MIST 2

STATISTICAL ANALYSIS PLAN

A clinical study to assess the feasibility of a controlled human *Plasmodium vivax* malaria infection model through experimental sporozoite infection in Thai adults.

Short title: MIST 2 study

Version 1.0

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1. INTRODUCTION

This project is the second part of a 5-year research program entitled "Malaria Infection Study in Thailand (MIST)" and known as MIST2. MIST2 primary objectives are to assess the safety and feasibility of blood-stage controlled human *P. vivax* malaria infection (CHMI) in healthy adult Thai volunteers through experimental injection of cryopreserved *P. vivax* infected erythrocytes, and to choose the optimal inoculation dose for future *P. vivax* CHMI studies. In this study, blood-stage CHMI will be conducted in 8 volunteers per inoculum stock who will be infected with *P. vivax* by experimental injection with cryopreserved *P. vivax* infected erythrocytes, which were collected in MIST1. As there are currently 2 stocks of inocula from 2 volunteers in the MIST1 study, which have different quantity and stage of parasites. The total number of volunteers would be up to 16. The volunteers will be monitored closely as in-patients in the Hospital for Tropical Diseases, and will be treated according to the Research Proposal Submission Form.

This documents sets out the statistical analysis plan for a MIST 2 to assess the feasibility and safety study and choosing the optimal inoculation dose for future *P. vivax* CHMI studies.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE

a) To assess the safety and feasibility of blood-stage controlled human *P. vivax* malaria infection in healthy adult Thai volunteers through experimental injection of cryopreserved *P. vivax* infected erythrocytes at different doses.

b) To choose the optimal inoculation dose for future *P. vivax* CHMI studies.

2.2 PRIMARY ENDPOINT

a) Safety and feasibility of primary *P. vivax* blood-stage CHMI, as measured by (S)AE occurrences and successful infection (development of detectable persistent parasitaemia by thick blood film +/- clinical symptoms).

b) Choosing the optimal inoculation dose for future *P. vivax* CHMI studies, which will be the lowest concentration that produces a reliable infection within a comparable timeframe as compare to the highest concentration.

2.3 SECONDARY OBJECTIVES AND ENDPOINTS

a) To assess the immune response to *P. vivax* infection in volunteers, through experimental injection of *P. vivax* infected erythrocytes. The endpoint of this objective is immune response to experimental *P. vivax* infection through blood-stage challenge, as measured by antibody, cytokines, B cell and T cell responses.

b) To assess gametocytaemia during *P. vivax* infection in volunteers, through experimental injection of *P. vivax* infected erythrocytes. The endpoint of this objective is gametocytaemia, as measured by qPCR in experimental *P. vivax* infection through blood-stage challenge.

c) To assess transmission of gametocytes from infected volunteers to Anopheles mosquitoes. The endpoint of this objective is transmissibility of gametocytes from the infected volunteer to Anopheles mosquito vector.

3. STUDY DESIGN

3.1 GENERAL

This blood-stage *P. vivax* human challenge study conducted for the first time in Asia has two primary aims: (1) to assess the safety and feasibility of the challenge model using the bank of cryopreserved *P. vivax* infected erythrocyte inocula prepared during the MIST1 study, and (2) to determine the optimal inoculation dose for future *P. vivax* CHMI studies. This will be assessed by intravenously injecting the volunteers with four different doses of inoculum: whole dose and 1:5, 1:10, and 1:20 dilutions. If safe and feasible, this study will serve as the basis for a challenge model for future *P. vivax* candidate vaccine efficacy studies. The secondary objectives are to determine the immune response to *P. vivax* infection, the resulting gametocytaemia, and transmissibility of the gametocytes from the infected volunteers.

Healthy, Thai adults aged between 20 and 55 years will be recruited and randomized at the Faculty of Tropical Medicine, Mahidol University in Bangkok.

CHMI will be induced by injection of *P. vivax* infected erythrocytes and all follow-up in the post-challenge period will be performed at the Faculty of Tropical Medicine, Mahidol University in Bangkok.

Volunteers will have blood taken at regular intervals post-CHMI to assess the immune response to *P. vivax* infection, as well as parasite growth dynamics and gametocytaemia. We will also assess transmission of *P. vivax* gametocytes from the infected volunteers to mosquitos using a membrane feeding assay (MFA).

Close monitoring will continue until volunteers meet criteria for treatment or until 21 days after challenge, when treatment will be started empirically.

