Clinical Trial Protocol

Efficacy and safety of Praziquantel for treatment of *Plasmodium falciparum* infection in asymptomatic Gabonese adults (CORMA-MAL)

Protocol version 1.0 (07-02-2022)

Trial Sponsor:	Bernhard Nocht Institute for Tropical Medicine (BNITM)
Funding:	German Center for Infection Research (DZIF)
Trial site:	Centre de Recherches Médicales de Lambaréné (CERMEL)

Coordinating Investigator:	Johannes Mischlinger, MD PhD
Principal Investigator:	Ghyslain Mombo-Ngoma, MD PhD
Trial Manager:	Lidwine Badjina
Co-Investigator:	Michael Ramharter, MD
	Rella Zoleko-Manego, MD
	Peter Kremsner, MD
	Andrea Kreidenweiss, PhD
	Ayola Akim Adegnika, MD PhD

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Synopsis

Study title	Efficacy and safety of Praziquantel for treatment of *Plasmodium falciparum* infection in asymptomatic Gabonese adults
Study acronym	**CORMA-MAL**
Protocol version	V.1.0
Protocol date	February 2022
Clinical Phase	IIa
Trial Centre(s)	Centre de Recherches Médicales de Lambaréné (CERMEL) B.P. 242, Lambaréné Gabon
Rationale	Malaria is a vector-borne disease caused by parasites of the genus *Plasmodium*. It is the most important parasitic disease and a major cause of childhood morbidity and mortality in highly endemic regions of sub-Saharan Africa. Artemisinin-based combination therapy (ACT) is the combination of an artemisinin derivative with a partner drug and constitutes to date the most successful treatment of malaria. However, over the course of the past decade, it became evident that the efficacy of this therapy declined dramatically in South East Asia due to the simultaneous development of artemisinin resistance and partner drug resistance. Therefore, treatment of malaria increasingly consists of triple or quadruple combinations to reduce the emergence and spread of drug resistance. Partner drugs for established ACTs are needed and re-purposing of drugs is an efficient way of developing such multidrug combinations. Occasionally, specific antimicrobial agents demonstrate simultaneous activity against multiple microorganisms. This introduces the promising possibility of creating drug regimens to be potentially used for more than only one treatment indication. Furthermore, the value of such multi-disease drug regimens rises when designed for important infectious diseases that affect a similar target population; an aspect making such regimens appealing to be operationally implemented not only, but

	particular in low resource settings. Epidemiologic data indicate that malaria and urogenital schistosomiasis are two infectious diseases affecting largely overlapping target populations. Treatment of urogenital schistosomiasis is based on praziquantel [PZQ], which is the only available drug for this indication. Interestingly, preliminary studies demonstrated that PZQ also exerts a relevant activity against *Plasmodium* parasites in vitro and in patients with falciparum malaria (Orlov et al. 1998; al-Waili 1998). However, this effect has not yet been further investigated. Given the established safety profile of PZQ, its clinical development in a paediatric drug formulation, PZQ may become an attractive option as partner drug for antimalarial combination therapy. In the **CORMA-MAL** study, existing preliminary evidence of PZQ antimalarial activity will be further investigated. **CORMA-MAL** is a placebo-controlled randomised trial to evaluate the in vivo efficacy, safety and tolerability of PZQ in monotherapy. Adult participants with asymptomatic *Plasmodium falciparum* infection will be randomly allocated to one of two study arms with 22 participants in a placebo arm and 22 in an intervention arm with PZQ 40mg/kg once-daily dosing for 3 days.
Aim	To assess efficacy of PZQ in asymptomatic participants with *Plasmodium falciparum* infection
Primary Objective(s)	To assess the proportion of participants with microscopically-determined parasite clearance on D7 after administration of PZQ compared with placebo
Secondary Objective(s)	1) To assess the proportion of participants with ≥90% parasitemia reduction on D7 compared with baseline between PZQ and placebo study arms 2) To assess the time to microscopically-determined parasite clearance in the PZQ study arm compared with the placebo arm 3) To assess the safety and tolerability of PZQ 40mg/kg once-daily dosing for 3 days

	4) To assess the time to qPCR-determined parasite clearance in the PZQ study arm compared with the placebo arm 5) To assess the qPCR-determined cure rate in the PZQ study arm compared with placebo at D7 after study drug administration 6) To assess and compare the baseline-adjusted parasite mass of participants in the PZQ study arm compared with participants in the placebo study arm
Exploratory Objectives	To assess activity of PZQ on gametocyte carriage
Main inclusion/exclusion criteria	**Inclusion criteria:** • Subject male or female with age ≥ 18 years • *Plasmodium* parasitaemia with 200 to 5000 parasites/µL • Asymptomatic malaria defined by: presence of *Plasmodium* parasites, with absence of fever (axillary temperature ≤ 37.5 ° C or oral / tympanic temperature ≤ 38 ° C, or absence of history of fever in recent 24 hours and the week before inclusion). • Written informed consent must be obtained before any study assessment is performed. • Willingness not to take drugs or substances which could have an impact on praziquantel blood levels. The timeframe for the abstinence of these drugs will be 2,5 days before and 2,5 days after intake of praziquantel or will be individually calculated by the study team, if necessary. • Women only: Must agree to practice continuous contraception for the duration of the study. **Exclusion criteria:** • Signs and symptoms of complicated malaria / severe malaria • Taking an experimental drug in the last 4 weeks. • Any antimalarial treatment in the last 4 weeks

	• Is using and intends to continuing using a medication known to cause drug reactions with artemether/lumefantrine (e.g. cimetidine, metoclopramide, antacids, kaolin, terfenadine etc.) • Use of systemic antibiotics with known antimalarial activity within 30 days of study enrolment (e.g. trimethoprim-sulfamethoxazole, doxycycline, tetracycline, clindamycin, erythromycin, fluoroquinolones, or azithromycin). • Use of praziquantel within 30 days of study enrolment. • Previous (within the last 10 years) participation in a malaria vaccine study • Moderate to severe anemia (Hemoglobin level < 8 g/dL) • Known history of hepatic disease or liver damage • Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection • Use of immunoglobulins or blood products within 3 months prior to enrolment • Contraindications or known allergy to praziquantel or the first-line anti-malarial medication artemether/lumefantrine, or known or suspected allergy or intolerance to any other ingredient of the drug products (IMP/Non-IMP) • Severe malnutrition (Body Mass Index (BMI) < 16.0) • Pregnancy, lactation or intention to become pregnant during the study • Known history of sickle cell anaemia, sickle cell trait, thalassemia or thalassemia trait • Participants unable to be closely followed for social, geographic or psychological reasons • Any other significant disease, disorder or finding which, in the opinion of the investigator, may significantly increase the risk to the participant because of participation in the study (e.g. renal transplantation), affect

	the ability of the participant to participate in the study or impair interpretation of the study data.
Study design	Single-center, assessor-blinded, randomized, placebo-controlled trial
Study population	Asymptomatic Gabonese adults (18 years or older) with confirmed *Plasmodium falciparum* parasite infection between 200-5000 parasites/µl
Subject numbers/study treatment arms	44 participants will be randomized to a placebo and a treatment arm with a ratio of 1:1 **PLACEBO Arm**: 22 participants (Control arm with three days of placebo) **PZQ Arm**: 22 participants (PZQ 40mg/kg once-daily dosing for 3 days)
Route of Administration	Oral
Dose level	- 40mg/kg once daily for 3 days
Treatment duration	three days
Follow-up duration	7 days (SCR, D0, D1, D2, D3, D4, D5, D6, D7)
Planned Trial Period	March 2022 – July 2023
Endpoints	Primary endpoint: - Parasitemia undetectable by thick blood smear on D7 after the start of administration of study drugs All those needing rescue treatment according to the physicians' judgement before day 7 will be counted as treatment failures together with all positives at day 7. Secondary endpoints:

	1) Parasitemia reduction ≥90% on D7 compared with baseline, assessed by light microscopy of thick blood smears 2a) Time to parasitemia level < 100 parasites/µl in the PZQ 3-day treatment group versus placebo assessed by microscopy 2b) Time to parasitemia level below microscopic limit of detection in the PZQ 3-day treatment group versus placebo assessed by microscopy 3) Occurrence of adverse events (AEs) in the PZQ 3-day treatment group versus placebo 4) Time to parasite clearance assessed by qPCR in the PZQ 3-day treatment group versus placebo 5) Parasitological cure rate assessed by qPCR on D7 after administration of study drugs 6) Area under the curve (AUC) of microscopically-determined parasite mass between D0 and D7 in the PZQ 3-day treatment group versus placebo
Data and Safety Monitoring Plan	Participants will be treated when criteria to initiate a rescue treatment (i.e. Coartem [artemether-lumefantrine]) are reached or at the end of the study follow-up period (day 7)

Modification history

Version	Dates	Authors
1.0	07/FEB/2022	Johannes Mischlinger

Efficacy and safety of Praziquantel for treatment of *Plasmodium falciparum* infection in asymptomatic Gabonese adults

