of ECG will be categorised as (Normal, Abnormal Clinically Significant and Abnormal Not Clinically Significant) Above categorizations and abnormal data will be flagged and presented in data listings.

Additionally, QTcF data will be summarized using frequencies & percentages (n and %) as follows:

Absolute QTcF interval prolongation

- QTcF interval > 450 ms
- QTcF interval > 480 ms
- QTcF interval > 500 ms

Change from baseline in QTcF interval

- QTcF interval increases from baseline > 30 ms
- QTcF interval increases from baseline > 60 ms

The mean value of change from baseline QTcF parameters will be plotted by group and time point.

18. Primary Endpoint Analysis

18.1 To determine the relative bioavailability of a single oral dose of PQP dispersible granule formulation (Test) as compared to PQP hard tablet formulation (Reference) in the fasted state.

18.1.1 Variables and derivations

- $AUC_{0\text{-}72h}$: Area under the plasma concentration curve from time zero to 72 hours
- $AUC_{0\text{-}168h}$: Area under the plasma concentration curve from time zero to 168 hours
- $AUC_{0\text{-}t}$: Area under the plasma concentration curve from time zero up to the last quantifiable concentration
- $AUC_{0\text{-}\infty}$: Area under the plasma concentration-time curve from time 0 extrapolated to infinite time.
- C_{max}: Maximal plasma concentration

Comparisons of interest are as follows:

- Group 1: PQP hard tablet with Group 2: PQP dispersible granule

18.1.2 Analysis

Population: Table: PK

Listing: PK

Stratification: Table: By part and group

Listing: By group, participant, timepoint & parameter

Statistics: The relative bioavailability will be assessed for PQP using the ratio of the geometric means for $AUC_{(0\text{-}72h)}$, $AUC_{(0\text{-}168h)}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$, and C_{max} as follows:

- For Part 1 the comparisons will be Group 2 PQP dispersible granule (320 mg, fasted) [test] over the Group 1 PQP hard tablet (320 mg, fasted) [reference].

To determine bioequivalence between PQP dispersible granule (320 mg) [test] and the PQP hard tablet (320 mg), ln-transformed PK parameters $AUC_{0\text{-}72h}$, $AUC_{0\text{-}168h}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max} will be analyzed using Type III sum of squares, with the fixed effect of treatment using General Linear Model (PROC GLM) in SAS software.

Each analysis of variance will include calculation of least square means (LSM). Two 1-sided tests procedure at 5% level of significance will be

used to compare the geometric LSM values of PK parameters determined after administration of test and reference products.

Point estimates of the ratio of geometric least squares means and its 90% CI of PQP dispersible granule (320 mg) and PQP hard tablet (320 mg) will be calculated and reported for ln-transformed PK parameters.

Total subject variability for the PQP dispersible granule (320 mg) [test] and PQP hard tablet (320 mg) PK data will be calculated and reported.

Summary statistics (i.e., mean, median, SD, CV%, minimum, maximum, n, geometric mean, geometric SD, and geometric CV%) will be calculated for blood concentrations for each time point and group. The same will be done for the PK parameters which will be listed for each individual and summarized by group.

19. Secondary Endpoints

19.1 To assess the effect of different types of meal composition on the PK of single doses of PQP dispersible granule formulation in healthy adult participants.

19.1.1 Variables and derivations

- $AUC_{0\text{-}72h}$: Area under for the plasma concentration curve from time zero to 72 hours
- $AUC_{0\text{-}168h}$: Area under the plasma concentration curve from time zero to 168 hours
- $AUC_{0\text{-}t}$: Area under the plasma concentration curve from time zero up to the last quantifiable concentration
- $AUC_{0\text{-}\infty}$: Area under the plasma concentration-time curve from time 0 extrapolated to infinite time.
- C_{max}: Maximal plasma concentration

Comparisons of the Interest are as follows:

- Group 3: High-fat meal with Group 2: PQP dispersible granule
- Group 4: Low-fat meal representative of African diet with Group 2: PQP dispersible granule
- Group 5: Whole milk 250 ml with Group 2: PQP dispersible granule

19.1.2 Analysis

Population: Table: PK
Listing: PK

Stratification: Table: By part and group
Listing: By part, group, participant, timepoint & parameter

Statistics: The relative bioavailability will be assessed for PQP using the ratio of the geometric means for $AUC_{(0\text{-}72)}$, $AUC_{(0\text{-}168)}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$, and C_{max} as follows:

For Part 2 the comparisons will be as follow.