Therapy will be with a standard course of chloroquine where not contraindicated. As infection will be induced via intravenous injection of blood-stage parasites, there will be no liver-stage infection and no hypnozoite formation, thereby eliminating the need for radical cure with primaquine therapy. Follow-up at study site will be up to 1 year after antimalarial treatment initiated.

3.2 DETERMINATION OF SAMPLE SIZE

In order to find the optimum dose of each blood-stage inoculum (the lowest concentration that the volunteers reliably develop infection, i.e., 2/2, within the comparable time frame as compare to the highest concentration and within 21 days), one blood-stage inoculum stock will be tested in 4 different doses: whole dose inoculum (neat vial), 1:5, 1:10, and 1:20 dilution. Each dose will be inoculated into two volunteers resulting in 8 volunteers. As two stocks of blood-stage inoculum were prepared from MIST1, 16 volunteers will be recruited: 8 to be challenged with inoculum stock 1, and 8 with inoculum stock 2.

4. ANALYSIS

4.1 GENERAL CONSIDERATIONS

The feasibility and safety of blood-stage controlled human *P. vivax* malaria infection, will be declared if there will be a successful infection in at least one of the 8 volunteers

from each blood bank i.e. if there will be development of detectable persistent parasitaemia +/- clinical symptoms.

The success of this study will also be declared if infection is successful and we are able to choose the optimal inoculation dose for future *P. vivax* CHMI studies.

The safety of this challenge study will be assessed by summarising and evaluating the SAEs and the AEs regarding severity and relatedness to the challenge.