Study code: **CORMA-MAL**

Coordinating Investigator	Johannes Mischlinger Bernhard Nocht Institute for Tropical Medicine (BNITM) Department of Tropical Medicine Bernhard-Nocht-Straße 74 D-20359 Hamburg +49-4042818-480 mischlinger@bnitm.de
Principal Investigator	Ghyslain Mombo-Ngoma, Centre de Recherches Médicales de Lambaréné (CERMEL) B.P. 242, Lambaréné Gabon ghyslain.mombongoma@cermel.org
Investigators	Michael Ramharter Bernhard Nocht Institute for Tropical Medicine (BNITM) Department of Tropical Medicine Bernhard-Nocht-Straße 74 D-20359 Hamburg +49-4042818-511 ramharter@bnitm.de Rella Zoleko-Manego Centre de Recherches Médicales de Lambaréné (CERMEL) B.P. 242, Lambaréné Gabon manegorella@gmail.com Peter G. Kremsner Universitätsklinikum Tübingen Institut für Tropenmedizin Wilhelmstraße 27 D-72074 Tübingen, Germany Tel: +49 7071 29 87179 email: peter.kremsner@uni-tuebingen.de Andrea Kreidenweiss Universitätsklinikum Tübingen Institut für Tropenmedizin Wilhelmstraße 27

	D-72074 Tübingen, Germany Tel: +49 7071 2985569 email: andrea.kreidenweiss@uni-tuebingen.de Ayola Akim Adegnika, Centre de Recherches Médicales de Lambaréné (CERMEL) B.P. 242, Lambaréné Gabon aadegnika@cermel.org
Study Manager	Lidwine Badjina Bernhard Nocht Institute for Tropical Medicine (BNITM) Department of Tropical Medicine Bernhard-Nocht-Straße74 D-20359 Hamburg +49-4042818-705 lidwine.badjina@bnitm.de
Study Monitor	Francisca Sarpong Bernhard Nocht Institute for Tropical Medicine (BNITM) Department of Tropical Medicine Bernhard-Nocht-Straße74 D-20359 Hamburg +49 40 42818 706 francisca.sarpong@bnitm.de
Sponsor	Bernhard Nocht Institute for Tropical Medicine (BNITM) Department of Tropical Medicine Bernhard-Nocht-Straße 74 D-20359 Hamburg +49-4042818-480
Sponsor representatives	Michael Ramharter Bernhard Nocht Institute for Tropical Medicine (BNITM) Department of Tropical Medicine Bernhard-Nocht-Straße 74 D-20359 Hamburg +49-4042818-511 ramharter@bnitm.de Johannes Mischlinger Bernhard Nocht Institute for Tropical Medicine (BNITM) Department of Tropical Medicine Bernhard-Nocht-Straße 74 D-20359 Hamburg +49-4042818-480 mischlinger@bnitm.de

Trial site	Centre de Recherches Médicales de Lambaréné (CERMEL) B.P. 242, Lambaréné Gabon
Safety Monitor	Selidji T Agnandji Centre de Recherches Médicales de Lambaréné (CERMEL) B.P. 242, Lambaréné Gabon
Statistician	Johannes Mischlinger Bernhard Nocht Institute for Tropical Medicine (BNITM) Department of Tropical Medicine Bernhard-Nocht-Straße 74 D-20359 Hamburg +49-4042818-480 mischlinger@bnitm.de

Modification history Investigator Agreement

"I have read this protocol and agree to abide by all provisions set forth therein. I agree to comply with the principles of the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice,"

Signature Date(dd.mm.yyyy)

(Principal Investigator)

Signature Date(dd.mm.yyyy)

(Sponsor representative)

Signature

Date(dd.mm.yyyy)

(Statistician)

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the trial Sponsor, the Investigator Team, and members of the Institutional Review Board. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the principal investigator.

Abbreviations

ACT	Artemisinin-based combination therapy
AE	Adverse Event
ALT	Alanine aminotransferase
ART	Artesunate
AST	Aspartate aminotransferase
BNITM	Bernhard Nocht Institute for Tropical Medicine
CERMEL	Centre de Recherches Médicales de Lambaréné
CRF	Case Report Form
EC	Ethics Committee
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
HCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IV	Intravenous
LDH	Lactate dehydrogenase
MDA	Mass drug administration
MFQ	Mefloquine
P.	Plasmodium
PCR	Polymerase Chain Reaction (used synonymously in this study protocol with quantitative PCR [qPCR])
PI	Principal Investigator
PY	Pyronaridine

PZQ	Praziquantel
SAE	Serious Adverse Event
S.	Schistosoma
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	Upper limit of the normal range
WHO	World Health Organization

Background and Rationale

Future challenges of malaria treatment

Malaria is a vector-borne disease caused by parasites of the genus *Plasmodium*. Currently there are six species known to infect humans, namely *Plasmodium (P.) falciparum*, *P. vivax*, the sympatric species *P. ovale curtisi* and *P. ovale wallikeri*, *P. malariae* and *P. knowlesi* among which *P. falciparum* is responsible for the vast amount of malaria-attributable mortality and morbidity (1–3). In 2004, 350 to 500 million cases had occurred world-wide in 107 countries of whom at least a million had resulted in death (3,4). 16 years later, in 2020 despite large achievements still 241 million malaria cases were reported of which 627 000 ended lethal (5). It is the most important parasitic disease and a major cause of childhood morbidity and mortality in highly endemic regions of sub-Saharan Africa.

Artemisinin-based combination therapy (ACT) is the combination of an artemisinin derivative with a partner drug and constitutes to date the most successful treatment of malaria (2,6). However, over the course of the past two decades, it became evident that the efficacy of this bi-therapy declined in South East Asia due to the simultaneous development of artemisinin resistance and partner drug resistance (7). Therefore, an increasing number of studies assess the antimalarial efficacy of triple or quadruple combinations to reduce the emergence and spread of drug resistance (8). Partner drugs for established ACTs are needed and re-purposing of drugs is an efficient way of developing such multidrug combinations. Occasionally, specific antimicrobial agents demonstrate simultaneous activity against multiple microorganisms. This introduces the promising possibility of creating drug regimens to be potentially used for more than only one treatment indication. Furthermore, the value of such multi-disease drug regimens rises when designed for important infectious diseases that affect a similar target population; an aspect making such regimens appealing to be operationally implemented not only, but particularly in low resource settings. Epidemiologic data indicate that malaria and schistosomiasis are two infectious diseases affecting largely overlapping target populations (2,9).

Urogenital schistosomiasis and malaria, two potentially well-suited tropical target diseases for anti-parasite broad-spectrum therapies

Urogenital schistosomiasis is caused by the parasite *Schistosoma (S.) haematobium* and is defined as an important so-called 'neglected tropical disease' (9). It accounts for a high morbidity particularly among children and adolescents in endemic areas where malaria is often highly co-endemic. This indicates that malaria and urogenital schistosomiasis are not only often co-endemic but mainly affect children and adolescents i.e. a similar target population.

Treatment of urogenital schistosomiasis is based on praziquantel (PZQ), which is the only available drug for this indication. However, pyronaridine (PY), mefloquine (MFQ) and artesunate (ART), three important antimalarial drugs, have been shown to exert clinically important activity against *Schistosoma spp.* in experimental laboratory and clinical research settings (10–13). On the other hand, comparatively little research has to date been conducted on whether PZQ exerts clinically relevant activities against *Plasmodium falciparum.* And yet, currently recommended schistosomiasis control programmes would potentially pose a synergistic programmatic framework that could contribute towards improved control and ultimately elimination of both schistosomiasis and malaria.

Besides disease-management approaches that focus on delivering care to individuals there are management approaches aimed at delivering care to whole groups of the population (6,14–17). Generally, the value of such so-called mass-drug-administration (MDA) campaigns was described as to favourably impact on disease prevalence, as well as, on population morbidity. Its importance was particularly highlighted for settings with generally lower quality of the local health system which are often prevalent in malaria-endemic and schistosomiasis-endemic countries. In such MDA campaigns everybody in a defined target group receives a given treatment for the disease of interest without any prior application of diagnostics.

For malaria, MDA campaigns have been known and occasionally applied for approximately a century (14). Due to concern of potential development of drug resistance MDAs have at present been limited to benefit vulnerable groups in populations, namely pregnant women

and children (18–20). As such it is currently recommended that pregnant women in regions of high malaria transmission receive an effective antimalarial medication monthly (IPTp) (18). Second, children living in regions of highly seasonal malaria transmission are advised to take chemoprevention during the malaria season (SMC) (20). Third, for regions of moderate to high malaria transmission it is recommended that infants receive antimalarial medication when they present at health centres for routine immunisation (IPTi) (19). In addition to that, population-wide MDAs for malaria have recently received increasing attention as a potential means to decrease regional malaria transmission, however, to date there is no clear consensus in the scientific community as to whether MDAs should be applied in that regard (14).