- Group 3: High-fat meal (Fed) [test] over the Group 2 PQP dispersible granule (fasting) [reference]
- Group 4: Low-fat meal representative of African diet (Fed) [test] over the Group 2 PQP dispersible granule (fasting) [reference]
- Group 5: Whole milk 250 ml (Fed) [test] over the Group 2 PQP dispersible granule (fasting) [reference]

To determine bioequivalence between PQP dispersible granule (320 mg) [test] and each of different type of meal, ln-transformed PK parameters ($AUC_{(0\text{-}72h)}$, $AUC_{(0\text{-}168)}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$, and C_{max}) will be

analyzed using Type III sum of squares, with the fixed effect of Treatment using General Linear Model (PROC GLM) of SAS software.

Each analysis of variance will include calculation of least square mean (LSM). Two 1-sided tests procedure at 5% level of significance will be used to compare the geometric LSM values of PK parameters determined after administration of test (different type of meal) and reference products.

Point estimates of the ratio of geometric least squares means of dispersible granules formulation between fed [high-fat meal, low-fat African meal, and milk] will be calculated and reported for ln-transformed PK parameters.

Total subject variability for the dispersible granules formulation between fed [high-fat meal, low-fat African meal, and milk] PK data will be calculated and reported.

Summary statistics (i.e., mean, median, SD, CV%, minimum, maximum, n, geometric mean, geometric SD, and geometric CV%) will be calculated for blood concentrations for each time point and group. The same will be done for the PK parameters which will be listed for each individual and summarized by group.

19.2 To further evaluate the PK of a single oral dose of PQP granule formulation in the fasted state and different fed states in healthy adult participants.

19.2.1 Variables and derivations

The following pharmacokinetic parameters will be calculated for piperaquine:

- C_{max}: Maximal plasma concentration
- T_{max}: Time at which the maximum plasma concentration occurs
- $t_{1/2}$: Terminal elimination half-life
- $AUC_{0-\infty}$: Area under the plasma concentration-time curve from time 0 extrapolated to infinite time
- AUC_{0-t}: Area under the plasma concentration curve from time zero up to the last quantifiable concentration
- AUC_{0-24h}: Area under the plasma concentration curve from time zero to 24 hours
- AUC_{0-72h}: Area under the plasma concentration curve from time zero to 72 hours
- AUC_{0-168h}: Area under the plasma concentration curve from time zero to 168 hours
- $\%AUC_{extrap}$: Percentage of AUC that is due to extrapolation from tlast to infinity
- $C_{L/F}$: Apparent total plasma clearance
- $V_{z/F}$: Apparent volume of distribution during the terminal phase
- Λ_z: Terminal rate constant

19.2.2 Analysis

Population:	Table: PK Listing: PK
Stratification:	Table: By part and group Listing: By part, group, participant, timepoint & parameter
Statistics:	PK concentration data will be descriptively summarized using: number of non-missing observations (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median) and maximum (Max). Graphical Presentation: Individual concentration versus time plots; linear and semi-log; using the actual time points by participants, and groups. Overlaying individual concentration time profiles will be displayed. Mean concentration time plots; linear with standard deviation and semi-log; using scheduled (nominal) time points, and meal group. Error bars should be included only in the linear plots.

PK Parameter Data will be descriptively summarized using number of non-missing observations (N), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median) and maximum (Max), Geometric mean (Geo mean), Geometric coefficient of variation (GCV%).

T_{max} will be summarized by treatment using Min, Max and Median.

Plots for Individual PQP AUC_{0-t} and C_{max} by dose group will be provided.

19.3 Physical examination

19.3.1 Variables and derivations

Following physical examination parameters will be reported & applicable to both part 1 & part 2 of the study:

- Skin
- Lymph Nodes
- Head
- Eyes
- Ear
- Nose
- Throat
- Respiratory
- Cardiovascular
- Abdomen
- Extremities
- Musculoskeletal
- Neurological

19.3.2 Analysis

For the analyses of laboratory parameters, vital signs & ECG parameters refer to sections 16.2 & 17.2 respectively.

Population:	Table: NA
	Listing: ENRL
Stratification:	Table: NA
	Listing: By part, group, participant, timepoint & parameter
Statistics:	The physical examination assessment will be presented in data listings at all assessment time points. Physical examination data will be classified as normal, abnormal not clinically significant & abnormal clinically significant.