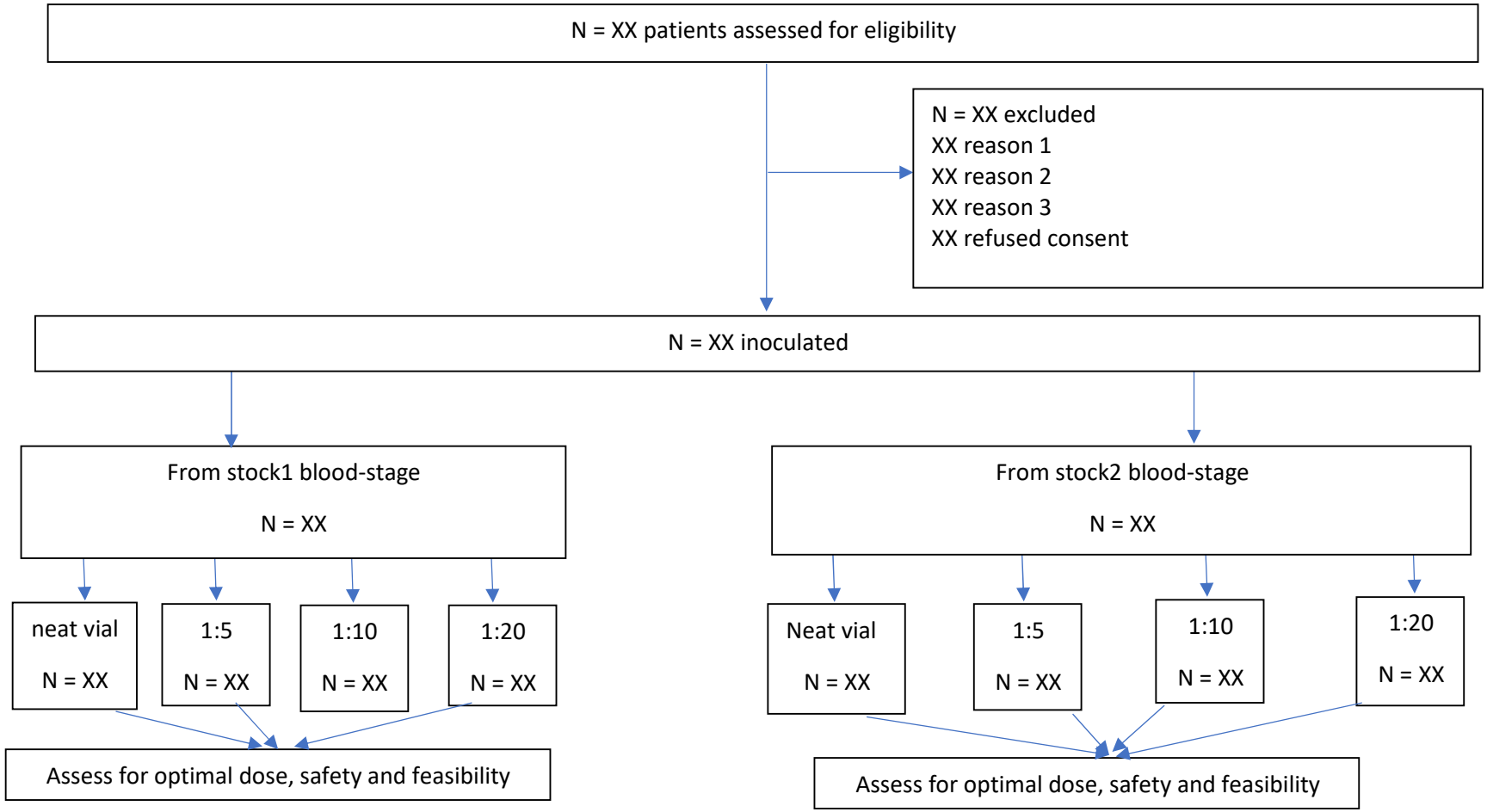
4.1.1 Data integrity

This study will be conducted in compliance with the protocol, relevant Standard Operating Procedures (SOPs), Work Instructions (WIs), Good Clinical Practice (GCP) and the applicable regulatory requirement(s). All the analyses will be performed on clean data only.

4.1.2 Data cleaning and verification

All data will be cleaned and verified prior to statistical analysis. The study site will be visited by the Monitor periodically at times agreed on with the Investigator. At the time of each monitoring visit, the Monitor will review the completed CRFs to ascertain that all items have been completed and that the data provided are accurate and obtained in the manner specified in the protocol. The Monitor will also check that the data in the CRF are consistent with the clinical records (Source Data Verification [SDV]) and that study results are recorded completely and correctly. Study Specific Audit will also be done to assess the clinical and laboratory study activities compliance with study protocol, SOPs and Plans, local QMS procedures, applicable standards and guidelines. The data manager will ensure that clean data is submitted to the statistician for analysis. The statistician will cross-check that the available data for analysis is clean. Any data cleaning queries will need to be resolved before statistical analyses.

4.2 DUMMY FIGURE 1 – STUDY PROFILE



4.3 STUDY ASSESSMENTS

4.3.1 Demographics and other baseline characteristics

The following baseline characteristics for each participant will be described and summarized for all participants in Table 1 below. Variables such as age, heart rate, respiratory rate, and laboratory data will be summarized using median and range. Continuous variables such as weight, height and hemoglobin will be summarized using mean and standard deviation. Categorical variables such as sex and symptoms will be summarized using frequencies. We will also compare the baseline characteristics for stock1 and stock2.

Table 1 Baseline Characteristics of the Subjects.

Characteristics	Neat vial	Dose 1:5	Dose 1:10	Dose 1:20	Total
Age (years), mean (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Male, n (%)	x (%)	x (%)	x (%)	x (%)	x (%)
Body temperature (°C), median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Blood pressure (mmHg), (Systolic/Diastolic), median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Heart rate (beats/min), median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Respiratory rate (breaths/min), median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Weight (kg), median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Height (cm), median (IQR)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Haematology					
WBC (103/µL), median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
RBC (10^6/µL), median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
Haemoglobin (g/dL), mean (SD)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Haematocrit (%),median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
Pletelets (103/µL), median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
Neutrophil (%),median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
Lymphocyte (%),median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)

Characteristics	Neat vial	Dose 1:5	Dose 1:10	Dose 1:20	Total
Monocyte (%),median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
Eosinophil (%),median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
Basophil (%),median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
Other abnormal WBC, median (IQR)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Platelet smear, n(%)					
Adequate	x (%)	x (%)	x (%)	x (%)	x (%)
Decrease	x (%)	x (%)	x (%)	x (%)	x (%)
Increase	x (%)	x (%)	x (%)	x (%)	x (%)
Biochemistry					
FBS (mg/dL), median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
BUN (mg/dL), median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
Creatinine (mg/dL), median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
Total bilirubin (mg/dL), median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
eGFR (mL/min), median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
Alkaline Phosphatase (U/L), median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
AST (U/L), median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
ALT (U/L), median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
Albumin (g/dL), median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
Globulin (U/L), median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
Sodium (mmol/L), median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
Potassium (mmol/L), median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
Calcium (mg/dL), median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
Magnesium (mg/dL), median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
Chloride (mmol/L), median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)

Characteristics	Neat vial	Dose 1:5	Dose 1:10	Dose 1:20	Total
Bicarbonate (mmol/L), median (IQR)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)
etc ...	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)	xx (xx – xx)

4.3.2 *Clinical efficacy assessments (an example of a possible heading)*

No clinical efficacy planned for MIST 2. However, Optimal dose will be assessed.