On the other hand, for schistosomiasis it is common that MDA campaigns are conducted in regular intervals in regions of high schistosomiasis-endemicity (16). While different medicines might be used for malaria MDAs, solely praziquantel is administered as part of schistosomiasis-related MDA disease control programmes. Traditionally communities have been classified as 'high risk', 'moderate risk' and 'low risk' for schistosomiasis, whereby each of these categories are equivalent to the prevalence of schistosomiasis among school-aged children. Furthermore, most schistosomiasis MDA campaigns target particularly children and adolescents as they carry the brunt of disease burden (9). Drug delivery algorithms are specific to the three afore-mentioned risk categories and determine not only the frequency of the MDA campaigns, but also whether other groups in a population should participate in mass treatment. Table 1 indicates a scheme of MDA based on schistosomiasis prevalence:

Table 1: Recommended treatment strategy for schistosomiasis mass chemotherapy (created after (16,17)*)*

Category	**Prevalence among school-aged children**	**Action to be taken**	
High risk community	50% by parasitological methods **OR** 30% by questionnaire for visible haematuria	Treat all school-age children once a year	Also treat adults considered to be at risk (from special groups to entire communities living in endemic areas – e.g. fishermen and irrigation workers)

Moderate risk community	10% to below 50% by parasitological methods **OR** <30% by questionnaire for visible haematuria	Treat all school-age children once every 2 years	Also treat adults considered to be at risk (special risk groups only – e.g. fishermen and irrigation workers)
Low risk community	<10% by parasitological methods	Treat all school-age children twice during their primary schooling	Praziquantel should be available in dispensaries and clinics for treatment of suspected cases

These recommendations for MDA to control malaria and schistosomiasis highlight the potential for synergism for elimination of both diseases if a drug regimen can be applied that is safe, tolerable and efficacious against both diseases. Given the pronounced role of praziquantel in the treatment of schistosomiasis it seems compelling to investigate whether it has an effect on *Plasmodium* parasites. The following paragraphs illuminate the available evidence on the safety and tolerability of praziquantel treatment and its potential efficacy on malaria.

Tolerability and safety profile of praziquantel

Praziquantel has been used for schistosomiasis control for over 40 years and its safety and tolerability has been assessed in a myriad of trials (9,16,21–28). Side effects are mild and mostly comprise nausea, vomiting, malaise and abdominal pain. From individuals with heavy schistosome infections less frequent side effects were reported occurring shortly after treatment, such as acute cholic with bloody diarrhoea, which is hypothesised to be due to a massive worm shift and antigen release (9). Furthermore, two treatment studies evaluating a combination of PZQ with ART in school children with urogenital schistosomiasis demonstrated a favourable safety profile (29,30). This favourable safety profile was confirmed by another treatment study evaluating a combination of PZQ with ART and MFQ in African school children with urogenital schistosomiasis (31).

The recommended standard regimen in MDA approaches is 40mg/kg bodyweight as a single dose (9,16). However, for individual case management higher doses up to 60mg/kg can be

administered for up to three days. This is for instance reflected by the recommended treatment guidelines of schistosomiasis by the German Society for Tropical Medicine and International Health (DTG). Such guidelines recommend dosages of 40mg/kg/day for three days, as well as, 60mg/kg/day for three days depending on the infective *Schistosoma* species (27). A favourable toxicity profile was described for praziquantel with reportedly very low toxicity in animals and no important long-term safety issues in humans (9,32). Traditionally, praziquantel was administered to children below 4 years of age as off-label use due to missing data in this age group. However, in the last decade many studies were conducted that demonstrated safety in pre-school aged children (21–24,26). Praziquantel is also considered safe for treatment of pregnant women (33). Furthermore, in analogy to many existing antimalarial drugs efforts are currently undertaken to make praziquantel available also as paediatric drug formulation which would facilitate favourable administrability to the target population of children and adolescents (34,35).

Praziquantel and current evidence on potential co-efficacy on malaria

To date, little research has been conducted on the efficacy of praziquantel on the treatment of malaria.

In 1998, a Russian research group assessed the role of praziquantel during *Plasmodium* infection in a *P. berghei* mouse model (36). They used a chloroquine-resistant strain (LNK65CHLFR) and a strain with naturally reduced sensitivity to chloroquine (LNK65) and tested the antimalarial efficacy of praziquantel, chloroquine, styrylquinazoline and combinations of praziquantel/chloroquine and praziquantel/styrylquinazoline. Praziquantel was dosed as 125mg/kg body weight. Study drugs were administered to mice on days 2, 3, 4 after infection; due to no apparent reason an additional dose of study drugs was administered on day 5 after infection only in the LNK65 model. Interestingly, a strong antimalarial potency of praziquantel as combination to chloroquine and styrylquinazoline was observed both in the LNK65 and LNK65CHLFR models, while antimalarial activity of single medical agents was comparatively smaller. It is of mention that in the LNK65 mouse model, praziquantel reduced parasitaemia as mono-therapy for as long as treatment was administered, however, rising again when praziquantel administration was stopped.

Similar evidence comes from a non-randomised clinical study from Pakistan which assessed nine (n=9) and one (n=1) patients (age range: 12-52 years) infected with *P. falciparum* and *P. vivax*, respectively. Patients were administered praziquantel 30 mg/kg/day in three divided doses for a maximum of 8 days (37). Although the study is of questionable methodological quality, the Pakistani authors corroborate the Russian preliminary evidence in favour of anti-malarial activity of praziquantel by indicating that 8/10 (80%) of patients were blood-smear-negative by day 6 after praziquantel treatment initiation. Reportedly, two patients showed response to praziquantel treatment, but were given anti-malarial drugs due to development of jaundice. The authors mention that over a three-month follow-up period none of the patients had a re-emergence of parasitaemia, concluding that praziquantel might represent an additional drug in the treatment of malaria.

Furthermore, a randomised, open-label, exploratory trial in Côte d'Ivoire assessed various antimalarial treatment in combination with praziquantel for efficacy against *S. haematobium* in 61 school-aged children (31). Praziquantel monotherapy (single dose 40mg/kg) was used as control arm (n=21). Although the study was not powered for endpoints related to malaria, 17/21 (81%) of children in the praziquantel control group had an asymptomatic *P. falciparum* concomitant infection at baseline with a mean parasite density of 3249 parasites/microliter blood compared with 86% (18/21) at 21-22 days after treatment with a mean parasite density of 711 parasites/microliter blood. Such preliminary results are indicative for no efficacy of praziquantel on concomitant *P. falciparum* infection prevalence in African school-aged children. However, in comparison with the other above-mentioned studies that applied multiple-day posologies, it might be possible that a single dose of praziquantel was not enough to sustainably reduce and ultimately clear parasitaemia.

This preliminary evidence indicates that PZQ might not only exhibit intrinsic antimalarial properties, but might also be a beneficial partner drug in existing or novel antimalarial drug combination regimens, due to synergistic properties. Therefore, in a first step the CORMA-MAL study will further investigate existing preliminary evidence of PZQ antimalarial activity. CORMA-MAL is a placebo-controlled randomised trial to evaluate the in vivo efficacy, safety

and tolerability of PZQ in monotherapy. Adult participants with asymptomatic *Plasmodium falciparum* infection will be randomly allocated to one of two study arms with 22 participants in a placebo arm and 22 in an intervention arm with PZQ 40mg/kg once-daily dosing for 3 days.

Study overview

Trial Design

Single-center, assessor-blinded, randomized, placebo-controlled trial

Population

Adult, male or female, aged ≥ 18 years with asymptomatic *Plasmodium falciparum* infection between 200-5000 parasites/µl

Intervention

Oral treatment with PZQ 40mg/kg/day administered as once-daily dose for 3 consecutive days.

Control

Placebo administered as once-daily dose for 3 consecutive days.

Outcome

Parasitemia undetectable by thick blood smear on D7 after the start of administration of study drugs

Aims

To assess efficacy of PZQ in asymptomatic participants with Plasmodium falciparum parasites

Objectives

Primary Objective:

- To assess the proportion of participants with microscopically-determined parasite clearance on D7 after administration of PZQ compared with placebo

Secondary Objectives:

1) To assess the proportion of participants with ≥90% parasitemia reduction on D7 compared with baseline between PZQ and placebo study arms

2) To assess the time to microscopically-determined parasite clearance in the PZQ study arm compared with the placebo arm

3) To assess the safety and tolerability of PZQ 40mg/kg once-daily dosing for 3 days

4) To assess the time to qPCR-determined parasite clearance in the PZQ study arm compared with the placebo arm

5) To assess the qPCR-determined cure rate in the PZQ study arm compared with placebo at D7 after study drug administration

6) To assess and compare the baseline-adjusted parasite mass of participants in the PZQ study arm compared with participants in the placebo study arm

Exploratory Objectives:

To assess activity of PZQ on gametocyte carriage

Rationale for trial design and praziquantel

Currently, the internationally recommended therapies for uncomplicated malaria are artemisinin-combination therapies which require 3-day dosing regimens. Therefore, it would be highly beneficial for any potential, novel antimalarial agent to be administered in one to three doses within a 3-day time interval (6,38). Then it could potentially match internationally defined so-called target candidate profiles and be considered either as single antimalarial treatment agent, or as a combination partner in an existing antimalarial regimen (8,38). Several reports demonstrate that the treatment of PZQ 40mg/kg/day for 3 days is considered safe and well-tolerated in adults, adolescents, children, preschool children and pregnant women (9,21–24,26,33). If an antimalarial effect is found the benefit of this could justify a clinical trial using a higher PZQ dose. The chosen dose of PZQ (40mg/kg/day) is based on

official recommendations of national and international institutions to treat schistosomiasis as part of individual case management and MDA campaigns (16,17,27).

The maximum plasma concentration (Cmax) of PZQ is described to at between one to three hours (39). Average plasma elimination half-lives (t1/2) are 0.8 to 1.5 hours for the parent drug and 4.5 hours for metabolites (39). Due to evidence for an increased bioavailability in the presence of concomitant food intake, PZQ will be co-administered with food as part of the CORMA-MAL trial (40). All substances which have an impact on blood levels of PZQ should be avoided in this study.