20. Exploratory endpoints

20.1 PK profile and PK parameters for Piperaquine N-oxide metabolite

20.1.1 Variables and derivations

The following pharmacokinetic parameters will be calculated for N-oxide PQP (metabolite), whenever possible:

- C_{max}: Maximal plasma concentration
- T_{max}: Time at which the maximum plasma concentration occurs
- $t_{1/2}$: Terminal elimination half-life
- $AUC_{0-\infty}$: Area under the plasma concentration-time curve from time 0 extrapolated to infinite time
- AUC_{0-t}: Area under the plasma concentration curve from time zero up to the last quantifiable concentration
- AUC_{0-24h}: Area under the plasma concentration curve from time zero to 24 hours
- AUC_{0-72h}: Area under the plasma concentration curve from time zero to 72 hours
- AUC_{0-168h}: Area under the plasma concentration curve from time zero to 168 hours
- $\%AUC_{extrap}$: Percentage of AUC that is due to extrapolation from tlast to infinity
- λ_z: Terminal rate constant

20.1.2 Analysis

Population:	Table: PK Listing: PK
Stratification:	Table: By part and group Listing: By part, group, participant, timepoint & parameter
Statistics:	PK concentration data will be descriptively summarized using: number of non-missing observations (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median) and maximum (Max). Graphical Presentation: Individual concentration versus time plots; linear and semi-log; using the actual time points by participants, and groups. Overlaying individual concentration time profiles will be displayed. Mean concentration time plots; linear with standard deviation and semi-log; using scheduled (nominal) time points, and meal group. Error bars should be included only in the linear plots.

PK Parameter Data will be descriptively summarized using number of non-missing observations (N), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median) and maximum (Max), Geometric mean (Geo mean), Geometric coefficient of variation (GCV%).

T_{max} will be summarized by treatment using Min, Max and Median.

Plots for Individual PQP N-oxide (metabolite) AUC_{0-t} and C_{max} by dose group will be provided.

20.2 To evaluate the palatability of the new PQP granule formulation in healthy adult participants.

20.2.1 Variables and derivations

Variables:

All the 3 questions (including sub-domains) and numerical answers (from 1 to 5) to these will be considered from the eCRF page of the Palatability Questionnaire [PALAQ].

20.2.2 Analysis

Population:	Table: SAF
	Listing: ENRL
Stratification:	Table: By part and group
	Listing: By part, group and participant
Statistics:	The questionnaire data will be presented in data listings and summarised as frequency and percentages (n and %).

21. Revision history

Version	Date	Change
1.0	19-DEC-2023	Initial document

22. Appendix 1: Programming Conventions for Tables, Data Listings, and Figures (TLFs)

22.1 Paper Size, Orientation, and Margins

The margin, page size, and line size specifications as stipulated in Table 22.1 will be used for the presentation of all TLFs.

Table 22.1: Output margin, page size, and line size specifications

	Landscape	Portrait
Margins (Inches):		
Top	1.25	1
Bottom	1	1
Left	1	1.25
Right	1	1
Header (Inches)	0.5	0.5
Footer (Inches)	0.5	0.5
SAS® specifications:		
PAGES	46	67
LINE SIZE	134	93

22.2 Fonts

The font type “Courier New” should be used as a default for tables and data listings, with a font size of 8. The font color should be black. No bolding, underlining, or italics are permitted.

Figures should have a default font of “Times Roman”, “Helvetica” or “Courier New”.

22.3 Header Information

Headers should be defined as follows:

- The header should be placed at the top of the page (same place on each page).
- The sponsor’s name should appear in row 1, left-aligned.
- The word “CONFIDENTIAL” should appear in row 1, right aligned.
- The protocol number should appear in row 2, left-aligned.
- The page identification in the format Page X of Y (where Y is the total number of pages for the TLF) should appear in row 2, right aligned.
- The TLF identification number should appear in row 3, centered.
- The TLF title should start in row 4, centered.

- The TLF population should appear in row 5, centered. The population should be spelled out in full, e.g., the *Safety analysis population* in preference to the *Safety analysis population*.
- Row 6 should be a continuous row of underscores ('_') (the number of underscores should equal the line size).
- Row 7 should be a blank line.
- Mixed cases should be used for titles.
- Titles should not contain quotation marks or footnote references.
- The column headings should be underlined with a row of underscores ('_').
- Column headings spanning more than one column should be underlined and have underscores on either side of the title and should be centered.
- Column headings containing numbers should be centered.
- Column headings should be in mixed case.
- In general, the analysis population count should appear in the column header in the form "(N=XX)".