Referring from the protocol the optimal inoculation dose for future *P. vivax* CHMI studies is the lowest concentration that produces a reliable infection within a comparable timeframe as compared to the highest concentration.

4.3.3 *Pharmacokinetic assessments (an example of a possible heading)*

No PK analyses planed for MIST 2

4.3.4 *Adverse events*

Adverse events will be summarized as shown in Tables 2a, 2b, 3a and 3b below. Firstly, all events will be captured.ie. including multiple events in an individual. Thereafter the number of individuals with at least an event will be recorded and the highest grade will be presented.

Table 2a Adverse events during the admission phase before treatment as assessed by blood-stage stock

Adverse event	Stock1 blood-stage (n=xx)	stock2 blood-stage (n=xx)	Total (n=xx)
CTCAE Grade 1 or 2 of symptom or disease, x/n (%)			
Fever	xx/xx (%)	xx/xx (%)	xx/xx (%)
Headache	xx/xx (%)	xx/xx (%)	xx/xx (%)
Myalgia	xx/xx (%)	xx/xx (%)	xx/xx (%)
Palpitation	xx/xx (%)	xx/xx (%)	xx/xx (%)
Dizziness	xx/xx (%)	xx/xx (%)	xx/xx (%)
Chills	xx/xx (%)	xx/xx (%)	xx/xx (%)
Abdominal pain	xx/xx (%)	xx/xx (%)	xx/xx (%)
Profuse sweating	xx/xx (%)	xx/xx (%)	xx/xx (%)
Anorexia	xx/xx (%)	xx/xx (%)	xx/xx (%)
Nausea	xx/xx (%)	xx/xx (%)	xx/xx (%)
Vomitting	xx/xx (%)	xx/xx (%)	xx/xx (%)
Diarrhea	xx/xx (%)	xx/xx (%)	xx/xx (%)
Muscle pain	xx/xx (%)	xx/xx (%)	xx/xx (%)
Anemia	xx/xx (%)	xx/xx (%)	xx/xx (%)
Other signs*	xx/xx (%)	xx/xx (%)	xx/xx (%)
CTCAE Grade 1 or 2 abnormal laboratory findings, x/n (%)			
Creatinine	xx/xx (%)	xx/xx (%)	xx/xx (%)
Total bilirubin	xx/xx (%)	xx/xx (%)	xx/xx (%)
Alkaline phosphatase	xx/xx (%)	xx/xx (%)	xx/xx (%)
Alanyl transfarase (ALT)	xx/xx (%)	xx/xx (%)	xx/xx (%)
Aspartate transfarase (AST)	xx/xx (%)	xx/xx (%)	xx/xx (%)
Haemoglobin	xx/xx (%)	xx/xx (%)	xx/xx (%)
Nadir Haemoglobin	xx/xx (%)	xx/xx (%)	xx/xx (%)

WBC	xx/xx (%)	xx/xx (%)	xx/xx (%)
Platelet	xx/xx (%)	xx/xx (%)	xx/xx (%)
Other signs*	xx/xx (%)	xx/xx (%)	xx/xx (%)
CTCAE Grade 3 or 4 of symptom or disease, x/n (%)			
Fever	xx/xx (%)	xx/xx (%)	xx/xx (%)
Headache	xx/xx (%)	xx/xx (%)	xx/xx (%)
Myalgia	xx/xx (%)	xx/xx (%)	xx/xx (%)
Palpitation	xx/xx (%)	xx/xx (%)	xx/xx (%)
Dizziness	xx/xx (%)	xx/xx (%)	xx/xx (%)
Chills	xx/xx (%)	xx/xx (%)	xx/xx (%)
Abdominal pain	xx/xx (%)	xx/xx (%)	xx/xx (%)
Profuse sweating	xx/xx (%)	xx/xx (%)	xx/xx (%)
Anorexia	xx/xx (%)	xx/xx (%)	xx/xx (%)
Nausea	xx/xx (%)	xx/xx (%)	xx/xx (%)
Vomitting	xx/xx (%)	xx/xx (%)	xx/xx (%)
Diarrhea	xx/xx (%)	xx/xx (%)	xx/xx (%)
Muscle pain	xx/xx (%)	xx/xx (%)	xx/xx (%)
Anemia	xx/xx (%)	xx/xx (%)	xx/xx (%)
Other*	xx/xx (%)	xx/xx (%)	xx/xx (%)
CTCAE Grade 3 or 4 abnormal laboratory findings, x/n (%)			
Creatinine	xx/xx (%)	xx/xx (%)	xx/xx (%)
Total bilirubin	xx/xx (%)	xx/xx (%)	xx/xx (%)
Alkaline phosphatase	xx/xx (%)	xx/xx (%)	xx/xx (%)
Alanyl transferase (ALT)	xx/xx (%)	xx/xx (%)	xx/xx (%)
Aspartate transferase (AST)	xx/xx (%)	xx/xx (%)	xx/xx (%)
Haemoglobin	xx/xx (%)	xx/xx (%)	xx/xx (%)
Nadir Haemoglobin	xx/xx (%)	xx/xx (%)	xx/xx (%)
WBC	xx/xx (%)	xx/xx (%)	xx/xx (%)