PZQ is primarily metabolized by Cytochrome P450 3A4 (CYP3A4) and to a lesser extent by Cytochrome P450 2D6 (CYP2D6) (39–41). Therefore, substances which could alter Cyp3A4 and Cyp2D6 activity should be avoided before and after intake of PZQ. This includes substrates as well as inhibitors and inducers of Cyp3A4 and Cyp2D6. Only participants willing to avoid the intake of these substances before and after intake of praziquantel will be enrolled in the study. Substances to be avoided are listed in the inclusion criteria section.

Sample size

To calculate the sample size, we estimated that only 10% of participants in the placebo group will have a parasitemia below the microscopic limit of detection on day 7 versus 50% in the intervention group. With a power of 80% and an alpha error of 5% and considering a ratio 1:1 (treatment versus placebo group), we need 20 subjects in the placebo group and 20 subjects in intervention group. Accounting for a possible dropout rate of 10% in each study arm the final sample size will require recruitment of a total of 44 subjects.

Endpoints and assessment methods

Primary endpoint:

Parasitemia undetectable by thick blood smear on D7 after the start of administration of study drugs

Assessment method: Light microscopy

All those needing rescue treatment according to the physicians' judgement before day 7 will be counted as treatment failures together with all positives at day 7.

Secondary endpoints:

1) Parasitemia reduction ≥90% on D7 compared with baseline assessed by light microscopy of thick blood smears

Assessment method: Light microscopy

2a) Time to parasitemia level < 100 parasites/µl in the PZQ 3-day treatment group versus placebo assessed by microscopy

Assessment method: Light microscopy

2b) Time to parasitemia level below microscopic limit of detection in the PZQ 3-day treatment group versus placebo assessed by microscopy

Assessment method: Light microscopy

3) Occurrence of adverse events (AEs) in the PZQ 3-day treatment group versus placebo

Assessment method: Clinical examination and laboratory analysis

4) Time to parasite clearance assessed by qPCR in the PZQ 3-day treatment group versus placebo

Assessment method: Quantitative PCR

5) Parasitological cure rate assessed by qPCR on D7 after administration of study drugs

Assessment method: Quantitative PCR

6) Area under the curve (AUC) of microscopically-determined parasite mass between D0 and D7 in the PZQ 3-day treatment group versus placebo

Assessment method: Light microscopy

Exploratory endpoints

Proportion of participants with detectable gametocytes during D3-D7 in the treatment group versus placebo

Assessment method: Light microscopy

Duration of the study

Participants will be hospitalized for at least 3 days or up to 7 days, depending on the participant convenience. After discharge, subjects will return daily to the Clinical Center for further assessments until Day 7. The duration of involvement in the study from day 0 (day of administration of first PZQ dose) will be 7 days. The start of the trial is defined as the date of the first visit (i.e. screening visit) of the first participant. The end of the trial is the date of the last visit of the last participant.

Potential risks for participants

Phlebotomy

The maximum volume of blood drawn over the study period is approximately 61 ml over 7 days. Additional blood samples could be required for safety reasons. However, this volume should not compromise these otherwise healthy participants. There may be minor bruising, local tenderness or presyncopal symptoms associated with venepuncture, which will not be documented as AEs if they occur. Rare side effects are infections, thrombophlebitis and nerval lesions. In the case a participant develops severe discomfort from repeated venepunctures, and only with the recommendation/concurrence of the clinical team, an intravenous catheter could be inserted in one of the upper limbs of the participant to take the remaining blood samples as per protocol. An additional 2 mL of blood will be taken with each blood drawn when using the intravenous catheter. The participant will be informed about this extra volume of blood to be drawn before the catheter insertion.

Praziquantel

Side effects of praziquantel include nausea (≥10%), vomiting (≥10%), gastrointestinal and abdominal pain (≥10%), headache (≥10%), drowsiness (≥10%), urticaria (≥10%), diarrhoea

(<10%), anorexia (<10%), dizziness (<10%), somnolence (<10%), fever (<10%), rash (<10%), myalgia (<10%), unspecific arrhythmia (<0.0001%), pruritus (<0.0001%), seizure (<0.0001%), allergic reaction (<0.0001%), eosinophilia (<0.0001%) (41).

Potential benefits for participants

Participants will not benefit directly from participation in this study. The only benefits for the participants will be information about their general health status and the treatment from the *Plasmodium falciparum* infection in the end of the follow up. However, it is hoped that the information gained from this study will contribute to the development of safe and effective antimalarial drug. Compensation for missed working day if any and transportation fee for follow-up visit will be reimbursed.

Recruitment and withdrawal of trial participants

Participants

The study is designed as a randomized placebo-controlled assessor-blinded clinical trial to assess the safety and efficacy of praziquantel to treat *Plasmodium falciparum* infections in asymptomatic subjects in an endemic area of Gabon. Potential adult participants living in CERMEL's catchment areas in Gabon will be screened for parasitemia of 200 to 5000 pf/µl without malaria signs for inclusion into the clinical trial.

Informed Consent

All participants will sign and date the informed consent form before any study specific procedure is performed. At the screening visit, the volunteer will be fully informed of all aspects of the trial, the potential risks and their obligations. The following general principles will be emphasized:

• Participation in the study is entirely voluntary
• Refusal to participate involves no penalty or loss of medical benefits
• The participant may withdraw from the study at any time
• The participant is free to ask questions at any time to allow him or her to understand the purpose of the study and the procedures involved

The aims of the study and all tests to be carried out will be explained. The volunteer will be given the opportunity to ask about details of the trial and will then have time to consider whether or not to participate. Potential participants will be asked to sign and date two copies of the consent form, one for them to take away and keep, and one to be stored in the Investigator`s File. These forms will also be signed and dated by the Investigator.

Inclusion Criteria

The subject must satisfy all the following criteria to be eligible for the study:

• Subject male or female with age ≥ 18 years

• *Plasmodium* parasitaemia with 200 to 5000 parasites/µL

• Asymptomatic malaria defined by: presence of *Plasmodium* parasites with absence of fever (axillary temperature ≤ 37.5 ° C or oral / tympanic temperature ≤ 38 ° C, or absence of history of fever in recent 24 hours and the week before inclusion).

• Written informed consent must be obtained before any study assessment is performed.

• Willingness not to take drugs or substances which could have an impact on praziquantel blood levels. The timeframe for the abstinence of these drugs will be 2,5 days before and 2,5 days after intake of praziquantel or will be individually calculated by the study team, if necessary.

• Women only: Must agree to practice continuous contraception for the duration of the study. Those methods include: combined (estrogen and progestogen containing) hormonal contraception, associated with inhibition of ovulation, oral, intravaginal or transdermal progestogen-only hormonal contraception associated with inhibition of ovulation, oral, injectable, implantable intrauterine device (IUD), intrauterine hormonereleasingsystem (IUS), bilateral tubal occlusion, vasectomised partner, sexual abstinence and use of condoms.

The following is a selection of drugs/substances to be avoided: Tacrolimus, Ciclosporin, Sirolimus, Cyclophosphamid, Erlotinib, Gefitinib, Doxorubicin, Etoposid, Vindesin, Vinblastin, Tamoxifen, Clotrimazol, Miconazole, Ketoconazol, Itraconazol, Clarithromycin, Erythromycin, Amitriptylin, Clomipramin, Imipramin, Citalopram, Escitalopram, Fluoxetin, Norfluoxetin, Sertralin, Aripiprazol, Haloperidol, Risperidon, Ziprasidon, Alfentanil, Codein, Fentanyl, Methadon, Alprazolam, Clonazepam, Flunitrazepam, Midazolam, Triazolam, Pimozid, Atorvastatin, Lovastatin, Simvastatin, Amlodipin, Diltiazem, Felodipin, Nifedipin, Verapamil, Sildenafil, Tadalafil, Buspiron, Venlafaxin, Amiodaron, Ivabradin, Rifampicin, Chinolone, Phenytoin, Carbamazepin, Oxcarbazepin, Phenobarbital, Primidon, Modafinil, Dexamethason, Telithromycin, Chloramphenicol, Fluconazol, Ketoconazol, Itraconazol, Ritonavir, Indinavir, Nelfinavir, Verapamil, Aprepitant, Nefazodon, Amiodaron, Cimetidin, Chloroquine, Abametapir, Aprepitant, Clofazimin, Deferasirox, Erdafitinib, Fosaprepitant, Fusidic Acid, Ivosidenib, Sarilumab, Siltuximab, Simeprevir, Stiripentol, Tocilizumab, Hypericum

("Johanniskraut"), Ginger ("Ingwer"), Garlic ("Knoblauch"), Liquorice ("Lakritz"), Grapefruit, Valeriana ("Baldrian"), Turmeric ("Gelbwurzel"), Ginseng.