22.4 Table and Data Listing Table, Listing and Figure (TLF) Conventions

22.4.1 General

- The first row in the body of the table or data listing should be blank.
- The left-hand column should start in Column 1. No indenting or centering of the TLF should occur.
- Rounding should be done with the SAS® function ROUND.
- Numerical values in tables should be rounded, not truncated.
- Numerical values should be decimal point aligned.
- Text values should be left aligned.
- The first letter of a text entry should be capitalized.
- The study drug should appear first in tables with the treatment group as columns.
- All variables contained on the eCRF (which have data present) should appear in the data listings, along with all derived data appearing in the corresponding tables.
- The width of the TLF should match the line size.

22.4.2 Univariate statistics

- Statistics should be presented in the same order across tables (i.e., n, mean, SD, minimum, median, and maximum).

- If the original data has N decimal places, then the summary statistics should have the following decimal places:
  - Minimum, maximum, and CV (%): N
  - Mean and median: N + 1.
  - SD: N + 2.

22.4.3 Frequencies and percentages [n, (m) and %]

- Mentions should be reported inside parentheses, with one space between the count and the left parenthesis of the mentions. An example is given below:
  - 124 (645)
- Percent values should be reported inside parentheses, with one space between the right parenthesis of the mention and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:
  - 77 (156) (100.0)
  - 50 (56) (64.9)
  - 0 (0) (0.0)
- Percentages will be reported to one decimal place, except percentages <100.0 but >99.9 will be presented as '>99.9' (e.g., 99.99 is presented as >99.9); and percentages <0.1 will be presented as '<0.1' (e.g., 0.08 is presented as <0.1). Rounding will be applied after the <0.1 and >99.9 rules.
  - (<0.1)
  - (6.8)
  - (>99.9)
- Percentages may be reported to 0 decimal places as appropriate (for example, where the denominator is relatively small).
- Where counts are zero, mentions of 0 and percentages of 0.0 should appear in the table.

22.4.4 Confidence intervals (CIs)

- CIs should be presented with one additional decimal place as that of the raw data, and SDs and standard errors (SEs) with two additional decimal places as that of the raw data.
- CIs should be justified so that parentheses are displayed on consecutive lines of a table "line up".

22.4.5 P-values

- P-values should be reported to four decimal places.

22.4.6 Ratios

- Ratios should be reported with one additional decimal place as that of the raw data.

22.4.7 Spacing

- There should be a minimum of 1 blank space between columns (preferably 2).

22.4.8 Missing values

- A “0” should be used to indicate a zero frequency.
- A blank will be used to indicate missing data in data listings.

22.5 Figure output conventions

Figures should be provided in RTF files using the SAS® Output Delivery System (ODS).

22.6 Dates and times

Depending on the data available, dates and times will take the form ddMMMyyyy and hh: mm.

22.7 Spelling format

The spelling format to be used is English US.

22.8 Presentation of treatment groups

- Part 1
  - Group 1 (PQP Hard Tablet - Fasted)
  - Group 2 (PQP Dispersible Granules - Fasted)
- Part 2
  - Group 3 (PQP Dispersible Granules - High-fat Meal)
  - Group 4 (PQP Dispersible Granules - Low-fat Meal)
  - Group 5 (PQP Dispersible Granules - Whole Milk 250ml)

22.9 Presentation of visits

- Screening

- Day -1 (Admission)
- Day 1
- Day 2
- Day 3
- Day 5
- Day 8
- Day 15
- Day 22
- Day 30

23. Appendix

23.1 Appendix 1: Partial date conventions for adverse events and prior and concomitant medication

Event	Missing	Imputation
Start Date	Day	If event start Month = Treatment start month and event start Year = Treatment start Year, then event start Day= minimum of (Treatment Start Day or event end Day). Otherwise, event start day = “01”.
	Day and Month	If event start Year = Treatment start Year, then event start Day and Month = minimum of (Treatment Start Day and Month or event end Day and Month). Otherwise, event start Day and Month = “01 Jan”.
	Day, Month and Year	No Imputation will be performed.
End Date	Day	If event End Month = Study conclusion Month and event End Year= Study conclusion Year, Then event End Day= Study Conclusion Day. Otherwise, event End Day = last day of respective month.
	Day and Month	If event End Year = Study Conclusion Year, then event End Day and Month = Study Conclusion Day and Month. Otherwise, event End Day and Month = “31 Dec”.
	Day, Month and Year	No Imputation will be performed.