Platelet	xx/xx (%)	xx/xx (%)	xx/xx (%)
Other signs*	xx/xx (%)	xx/xx (%)	xx/xx (%)

*Other symptoms or signs

Table 2b Adverse events during the admission phase before treatment as assessed by dose.

Adverse event	Total event (n=xx)	Neat vial (n=xx)	Dose 1:5 (n=xx)	Dose 1:10 (n=xx)	Dose 1:10 (n=xx)	P-value (n=xx)
CTCAE Grade 1 or 2 of symptom or disease, x/n (%)						
Fever	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Headache	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Myalgia	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Palpitation	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Dizziness	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Chills	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Abdominal pain	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Profuse sweating	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Anorexia	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Nausea	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Vomitting	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Diarrhea	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Muscle pain	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Anemia	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Other signs*	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
CTCAE Grade 1 or 2 abnormal laboratory findings, x/n (%)						
Creatinine	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Total bilirubin	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Alkaline phosphatase	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Alanyl transfarase (ALT)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Aspartate transfarase (AST)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx

Haemoglobin	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Nadir Haemoglobin	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
WBC	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Platelet	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Other signs*	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
CTCAE Grade 3 or 4 of symptom or disease, x/n (%)						
Fever	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Headache	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Myalgia	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Palpitation	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Dizziness	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Chills	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Abdominal pain	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Profuse sweating	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Anorexia	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Nausea	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Vomitting	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Diarrhea	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Muscle pain	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Anemia	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Other*	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
CTCAE Grade 3 or 4 abnormal laboratory findings, x/n (%)						
Creatinine	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Total bilirubin	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Alkaline phosphatase	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Alanyl transferase (ALT)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Aspartate transferase (AST)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Haemoglobin	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx

Nadir Haemoglobin	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
WBC	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Platelet	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Other signs*	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx

*Other symptoms or signs

Table 3a Adverse events during the treatment phase as assessed by blood-stage stock.

Adverse event	Stock1 blood-stage (n=xx)	stock2 blood-stage (n=xx)	Total (n=xx)
CTCAE Grade 1 or 2 of symptom or disease, x/n (%)			
Fever	xx/xx (%)	xx/xx (%)	xx/xx (%)
Headache	xx/xx (%)	xx/xx (%)	xx/xx (%)
Myalgia	xx/xx (%)	xx/xx (%)	xx/xx (%)
Palpitation	xx/xx (%)	xx/xx (%)	xx/xx (%)
Dizziness	xx/xx (%)	xx/xx (%)	xx/xx (%)
Chills	xx/xx (%)	xx/xx (%)	xx/xx (%)
Abdominal pain	xx/xx (%)	xx/xx (%)	xx/xx (%)
Profuse sweating	xx/xx (%)	xx/xx (%)	xx/xx (%)
Anorexia	xx/xx (%)	xx/xx (%)	xx/xx (%)
Nausea	xx/xx (%)	xx/xx (%)	xx/xx (%)
Vomitting	xx/xx (%)	xx/xx (%)	xx/xx (%)
Diarrhea	xx/xx (%)	xx/xx (%)	xx/xx (%)
Muscle pain	xx/xx (%)	xx/xx (%)	xx/xx (%)
Anemia	xx/xx (%)	xx/xx (%)	xx/xx (%)
Other signs*	xx/xx (%)	xx/xx (%)	xx/xx (%)
CTCAE Grade 1 or 2 abnormal laboratory findings, x/n (%)			