Exclusion Criteria

The subject may not enter the study if any of the following apply:

• Signs and symptoms of complicated malaria / severe malaria
• Taking an experimental drug in the last 4 weeks.
• Any antimalarial treatment in the last 4 weeks
• Is using and intends to continuing using a medication known to cause drug reactions with artemether/lumefantrine (e.g. cimetidine, metoclopramide, antacids, kaolin, terfenadine etc.)
• Use of systemic antibiotics with known antimalarial activity within 30 days of study enrolment (e.g. trimethoprim-sulfamethoxazole, doxycycline, tetracycline, clindamycin, erythromycin, fluoroquinolones, or azithromycin).
• Use of praziquantel within 30 days of study enrolment.
• Previous (within the last 10 years) participation in a malaria vaccine study
• Moderate to severe anemia (Hemoglobin level < 8 g/dL)
• Known history of hepatic disease or liver damage
• Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection
• Use of immunoglobulins or blood products within 3 months prior to enrolment
• Contraindications or known allergy to praziquantel or the first-line anti-malarial medication artemether/lumefantrine, or known or suspected allergy or intolerance to any other ingredient of the drug products (IMP/Non-IMP)
• Severe malnutrition (Body Mass Index (BMI) < 16.0)
• Pregnancy, lactation or intention to become pregnant during the study
• Known history of sickle cell anaemia, sickle cell trait, thalassemia or thalassemia trait
• Participants unable to be closely followed for social, geographic or psychological reasons
• Any other significant disease, disorder or finding which, in the opinion of the investigator, may significantly increase the risk to the participant because of participation in the study (e.g.

renal transplantation), affect the ability of the participant to participate in the study or impair interpretation of the study data.

Withdrawal of Participants

In accordance with the principles of the current revision of the Declaration of Helsinki (updated 2013) and any other applicable regulations, a participant has the right to withdraw from the study at any time and for any reason, and is not obliged to give his or her reasons for doing so. The Investigator may withdraw the participant at any time in the interests of the participant's health and well-being. In addition, the participant may withdraw/be withdrawn for any of the following reasons:

- Administrative decision by the Investigator
- Ineligibility (either arising during the study or retrospectively, having been overlooked at screening)
- Significant protocol deviation
- Participant non-compliance with study requirements
- An AE, which requires discontinuation of the study involvement or results in inability to continue to comply with study procedures

The reason for withdrawal will be recorded in the case report form (CRF). If withdrawal is due to an AE, appropriate follow-up visits or medical care will be arranged, with the agreement of the participant, until the AE has resolved, stabilised or a non-trial related causality has been assigned. Any participant who is withdrawn from the study may be replaced, if that is possible within the specified time frame. The medical monitor may recommend withdrawal of participants. If a participant withdraws/is withdrawn from the study before reaching the criterion for malaria diagnosis, a complete, appropriate, curative course of anti-malarial therapy must be completed. The importance of this will be emphasised to study participants at screening. If a participant withdraws from the study, blood samples collected before their withdrawal from the trial will be used/ stored unless the participant specifically requests otherwise.

Pregnancy

Praziquantel is also considered safe for treatment of pregnant women (33). However, based on differential parasite kinetics between pregnant and non-pregnant participants, pregnant women should not be included in this current Phase II trial. Should a study participant become pregnant during the trial, she will be followed up as other participants and in addition will be followed until pregnancy outcome. We will not routinely perform nonessential venepuncture on such participants. All initial reports of pregnancy must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported using the Serious Adverse Event (SAE) Form. Any subject who becomes pregnant during the study must discontinue further study treatment and be withdrawn from the study. An antimalarial treatment will be administered to treat the *Plasmodium falciparum* infection according to national guidelines.

Treatment of trial participants

Allocation of the groups

Participants fulfilling all inclusion/exclusion criteria will be randomly allocated to receive either placebo once-daily dosing for 3 days, or PZQ 40mg/kg once-daily dosing for 3 days. The allocation ratio is 1:1. Randomization lists will be created using permuted blocks. Treatment allocation codes will be stored in opaque-sealed envelopes on whose surface is a pre-defined allocation sequence number. Each time a participant fulfils the inclusion criteria the opaque-sealed envelope with the next allocation sequence number is opened by the pharmacist or his delegate. During the treatment period all participants will be hospitalized for three days. Study procedures during the treatment period and follow-up visit will be the same in the two study arms.

Study procedures

Blinding

Laboratory investigators processing and analysing biological samples will be blinded to group allocation. The unblinded pharmacist or designate will prepare the treatment assigned by the randomization system and complete the corresponding treatment record form. Subsequently, verum and placebo will be administered by a physician who is not involved in diagnostic and analytic processes of the study. Other study physicians and study participants will be unaware of group allocation. Only the pharmacists and the physician administering verum and placebo know the group allocation. Verum and placebo are similar but not identical and will be administered to each participant separately out of the original packaging without changing labels.

Procedures will be performed at the time points indicated in the schedule of procedures (Table 2). Additional procedures or laboratory tests may be performed at any time, at the discretion of the investigators if clinically necessary.

Ascertainment of basic demographic information, clinical and past medical history

- Full medical history
- Prior concomitant medication
-Demographic data (gender, age)
- Clinical examination (including measurement of height and weight)
- Vital signs (including pulse, blood pressure and body temperature)

Blood sampling and laboratory tests

A series of blood samples will be drawn to perform different tests. Types of tests to be performed include molecular biology, biochemistry, haematology and parasitology.

Details of these tests are as follows:

Parasitology:

These tests include thick and thin blood smears and qPCR to detect the malaria parasite.

- **Thick and thin blood smears** are prepared at screening. During the treatment period (D0, D1 and D2) thick and thin blood smears are prepared 6-hourly. Between D3 and D7 thick and thin blood smears will be prepared once daily. While thick blood smears will be used for quantification of parasitemia, thin blood smears will be used for determination of *Plasmodium* species.
- **Blood in RNA later (for qPCR)** is sampled at the same time as thick and thin blood smears. It is sampled at screening and during the treatment period (D0, D1 and D2) blood in RNA later it is sampled 6-hourly. Between D3 and D7 blood in RNA later will be sampled once daily.

Hematology, biochemistry tests:

These tests include full blood count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT), total bilirubin, conjugated bilirubin, albumin, lactate dehydrogenase (LDH), creatinine, urea, glucose, sodium, potassium, calcium, and magnesium. These tests will be performed at screening, D3 and D7.

Urine sampling

- **Urine β-HCG test in female participants**: This is performed at screening to rule out any potential pregnancy at the beginning of the trial.

Administration of praziquantel

Participants allocated to the PZQ intervention group will receive PZQ orally on D0 once that the presence of all inclusion criteria and the absence of all exclusion criteria are secured. The dose will be 40 mg/kg once-daily for 3 days. Also, placebo will be administered orally, once daily for 3 days. To increase PZQ plasma levels study drugs will be administered with a standardised meal (40,42,43). Co-administration with food will also help to mask the taste of PZQ, thereby making it more similar to placebo and reducing the chance of reporting bias.

Clinical visits

The procedures to be included in each visit are documented in Table 2. In General, during the treatment period (D0-D2) each visit is assigned a time point and a window period of ± 2 hours within which the visit will be conducted. Only the visits with study drug dosing time points (i.e. H0, H24, H48) are exempted from this and have a stricter window period of ± 1 hour. Between D3 and D7 the visit can be performed at any given timepoint on the respective day considering participant and study team convenience. Patients must be seen for all visits on the designated day within the given window period, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Screening visit

All potential participants will have a screening visit, which shall take place on the same day (i.e. within 24 hours) as the administration of study drugs. Informed consent will be obtained from those eligible as described above. Once the informed consent is signed, the following screening procedures indicated in Table 2 will be undertaken:

- Full medical history, clinical examination (including measurement of height and weight) and ascertainment of demographic details
- Vital signs (pulse, blood pressure and temperature);
- urine β-HCG test in female participants;
- Blood samples will be taken for full blood count, biochemistry, thick and thin blood smears, blood for RNA later.
- The inclusion and exclusion criteria for the study will be assessed

AEs will be recorded from the signature of the informed consent onwards. Abnormal clinical findings from the medical history, vital signs assessment or blood tests at any point in the study will be assessed using established reference intervals of CERMEL laboratory. If a laboratory test is out of range it may be repeated to ensure it is not a single occurrence. If an abnormal finding is deemed to be clinically significant, the participant will be informed and appropriate medical care arranged with the permission of the participant.

Study drug administration (D0-D2; H0, H24 and H48)

Medication will take place at CERMEL and participants will be hospitalized for 3 days. Before the medication is administered the following measures will be performed on all participant:

- Vital signs
- Thick and thin blood smears
- Blood in RNA later
- Potential adverse events (AEs)
- Potential concomitant medication is ascertained
- Clinical examination (Note that it does not need to be performed at H0, since it was performed just hours earlier during the screening visit)

Afterwards study medication is administered.

Time of hospitalization (D0-D2)

From the administration of the first dose of study medication (D0; H0) participants will be seen in 6-hourly intervals. These intervals continue until D2 (H66) when the patient can be discharged. The following assessments will be performed:

- Vital signs
- Thick and thin blood smears
- Blood in RNA later
- Potential adverse events (AEs)
- Potential concomitant medication is ascertained

Days 3-7

During D3-D7 participants are seen once daily. The following assessments will be performed per visit:

- Vital signs
- Thick and thin blood smears

- Blood in RNA later
- Potential adverse events (AEs)
- Potential concomitant medication is ascertained
- Clinical examination

Blood samples will be taken for full blood count and biochemistry on D3 and D7

Days 7 – end of study

After the performance of all assessments on D7 (i.e. at the end of the study), the rescue treatment (artemether/lumefantrine) will be given to all study participants irrespective of results in parasitaemia. This ensures that all study participants will reach complete parasite clearance. In accordance with national guidelines, six weight-adjusted doses of the rescue treatment will be given to study participants including an explanation on how to self-administer the medication at home.