23.2 Appendix 2: PLANNED LISTINGS

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

	Listing Number	Listing Title	Population
16.2.1 Participants Discontinuation/Completion			
	Listing16.2.1.1	Screening Status	Enrolled
	Listing16.2.1.2	Participants Disposition Status	Enrolled
	Listing 16.2.1.3	Visit Dates	Enrolled
	Listing 16.2.1.4	Treatment Assignment	Enrolled
16.2.2 Protocol Deviations			
	Listing16.2.2.1	Protocol Deviations	Enrolled
16.2.3 Subject Excluded from Analyses			
	Listing16.2.3.1	Patients Excluded from the Analysis Sets	Enrolled
16.2.4 Demographic and Other Baseline Data			
	Listing16.2.4.1	Informed Consent	Enrolled
	Listing16.2.4.2	Participant Demographics	Enrolled
	Listing16.2.4.3	Inclusion and Exclusion Criteria	All Participants
	Listing16.2.4.4	Medical History	Enrolled
	Listing16.2.4.5	Participants Substance Use - Drugs	Enrolled
	Listing16.2.4.6	Participants Substance Use - Tobacco	Enrolled
	Listing16.2.4.7	Participants Substance Use - Alcohol	Enrolled
	Listing 16.2.4.8	Prior Medication	Enrolled
	Listing 16.2.4.9	Concomitant Medication	Enrolled
16.2.5 Compliance and Drug Concentration Data			
	Listing16.2.5.1	Study drug administration	Safety
	Listing16.2.5.2	Blood Collection for PK Assessments	Enrolled
	Listing16.2.5.3	PK Concentrations	Enrolled
	Listing16.2.5.4	PK Parameters for PQP	PK
	Listing16.2.5.5	PK Parameters for PQP N-oxide (metabolite)	PK
16.2.6 Individual response data			
	16.2.6.1	Palatability Questionnaire	Safety
16.2.7 Adverse Event listings			
	Listing16.2.7.1	All Adverse Events	Enrolled
	Listing16.2.7.2	Study discontinuation of participants due to Serious Adverse Event and Death	Enrolled
	Listing16.2.7.3	Participant Deaths	Enrolled
16.2.8 Laboratory Assessment and other safety assessment			
	Listing16.2.8.1	Listing of Laboratory Results - Haematology	Enrolled
	Listing16.2.8.2	Listing of Laboratory Results - Biochemistry	Enrolled
	Listing16.2.8.3	Listing of Laboratory Results - Coagulation	Enrolled
	Listing16.2.8.4	Listing of Laboratory Results - Thick Blood Smear - Malaria	Enrolled
	Listing16.2.8.5	Listing of Laboratory Results - Urinalysis	Enrolled
	Listing16.2.8.6	Vital Signs	Enrolled
	Listing16.2.8.7	Pregnancy Test	Enrolled
	Listing16.2.8.8	Follicle-stimulating hormone	Enrolled
	Listing16.2.8.9	Serology and Special Tests	Enrolled
	Listing16.2.8.10	Urine Drug Screen and Alcohol Breath Test	Enrolled

	Listing Number	Listing Title	Population
	Listing16.2.8.11	12- Lead ECG	Enrolled
	Listing16.2.8.12	Physical Examination	Enrolled