Creatinine	xx/xx (%)	xx/xx (%)	xx/xx (%)
Total bilirubin	xx/xx (%)	xx/xx (%)	xx/xx (%)
Alkaline phosphatase	xx/xx (%)	xx/xx (%)	xx/xx (%)
Alanyl transfarase (ALT)	xx/xx (%)	xx/xx (%)	xx/xx (%)
Aspartate transfarase (AST)	xx/xx (%)	xx/xx (%)	xx/xx (%)
Haemoglobin	xx/xx (%)	xx/xx (%)	xx/xx (%)
Nadir Haemoglobin	xx/xx (%)	xx/xx (%)	xx/xx (%)
WBC	xx/xx (%)	xx/xx (%)	xx/xx (%)
Platelet	xx/xx (%)	xx/xx (%)	xx/xx (%)
Other signs*	xx/xx (%)	xx/xx (%)	xx/xx (%)
CTCAE Grade 3 or 4 of symptom or disease, x/n (%)			
Fever	xx/xx (%)	xx/xx (%)	xx/xx (%)
Headache	xx/xx (%)	xx/xx (%)	xx/xx (%)
Myalgia	xx/xx (%)	xx/xx (%)	xx/xx (%)
Palpitation	xx/xx (%)	xx/xx (%)	xx/xx (%)
Dizziness	xx/xx (%)	xx/xx (%)	xx/xx (%)
Chills	xx/xx (%)	xx/xx (%)	xx/xx (%)
Abdominal pain	xx/xx (%)	xx/xx (%)	xx/xx (%)
Profuse sweating	xx/xx (%)	xx/xx (%)	xx/xx (%)
Anorexia	xx/xx (%)	xx/xx (%)	xx/xx (%)
Nausea	xx/xx (%)	xx/xx (%)	xx/xx (%)
Vomitting	xx/xx (%)	xx/xx (%)	xx/xx (%)
Diarrhea	xx/xx (%)	xx/xx (%)	xx/xx (%)
Muscle pain	xx/xx (%)	xx/xx (%)	xx/xx (%)
Anemia	xx/xx (%)	xx/xx (%)	xx/xx (%)
Other signs*	xx/xx (%)	xx/xx (%)	xx/xx (%)
CTCAE Grade 3 or 4 abnormal laboratory findings, x/n (%)			
Creatinine	xx/xx (%)	xx/xx (%)	xx/xx (%)

Total bilirubin	xx/xx (%)	xx/xx (%)	xx/xx (%)
Alkaline phosphatase	xx/xx (%)	xx/xx (%)	xx/xx (%)
Alanyl transfarase (ALT)	xx/xx (%)	xx/xx (%)	xx/xx (%)
Aspartate transfarase (AST)	xx/xx (%)	xx/xx (%)	xx/xx (%)
Haemoglobin	xx/xx (%)	xx/xx (%)	xx/xx (%)
Nadir Haemoglobin	xx/xx (%)	xx/xx (%)	xx/xx (%)
WBC	xx/xx (%)	xx/xx (%)	xx/xx (%)
Platelet	xx/xx (%)	xx/xx (%)	xx/xx (%)
Other signs*	xx/xx (%)	xx/xx (%)	xx/xx (%)

*Other symptoms or signs

Table 3b Adverse events during the treatment phase as assessed by dose.

Adverse event	Total event (n=xx)	Neat vial (n=xx)	Dose 1:5 (n=xx)	Dose 1:10 (n=xx)	Dose 1:10 (n=xx)	P-value (n=xx)
CTCAE Grade 1 or 2 of symptom or disease, x/n (%)						
Fever	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Headache	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Myalgia	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Palpitation	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Dizziness	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Chills	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Abdominal pain	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Profuse sweating	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Anorexia	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Nausea	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Vomitting	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Diarrhea	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Muscle pain	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx

Anemia	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Other signs*	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
CTCAE Grade 1 or 2 abnormal laboratory findings, x/n (%)						
Creatinine	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Total bilirubin	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Alkaline phosphatase	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Alanyl transfarase (ALT)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Aspartate transfarase (AST)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Haemoglobin	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Nadir Haemoglobin	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
WBC	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Platelet	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Other signs*	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
CTCAE Grade 3 or 4 of symptom or disease, x/n (%)						
Fever	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Headache	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Myalgia	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Palpitation	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Dizziness	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Chills	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Abdominal pain	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Profuse sweating	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Anorexia	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Nausea	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Vomitting	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Diarrhea	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Muscle pain	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Anemia	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx

Other*	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
CTCAE Grade 3 or 4 abnormal laboratory findings, x/n (%)						
Creatinine	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Total bilirubin	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Alkaline phosphatase	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Alanyl transfarase (ALT)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Aspartate transfarase (AST)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Haemoglobin	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Nadir Haemoglobin	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
WBC	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Platelet	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx
Other signs*	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	xx/xx (%)	0.xxx

*Other symptoms or signs

Relationship of adverse events to either treatment or infection will be summarized in Table 4 below.