Treatment of *Plasmodium falciparum* Infection:

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

- Any parasitaemia based on microscopy with fever post-dose
- Development of complicated signs or severe malaria on any day between Study Day 0 and Day 7 in the presence of parasitaemia.
- Investigator judgment

If applicable: Rescue medication according to local guidance will be used for severe malaria.

Table 2: Study procedures. Safety related procedures may be added if clinical investigator or the local safety monitor consider it necessary.

Visit (days)	**Screening**	**D0**				**D1**				**D2**				**D3**	**D4**	**D5**	**D6**	**D7**	**UNS**
Visit (hours)		H0 ± 1h	H6 ± 2h	H12 ± 2h	H18 ± 2h	H24 ± 1h	H30 ± 2h	H36 ± 2h	H42 ± 2h	H48 ± 1h	H54 ± 2h	H60 ± 2h	H66 ± 2h						
Demographics, medical history	x																		
Clinical examination	x					x				x				x	x	x	x	x	x
Vital signs*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	(x)
Incl./Excl. criteria	x																		
Urine ß-HCG	x									x									(x)
'Adverse events' and 'concomitant medication'		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Study drug administration		x				x				x									
Malaria rescue treatment																			(x)
Full blood count (1.2ml)	x													x				x	(x)
Biochemistry** (2.7ml)	x													x				x	(x)
Thick and thin blood smears (0.2ml)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood in RNA later (0.5ml)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood volume (total = 24.3 ml)	4.6 ml	0.7 ml	0.7 ml	0.7 ml	0.7 ml	0.7 ml	0.7 ml	0.7 ml	0.7 ml	0.7 ml	0.7 ml	0.7 ml	0.7 ml	4.6 ml	0.7 ml	0.7 ml	0.7 ml	4.6 ml	

(x) = if judged necessary by clinical investigator; Note that additional assessments at other time points may be performed if judged medically necessary by the clinical investigator

* Including pulse, blood pressure, temperature;

** Biochemistry: Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyltransferase (GGT), total bilirubin, conjugate bilirubin, albumin, lactate dehydrogenase (LDH), creatinine, urea, glucose, sodium, potassium, calcium, and magnesium

Assessment of safety

Safety of PZQ treatment will be assessed by analysing the frequency, incidence and nature of adverse events and serious adverse events arising during the study.

Definitions

Adverse Event (AE)

An Adverse Event (AE) is any new unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE hast to be documented in order of appearance, given by a number. In addition, the start and end time of the AE has to be noted precisely. The investigator must enter the information within 24 hours in the paper-based source document and eCRF using the AE section.

The term 'new' unfavourable and unintended sign/symptom/disease implies that this 'new' sign/symptom/disease was not present at baseline or was not part of the past medical history of the participant.

Example: In case a patient reports sleeping problems at baseline and further reports 'sleeping problems' during follow up, then 'sleeping problems' will not be counted as adverse events.

Exceptions from this rule can be made if the problem, if a clinician is convinced the respective sign/symptom/disease has become much different in severity/intensity, quality etc.

Grading of adverse events

The investigator will assess the **severity/intensity** of the adverse event using the following terms:

Table 3: Severity of Adverse Events

Grade 1	**Mild**	Awareness of sign or symptom, but easily tolerated; Transient or mild discomfort (< 48 hours); no medical intervention/therapy required
Grade 2	**Moderate**	Enough discomfort to cause interference with usual activity; Mild to moderate limitation in activity* - some assistance may be needed; no or minimal medical intervention/therapy required
Grade 3	**Severe**	Incapacitating with inability to work or do usual activity; Marked limitation in activity**, some assistance usually required; medical intervention/therapy required, hospitalisations possible
Grade 4	**Life-threatening**	Note: this must also be reported as Serious Adverse Event; Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalisation or hospice care probable
Grade 5	**Death**	Note: this must also be reported as Serious Adverse Event

***Includes limitation in instrumental activities of life: preparing meals, shopping for groceries or clothes etc**

****Includes limitation in self-care activities of life: bathing/showering, dressing/undressing, feeding self, using the toilet etc**

Serious or Life-Threatening AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

Causality assessment between study medication and AE

Afterwards the investigator has to decide a term for describing the relationship to the study drug:

Table 4: Relationship to Study Drug (Causality assessment)

Definite	Clear-cut temporal association, with a positive re-challenge test or laboratory confirmation; Event or laboratory test abnormality, with plausible time relationship to drug intake; Cannot be explained by disease or other drugs; Response to withdrawal plausible (pharmacologically, pathologically) event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon).
Probable	Clear-cut temporal association, with improvement upon drug withdrawal and not reasonably explained by the participant's known clinical state. Event or laboratory test abnormality, with reasonable time relationship to drug intake. Unlikely to be attributed to disease or other drugs response to withdrawal clinically reasonable.
Possible	Event or laboratory test abnormality, with reasonable time relationship to drug intake. Less clear temporal association, other aetiologies are possible. Could also be explained by disease or other drugs, other possible aetiologies should be recorded on the Source Document Information on drug withdrawal may be lacking or unclear.
None	No temporal association with the study drug; related to other aetiologies such as concomitant medications or conditions or subject's known clinical state. Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) Disease or other drugs provide plausible explanations.

The investigator will document the **taken action(s)** following identification of the adverse event:

- No action taken
- Study drug discontinued
- Patient withdrawn from study
- Concomitant medication required

- Hospitalisation required or prolonged (this should also be reported as a SAE)
- Other

The investigator will follow-up the adverse event until resolution or until no further medically relevant information can be expected. **Adverse event outcome** will be classified as follows:

- Resolved
- Resolved with sequelae
- Continuing (at the end of the study)
- Death
- Unknown (if patient is lost-to-follow up and AE outcome is unknown)

Serious Adverse Event (SAE)

A SAE is an adverse event which:

- causes death or
- is life-threatening or
- necessitates or prolongs hospitalisation or
- results in persistent or significant disability/incapacity or
- is a congenital defect or malformation
- is another medically important event

A decision on medical and scientific grounds is required to assess whether an immediate notification of an event is warranted in other situations, such as medically important events which are not life-threatening, fatal or cause hospitalization, but could endanger the patient or required an intervention to prevent one of the above conditions developing.

Remark: Examples of such events are intensive care in the emergency room or at home to treat a bronchospasm; convulsions not causing hospitalisation, or the development of drug addiction or drug abuse.

Monitoring of AEs (including SAEs)

The Site Principal Investigator (PI) will make a causality assessment. He should be informed about any new data on a participant for whom a causality link had already been established to reconsider its analysis and if necessary reassess the causality. Data shall only be modified following an official query procedure. Source Document review meetings shall be organised regularly, during which the site PI and the local study team shall review AE data (intensity, causality, and date of event manifestation in relation to the start of treatment). Safety data should be entered immediately in the eCRF.

A Medical Monitor will be available for the trial site to resolve arising safety related questions and uncertainties. He will oversee the medical aspects of the clinical trial and will actively collaborate with the sites. The medical monitor will have access to the eCRF and can address a request to the site PI concerned to add any further information needed for the safety analysis. The medical monitor will conduct the final review of the eCRF for any participants who have had an adverse event.

Obligation of AE and SAE notification

Adverse Events

The AEs, regardless of their seriousness and causal relationship to the study drug, arising between the first administration of study medication and the last study visit (as per the protocol), must all be recorded on the participant's Source Document (AE recording section). When possible, the symptoms must be regrouped within a single syndrome or diagnosis. The healthcare personnel shall have to specify the date of manifestation of the event, its intensity, final evolution, the measures taken and the treatment undertaken (if any).

Serious Adverse Events (SAEs)

In case of SAEs, the healthcare personnel must immediately contact the Investigator for validation of the seriousness and determination of the causality. Subsequently, the procedure described below must be followed, independent of causality:

- Send (within 24 hours of knowledge) the signed and dated copy of the "Adverse Event form" and the "SAE form" electronically to the medical monitor, sponsor, clinical monitor and the international study coordinator
- Contact immediately (the same day) the medical monitor, responsible for safety in case of death or life-threatening events.
- Inform the Ethics Committees of the occurrence of any SAE or if applicable as per local regulation.
- The follow-up of each fatal or life-threatening AE must be provided to the medical monitor, sponsor-coordinating PI, clinical monitor and the international study coordinator within the same timeline as the initial report (within 24 hours of knowledge and preferably by email).
- Attach to the Source Document the photocopy of all available results and examinations which were undertaken (and their date). Analysis results must be accompanied by the laboratory normal ranges. Special consideration shall be taken to ensure participant anonymity, and to the correct completion of the participant's study specific identifier in the copies of the source documents provided to the sponsor.

Emergency procedures

The site PI is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study.

Follow-up of Adverse Events

The healthcare personnel must take all appropriate measures to protect the safety of the participants. Personnel must ensure to document follow-up of the evolution of each AE (clinical, biological or other) until resolution or until the stabilization of the participant's status.