23.3 Appendix 3: PLANNED SUMMARY TABLES

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

	Table Number	Table Title	Population
14.1 Demographic Data			
	Table14.1.1.1	Participant Disposition at Screening	Enrolled
	Table14.1.1.2	Participant Disposition Status by Parts	Randomized Participants
	Table14.1.1.3	Summary of Analysis Set by Parts	Randomized Participants
	Table14.1.1.4	Summary of Protocol Deviation by Parts	Safety
14.1.2 Participants Baseline Characteristics			
	Table14.1.2.1.1	Summary of Demographics by Parts	Safety
	Table14.1.2.1.2	Summary of Demographics by Parts	PK
	Table14.1.2.2	Study drug administration by Parts	Safety
	Table14.1.2.3	Summary of Prior Medications by Parts	Safety
	Table14.1.2.4	Summary of Concomitant Medications by Parts	Safety
14.2.1 Primary and Secondary Endpoint Analysis			
	Table14.2.1.1	Summary of PQP pasma concentrations by Parts	PK
	Table14.2.1.2	Summary of PQP PK parameters by Parts	PK
	Table14.2.1.3	Assessment of bioequivalence between PQP dispersible granule and PQP hard tablet	PK
	Table14.2.1.4	Assessment of Bioequivalence between PQP dispersible granule (Fasted) and High-fat meal, Low-fat African meal, and Milk	PK
14.2.2 Exploratory Endpoint Analysis			
	Table14.2.2.1	Summary of PQP N-oxide (metabolite) plasma concentrations by Parts	PK
	Table14.2.2.2	Summary of PQP N-oxide (metabolite) PK Parameters by Parts	PK
	Table14.2.2.3	Summary of Palatability questionnaire by Parts	Safety
14.3.1 Adverse Events- Safety Analysis			
	Table14.3.1.1	Overall Adverse Events by Parts	Safety
	Table14.3.1.2	Summary of Pre-Treatment Adverse Events by System Organ Class and Preferred Term and by Parts	Safety
	Table14.3.1.3	Summary of TEAEs by System Organ Class and Preferred Term and by Parts	Safety
	Table14.3.1.4	Summary of Serious TEAEs by System Organ Class and Preferred Term and by Parts	Safety
	Table14.3.1.5	Summary of TEAEs and SAEs leading to withdrawal/discontinuation from the study by Parts	Safety
	Table14.3.1.6	Summary of TEAEs leading to death by Parts	Safety
	Table14.3.1.7	Summary of TEAEs by Relationship, System Organ Class, and Preferred Term and by Parts	Safety

	Table Number	Table Title	Population
	Table14.3.1.8	Summary of TEAEs by Outcome, System Organ Class, and Preferred Term and by Parts	Safety
	Table14.3.1.9	Summary of TEAEs by Action taken, System Organ Class, and Preferred Term and by Parts	Safety
	Table14.3.1.10	Summary of TEAEs by Toxicity Grade, System Organ Class, and Preferred Term and by Parts	Safety
	Table14.3.1.11	Summary of Drug related TEAEs by Severity and by Parts	Safety
	Table14.3.2.1	Listing of Deaths	Safety
	Table14.3.2.2	Participant Listing of Serious Adverse Events	Safety
14.3.4 Laboratory Assessment			
	Table14.3.4.1	Summary of Abnormal Clinical Laboratory Values	Safety
	Table14.3.4.2	Summary of Clinical Laboratory tests by Parts	Safety
	Table14.3.4.3	Cross-Tabulation of Laboratory Abnormalities Versus Baseline by Parts and Groups	Safety
14.3.5 Other Safety Assessment			
	Table14.3.5.1	Descriptive Statistics of Vital Signs by Parts	Safety
	Table14.3.5.2	Overall Abnormal Vital Signs Results by Parts	Safety
	Table14.3.5.3	Descriptive Statistics of 12-Lead ECG by Parts	Safety
	Table14.3.5.4	Abnormal ECG Results by Parts	Safety
	Table14.3.5.5	Summary of 12-Lead Electrocardiograms Interpretation Categories by Parts	Safety
	Table14.3.5.6	Summary of QTcF by Parts	Safety

23.4 Appendix 4: PLANNED SUMMARY FIGURES

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

	Figure Number	Figure Title	Population
14.2.1 Primary and Secondary Endpoint Analysis			
	Figure14.2.1.1	Arithmetic mean (SD) of PQP plasma concentration-time profiles by dose group	PK
	Figure14.2.1.2	Geometric mean (SD) of PQP concentration time-profiles by dose group	PK
	Figure14.2.1.3	Overlaying individual PQP plasma concentration-time profiles by dose group	PK
	Figure14.2.1.4	Individual PQP plasma concentration-time profiles by dose group	PK
	Figure14.2.1.5	Individual PQP AUC/C_{max} by Dose Group	PK
14.2.2 Exploratory Endpoint Analysis			
	Figure14.2.2.1	Arithmetic mean (SD) of PQP N-oxide (metabolite) plasma concentration-time profiles by dose group	PK
	Figure14.2.2.2	Geometric mean (SD) of PQP N-oxide (metabolite) plasma concentration-time profiles by dose group	PK
	Figure14.2.2.3	Overlaying individual PQP N-oxide (metabolite) plasma concentration-time profiles by dose group	PK
	Figure14.2.2.4	Individual PQP N-oxide (metabolite) plasma concentration-time profiles by dose group	PK
	Figure14.2.2.5	Individual PQP N-oxide (metabolite) AUC/C_{max} by Dose Group	PK
14.3.5 Other Safety Assessment			
	Figure 14.3.5.1	Mean value of change from baseline QTcF	Safety