Table 4 Distribution of adverse events by relationship to study procedures.

Adverse event	During admission (infection) phase		During treatment phase	
	Any relationship to study drugs (n=xx)	Possibly, probably, definitely related to study drugs (n=xx)	Any relationship to study drugs (n=xx)	Possibly, probably, definitely related to study drugs (n=xx)
Abdominal discomfort	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Abdominal pain.	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Anorexia	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Back pain	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Bruising	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Chills	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)

Diarrhea	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Dizziness	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Dry mouth	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Dyspepsia	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Fatigue	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Fever	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Flushing	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Gingivitis	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Headache	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Insomnia	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Malaise	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Maculopapular	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Mucositis oral	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Myalgia	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Nausea	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Neck pain	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Palpitation	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Profuse sweating on palms & soles	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Pruritus.	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Sore throat	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Tachycardia	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Urinary tract infection	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Urticaria	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Vomiting	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Other signs*	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)

Values in cells are x/n (%).

*Other symptoms or signs

Serious adverse events will be summarized in Tables 5a and 5b below.

Table 5a Serious adverse events as assessed by dose.

Serious adverse event	Total event (n=xx)	Neat vial (n=xx)	Dose 1:5 (n=xx)	Dose 1:10 (n=xx)	Dose 1:10 (n=xx)	P-value (n=xx)
Death, x/n (%)	xx/xx (%)	xx/xx(%)	xx/xx(%)	xx/xx(%)	xx/xx(%)	0.xxx
Life-threatening event, x/n (%)	xx/xx (%)	xx/xx(%)	xx/xx(%)	xx/xx(%)	xx/xx(%)	0.xxx
Persistent or significant disability or incapacity, x/n (%)	xx/xx (%)	xx/xx(%)	xx/xx(%)	xx/xx(%)	xx/xx(%)	0.xxx
Transfer of inpatient care to the intensive care unit, x/n (%)	xx/xx (%)	xx/xx(%)	xx/xx(%)	xx/xx(%)	xx/xx(%)	0.xxx
An important medical event, x/n (%)	xx/xx(%)	xx/xx(%)	xx/xx(%)	xx/xx(%)	xx/xx(%)	0.xxx
Congenital anomaly or birth defect, x/n (%)	xx/xx (%)	xx/xx(%)	xx/xx(%)	xx/xx(%)	xx/xx(%)	0.xxx

Table 5b Serious adverse events by relationship to study procedures.

Adverse event	During admission (infection) phase		During treatment phase	
	Any relationship to study drugs (n=xx)	Possibly, probably, definitely related to study drugs (n=xx)	Any relationship to study drugs (n=xx)	Possibly, probably, definitely related to study drugs (n=xx)
Death, x/n (%)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Life-threatening event, x/n (%)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
Persistent or significant disability or incapaci-ty, x/n (%)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)

Adverse event	During admission (infection) phase		During treatment phase	
	Any relationship to study drugs (n=xx)	Possibly, probably, definitely related to study drugs (n=xx)	Any relationship to study drugs (n=xx)	Possibly, probably, definitely related to study drugs (n=xx)
Transfer of inpatient care to the intensive care unit, x/n (%)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)
An important medical event, x/n (%)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)	x/xx (x.x)

A detailed listing will also be shown.

Immune response

The assessment of the immune response to *P. vivax* infection in volunteers, through experimental injection of *P. vivax* infected erythrocytes will be analysed as detailed below:

4.3.5 Cellular Response

The dynamic of cellular response will be determined using peripheral blood mononuclear cells (PBMCs). The data will be summarized as frequencies, percentages (%), and expression level (median fluorescence intensity (MFI)) as shown in Table 6 below. A spaghetti plot will be constructed and presented to show the profile of each of the important parameters over time across the participants. The profiles will also be presented as a plot of box and whisker plot indicating the profile of median and quartiles of the absolute parameters over-time. Where tests of hypothesis will be necessary, paired tests such as Wilcoxon's signed rank test will be used to compare parameters at a specified day with the baseline will be performed. Caution will be considered when interpreting such significant tests considering that sample sizes are very small. Tests of significance will be performed at 5% significance level. Stata software of at least version 15.0 will be used to analyse the data and make plots. Some plots will be done in GraphPad Prism where necessary. MFI value will be analysed and plotted by FlowJo software.