In case of a SAE the participant must be followed until complete resolution and normalization of all analysis results, or until chronicity of the participant's status. This can imply that the follow-up of the participant may continue beyond the period of follow-up per protocol, and that additional investigations could be requested by the sponsor.

All new relevant information concerning the initial SAE shall be recorded on the "SAE form" by the local study team, and shall be validated by the site PI/co-PI who shall transfer the form to the medical monitor, sponsor-coordinating PI, clinical monitor and the international study coordinator.

Procedures for unblinding in case of safety issues

If it is medically imperative to know which trial medication the subject is receiving, the investigator or authorized person should unblind the treatment allocation. A trial-specific SOP that describes unblinding in detail will be implemented before trial initiation.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

Upon receiving the SAE form, the sponsor and medical monitor will discuss and decide on the expectedness of the SAE. Any AE that is mentioned in the investigator brochure or summary of product characteristics (SmPCs) is considered 'expected'. An AE not mentioned in the investigator brochure or SmPC is considered 'unexpected'. A SUSAR is an SAE that is both 'unexpected' and at least 'possibly related' to the study medication (i.e. if there is no association to the study medication it is no SUSAR).

The Principal Investigator (PI) will report all SUSARs to the Ethics Committee (EC) within 7 calendar days in case of Fatal and life-threatening SUSARs and within 15 calendar days in case of SUSARs that are not fatal or life threatening.

The PI will also inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

Laboratory safety

When grading abnormal laboratory values the investigator needs to first judge if the abnormal lab value entails clinical significance. If this is the case (i.e. **abnormal lab value & clinical significance**) then routine grading shall be performed as explained above for clinical symptoms (by primarily using 'Table 3 Severity of Adverse Events'). In case the laboratory value is outside of local laboratory ranges, but **not clinically significant** then grading shall be performed according to

modified ‘Common Terminology Criteria for Adverse Events (CTCAE) v5.0’. Tables with modified CTCAE criteria are attached in ANNEX 1.

Generally, ‘ULN = Upper Limit of Normal’ and ‘LLN = Lower Limit of Normal’ are given to grade adverse events. Thereby usage of different blood value units in different laboratories can be largely respected. In the rare case that international grading classification systems used only one specific blood value unit (which might not be used in a given laboratory) investigators are asked to do the following: convert the result as given by your local laboratory to a result (and unit) which is required to adequately grade the abnormal laboratory value. Afterwards grade the adverse event based on the converted result by using adequate tables below. This approach will ensure timely grading of adverse events. Any method/source deemed appropriate by expert study staff can be used for conversion.

Statistics

Data analysis will consist of descriptive summaries for treatment groups. The primary endpoint of successful clearance of *Plasmodium falciparum* infection on Day 7 will be assessed for each patient and the number and percent of participants achieving this endpoint summarised for each group. Chi-square tests will be used for hypothesis testing between study groups.

For secondary endpoints descriptive summaries and plots over the time course for both individual patient results and groups will be presented. Where appropriate numbers and percent of participants achieving the given endpoint will be presented per group. Where appropriate highly skewed data will be log-transformed and presented as geometric means with 95% confidence intervals. Time to event data will be described using the Kaplan-Meier method and if appropriate by Cox proportional hazards models. Area under the curve (AUC) will be computed using the trapezoidal rule.

Quality control and quality assurance procedures

Monitoring

Monitoring will be performed according to ICH Good Clinical Practice (GCP) by a monitor who is independent from the study. The monitor will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. The investigators will provide direct access to all trial related source data/documents and reports for the purpose of monitoring and auditing by the sponsor and inspection by local and regulatory authorities.

Medical monitor

A medical monitor, i.e. a clinician with experience in clinical trials who is permanently on site and is independent of the clinical trial team, will oversee participant safety.

Ethics

This study will be performed in accordance with the current revision of the Declaration of Helsinki and the latest versions of the ICH guidelines for Good Clinical Practice (GCP) and guidelines for Good Clinical Laboratory Practice (GCLP).

Informed Consent

Written, informed consent will be obtained from all study subjects prior to inclusion, as described above. This consent may be withdrawn by the study subject at any time, without being required to provide a reason.

Research Ethics Committee

This trial will be submitted for ethical review to the Institutional Review Board (Comité d'Ethique institutionel, CEI) of the Centre de Recherches Médicales de Lambaréné (CERMEL), which is

registered with the Registration Office for Human Research Protections (OHRP) with the numbers: IORG0007336 / IRB00008812.

Participant Confidentiality

All data will be pseudononymized. Participant data will be identified by a unique study number in the database. Separate confidential files containing identifiable information will be stored in secured locations. Only the Sponsor representative, investigators, the clinical monitor, and the Institutional Review Board will have access to the records.

Data handling and record keeping

Data Handling

The PI or his designee will be the data manager with responsibility for delegating the receiving, entering, cleaning, querying, analysing and storing all data that accrues from the study. All data will be recorded in case record forms. This includes safety data, laboratory data and outcome data.

Record Keeping

All files and source documents will be kept confidentially in locked safety cabinets. The PI, co-investigators and clinical research nurses will have access to records. The investigators will permit authorized representatives of the sponsor, regulatory agencies and the monitors to examine clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source Data and Case Report Forms (CRFs)

All protocol-required information will be collected in CRFs designed by the investigator. Source documents will be in paper form, and the data will be entered into the clinical trial software (e.g. RedCap). Source documents are original documents, data, and records from which the participant's CRF data are obtained. For this study these will include, but are not limited to;

participant consent form, blood results, laboratory records and correspondence. In this study this will include, but is not limited to medical history, medication records, vital signs, physical examination records, blood results, adverse event data and details of study interventions. All source data and participant CRFs will be stored securely.

Data Protection

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the sponsor.

Procedures for the collection, storage and future use of biological sample

All of the stored study research samples are labelled by a code that only the trial site can link to the subject. Samples are stored at the trial site in secure facilities with limited access. Data will be kept in password-protected computers. Only investigators or their designees will have access to the samples and data. Samples may be transferred to another facility in the purpose of analysis if the site is not able to analyse the sample for logistical reasons. Data will be archived in compliance with national and international guidelines.

References

1. Groger M, Veletzky L, Lalremruata A, Cattaneo C, Mischlinger J, Manego Zoleko R, et al. Prospective Clinical and Molecular Evaluation of Potential Plasmodium ovale curtisi and wallikeri Relapses in a High-transmission Setting. Clin Infect Dis. 2019 Nov;69(12):2119–26.
2. White NJ, Pukrittayakamee S, Hien TT, Faiz MA, Mokuolu OA, Dondorp AM. Malaria. Lancet (London, England). 2014 Feb;383(9918):723–35.
3. World Health Organization. World Malaria Report 2019 [Internet]. 2019. Available from: https://www.who.int/publications-detail/world-malaria-report-2019
4. World Health Organization. World Malaria Report 2015 [Internet]. 2015. Available from: https://www.who.int/malaria/publications/world-malaria-report-2015/report/en/
5. World Health Organization. World Malaria Report 2021 [Internet]. 2021 [cited 2022 Jan 23]. Available from: https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2021
6. World Health Organization. Guidelines for the treatment of malaria. Third edition [Internet]. 2015. Available from: https://www.who.int/malaria/publications/atoz/9789241549127/en/
7. Noedl H, Socheat D, Satimai W. Artemisinin-resistant malaria in Asia. Vol. 361, The New England journal of medicine. United States; 2009. p. 540–1.
8. Krishna S. Triple artemisinin-containing combination anti-malarial treatments should be implemented now to delay the emergence of resistance: the case against. Malar J. 2019 Oct;18(1):339.
9. Gryseels B, Polman K, Clerinx J, Kestens L. Human schistosomiasis. Lancet (London, England). 2006 Sep;368(9541):1106–18.
10. Xiao S. Mefloquine, a new type of compound against schistosomes and other helminthes in experimental studies. Parasitol Res. 2013 Nov;112(11):3723–40.
11. Basra A, Mombo-Ngoma G, Melser MC, Diop DA, Würbel H, Mackanga J-R, et al. Efficacy of mefloquine intermittent preventive treatment in pregnancy against Schistosoma haematobium infection in Gabon: a nested randomized controlled assessor-blinded

clinical trial. Clin Infect Dis. 2013 Mar;56(6):e68-75.