Table 6 Immunological profile (frequency, %, MFI)

Immune cell subset	Screening phase (Baseline)		Admission phase			Follow-up phase					
	Within 14 days prior to Day 0	Admission Day-1	Day_4	Day $qPCR^+$	Day_{reach} treatment criteria	Day_{Rx7}	Day_{Rx28}	Day_{Rx60}	Day_{Rx90}	Day_{Rx180}	$Day_{Rx1Year}$
Conventional Dendritic cell (cDC)											
Myeloid Dendritic cell (MDC)											
Plasmacytoid Dendritic cell (PDC)											
Natural Killer (NK)											
Natural Killer T (NKT)											

Immune cell subset	Screening phase (Baseline)		Admission phase			Follow-up phase					
	Within 14 days prior to Day 0	Admission Day-1	Day_4	Day qPCR$^+$	$Day_{reach\ treatment\ criteria}$	Day_{Rx7}	Day_{Rx28}	Day_{Rx60}	Day_{Rx90}	Day_{Rx180}	$Day_{Rx1Year}$
Mucosal Associated Invariant T cell (MAIT)											
Helper T-cell											
Cytotoxic T-cell											
Regulatory T-cell											
γδ T-cell											
Typical B-cell											
Plasmablast											

4.3.6 Humoral Response

Cytokine response (median fluorescence intensity, relative antibody unit)

The level of cytokine responses related blood stage inoculum will be assessed by using Multiplex Bead Based Immunoassay (Luminex) and/or ELISA, and summarised in Table 7 below. Luminex and/or ELISA will be used to explore the level of antibodies and cytokines responses during different phases of infection. P-values for the test of significance will be indicated where applicable. However, Caution will be considered when interpreting such significant tests considering that sample sizes are very small.

Table 7 Cytokine/Chemokine response profile (plasma level pg/ml)

Cytokine/ Chemokine	Screening phase (Baseline)		Admission phase			Follow-up phase					
	Within 14 days prior to Day 0	Admission Day-1	Day_4	Day $qPCR^+$	Day_{reach} treatment criteria	Day_{Rx7}	Day_{Rx28}	Day_{Rx60}	Day_{Rx90}	Day_{Rx180}	$Day_{Rx1Year}$
FGF basic											
Eotaxin											
G-CSF											
GM-CSF											
IFN-γ											
IL-1β											

Cytokine/ Chemokine	Screening phase (Baseline)		Admission phase			Follow-up phase					
	Within 14 days prior to Day 0	Admission Day-1	Day_4	Day qPCR$^+$	$Day_{reach\ treatment\ criteria}$	Day_{Rx7}	Day_{Rx28}	Day_{Rx60}	Day_{Rx90}	Day_{Rx180}	$Day_{Rx1Year}$
IL-1ra											
IL-2											
IL-4											
IL-5											
IL-6											
IL-7											
IL-8											
IL-9											
IL-10											
IL-12 (p70)											
IL-13											
IL-15											

Cytokine/ Chemokine	Screening phase (Baseline)		Admission phase			Follow-up phase					
	Within 14 days prior to Day 0	Admission Day-1	Day_4	Day qPCR$^+$	$Day_{reach\ treatment\ criteria}$	Day_{Rx7}	Day_{Rx28}	Day_{Rx60}	Day_{Rx90}	Day_{Rx180}	$Day_{Rx1Year}$
IL-17A											
IP-10											
MCP-1 (MCAF)											
MIP-1α											
MIP-1β											
PDGF-BB											
RANTES											
TNF-α											
VEGF											
TGF-β1											

4.3.7 Gametocyte Analysis

Another secondary objective of MIST2 study is to assess gametocytaemia following *P. vivax* infection delivered by blood-stage inoculum. The endpoint is gametocytaemia pre-treatment, as measured by qRT-PCR.

The endpoint for gametocyte detection will be the Pvs25 gene transcript copy number/ul blood collected at each time point as follows: challenge day; day 1 to 5 or up to day of treatment and during subsequent days of follow-up. The data will be summarized using the geometric mean and standard deviation/error at each time point. The trend in geometric means will be assessed and where necessary will be presented graphically using trend lines.