12. Koehne E, Zander N, Rodi M, Held J, Hoffmann W, Kreidenweiss A. In vitro and in vivo activity of antiplasmodial compounds against Schistosoma mansoni.
13. Kramer C V, Zhang F, Sinclair D, Olliaro PL. Drugs for treating urinary schistosomiasis. Cochrane database Syst Rev. 2014 Aug;2014(8):CD000053.
14. von Seidlein L, Greenwood BM. Mass administrations of antimalarial drugs. Trends Parasitol. 2003 Oct;19(10):452–60.
15. Webster JP, Molyneux DH, Hotez PJ, Fenwick A. The contribution of mass drug administration to global health: past, present and future. Philos Trans R Soc London Ser B, Biol Sci. 2014;369(1645):20130434.
16. World Health Organization. Prevention and control of schistosomiasis and soil-transmitted helminthiasis. Report of a WHO Export Committee [Internet]. 2002 [cited 2021 May 12]. Available from: https://apps.who.int/iris/bitstream/handle/10665/42588/WHO_TRS_912.pdf?sequence=1&isAllowed=y
17. World Health Organization. Schistosomiasis [Internet]. 2006. Available from: http://www.who.int/schistosomiasis/en/index.html
18. World Health Organization. Intermittent preventive treatment in pregnancy (IPTp) [Internet]. 2019 [cited 2021 May 17]. Available from: https://www.who.int/malaria/areas/preventive_therapies/pregnancy/en/
19. World Health Organization. Intermittent preventive treatment in infants (IPTi) [Internet]. 2017 [cited 2021 May 17]. Available from: https://www.who.int/malaria/areas/preventive_therapies/infants/en/
20. World Health Organization. Seasonal malaria chemoprevention (SMC) [Internet]. 2017 [cited 2021 May 17]. Available from: https://www.who.int/malaria/areas/preventive_therapies/children/en/
21. Coulibaly JT, Panic G, Silué KD, Kovač J, Hattendorf J, Keiser J. Efficacy and safety of praziquantel in preschool-aged and school-aged children infected with Schistosoma mansoni: a randomised controlled, parallel-group, dose-ranging, phase 2 trial. Lancet Glob Heal [Internet]. 2017 Jul;5(7):e688–98. Available from: https://pubmed.ncbi.nlm.nih.gov/28619227

22. Coulibaly JT, Panic G, Yapi RB, Kovač J, Barda B, N'Gbesso YK, et al. Efficacy and safety of ascending doses of praziquantel against Schistosoma haematobium infection in preschool-aged and school-aged children: a single-blind randomised controlled trial. BMC Med. 2018 Jun;16(1):81.
23. Kabuyaya M, Chimbari MJ, Mukaratirwa S. Efficacy of praziquantel treatment regimens in pre-school and school aged children infected with schistosomiasis in sub-Saharan Africa: a systematic review. Infect Dis poverty. 2018 Jul;7(1):73.
24. Montresor A, Garba A. Treatment of preschool children for schistosomiasis. Lancet Glob Heal. 2017 Jul;5(7):e640–1.
25. Zwang J, Olliaro PL. Clinical efficacy and tolerability of praziquantel for intestinal and urinary schistosomiasis-a meta-analysis of comparative and non-comparative clinical trials. PLoS Negl Trop Dis. 2014;8(11):e3286.
26. Kimani BW, Mbugua AK, Kihara JH, Ng'ang'a M, Njomo DW. Safety, efficacy and acceptability of praziquantel in the treatment of Schistosoma haematobium in pre-school children of Kwale County, Kenya. PLoS Negl Trop Dis. 2018 Oct;12(10):e0006852.
27. Deutsche Gesellschaft für Tropenmedizin und Internationale Gesundheit. Leitlinie: Diagnostik und Therapie derSchistosomiasis (Bilharziose) [Internet]. 2017 [cited 2021 May 12]. Available from: https://www.awmf.org/uploads/tx_szleitlinien/042-005l_S1_Schistosomiasis-Bilharziose-Diagnostik-Therapie_2017-12.pdf
28. Bayer. Product Monograph - Praziquantel [Internet]. [cited 2021 May 12]. Available from: https://omr.bayer.ca/omr/online/biltricide-pm-en.pdf
29. Borrmann S, Szlezák N, Faucher JF, Matsiegui PB, Neubauer R, Binder RK, et al. Artesunate and praziquantel for the treatment of Schistosoma haematobium infections: a double-blind, randomized, placebo-controlled study. J Infect Dis. 2001 Nov;184(10):1363–6.
30. Keiser J, N'Guessan NA, Adoubryn KD, Silué KD, Vounatsou P, Hatz C, et al. Efficacy and safety of mefloquine, artesunate, mefloquine-artesunate, and praziquantel against Schistosoma haematobium: randomized, exploratory open-label trial. Clin Infect Dis. 2010 May;50(9):1205–13.
31. Keiser J, Silué KD, Adiossan LK, N'Guessan NA, Monsan N, Utzinger J, et al. Praziquantel, mefloquine-praziquantel, and mefloquine-artesunate-praziquantel against

Schistosoma haematobium: a randomized, exploratory, open-label trial. PLoS Negl Trop Dis. 2014 Jul;8(7):e2975.

32. Dayan AD. Albendazole, mebendazole and praziquantel. Review of non-clinical toxicity and pharmacokinetics. Acta Trop. 2003 May;86(2–3):141–59.
33. World Health Organization. Report of the WHO informal consultation on the use of praziquantel during pregnancy/lactation and albendazole/mebendazole in children under 24 months [Internet]. 2002 [cited 2021 May 12]. Available from: https://www.who.int/publications/i/item/WHO-CDS-CPE-PVC-2002.4
34. Bélard S, Ramharter M, Kurth F. Paediatric formulations of artemisinin-based combination therapies for treating uncomplicated malaria in children. Cochrane database Syst Rev. 2020 Dec;12(12):CD009568.
35. Paediatric Praziquantel Consortium. The pediatric formulation [Internet]. [cited 2021 May 17]. Available from: https://www.pediatricpraziquantelconsortium.org/pediatric-formulation
36. Orlov VS, Rabinovich SA, Bukhtin BA, Dadasheva NR, Maksakovskaia E V. [Ca++ ion transport blockers as reversants of the drug resistance of malarial parasites. 2. The effect of praziquantel on the resistance to chloroquine and compound R-70-Zh of Plasmodium berghei]. Med Parazitol (Mosk). 1998;(1):26–9.
37. al-Waili NS. Praziquantel for treatment of malaria. J Pak Med Assoc [Internet]. 1998 Dec;48(12):378—379. Available from: http://europepmc.org/abstract/MED/10531774
38. Burrows JN, Duparc S, Gutteridge WE, Hooft van Huijsduijnen R, Kaszubska W, Macintyre F, et al. New developments in anti-malarial target candidate and product profiles. Malar J [Internet]. 2017;16(1):26. Available from: https://doi.org/10.1186/s12936-016-1675-x
39. UpToDate. Praziquantel: Drug Information - UpToDate. 2021.
40. Vale N, Gouveia MJ, Rinaldi G, Brindley PJ, Gärtner F, Correia da Costa JM. Praziquantel for Schistosomiasis: Single-Drug Metabolism Revisited, Mode of Action, and Resistance. Antimicrob Agents Chemother [Internet]. 2017 May 1;61(5):e02582-16. Available from: http://aac.asm.org/content/61/5/e02582-16.abstract
41. Bayer. FACHINFORMATION - Praziquantel (Biltricide 600mg). Frankfurt; 2020.
42. Kovač J, Meister I, Neodo A, Panic G, Coulibaly JT, Falcoz C, et al. Pharmacokinetics of

Praziquantel in Schistosoma mansoni- and Schistosoma haematobium-Infected School- and Preschool-Aged Children. Antimicrob Agents Chemother. 2018 Aug;62(8).

43. Mandour ME, el Turabi H, Homeida MM, el Sadig T, Ali HM, Bennett JL, et al. Pharmacokinetics of praziquantel in healthy volunteers and patients with schistosomiasis. Trans R Soc Trop Med Hyg. 1990;84(3):389–93.

Annexes

List of Annexes:

1. Laboratory reference intervals and toxicity margins

Annex 1: Grading of abnormal lab values which are 'not clinically significant'

Laboratory values and grading:

Table 5 Biochemistry Values and Grading

	Biochemistry (modified CTCAE v5)			
Variable	**Grade 1**	**Moderate Grade 2**	**Severe Grade 3**	**Potentially Life Threatening Grade 4**
ALT (GPT)	None	>3.0 – 5.0 ULN if baseline was normal; baseline was normal; >3.0 – 5.0 x baseline if baseline was abnormal	>5.0 – 20.0 x ULN if baseline was normal; baseline was normal; >5.0 – 20.0 x baseline if baseline was abnormal	> 20.0 x ULN if baseline was normal; baseline was normal; > 20.0 x baseline if baseline was abnormal
AST (GOT)	None	>3.0 – 5.0 ULN if baseline was normal; >3.0 – 5.0 x baseline if baseline was abnormal	>5.0 – 20.0 x ULN if baseline was normal; >5.0 – 20.0 x baseline if baseline was abnormal	> 20.0 x ULN if baseline was normal; > 20.0 x baseline if baseline was abnormal
Alkaline Phosphatase	None	>2.5 – 5.0 ULN if baseline was normal; >2.5 – 5.0 x baseline if baseline was abnormal	>5.0 – 20.0 x ULN if baseline was normal; >5.0 – 20.0 x baseline if baseline was abnormal	> 20.0 x ULN if baseline was normal; > 20.0 x baseline if baseline was abnormal
Total Bilirubin	None	>1.5 – 3.0 ULN if baseline was normal; >1.5 – 3.0 x baseline if baseline was abnormal	>3.0 – 10.0 x ULN if baseline was normal; >3.0 – 10.0 x baseline if baseline was abnormal	> 10.0 x ULN if baseline was normal; > 10.0 x baseline if baseline was abnormal

Albumin	None	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening Death consequences; urgent intervention indicated
Creatine Kinase	None	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN
Sodium (Hypernatremia)	None	>150 - 155 mmol/L; intervention initiated	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences
Sodium (Hyponatremia)	None	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	<120 mmol/L; life-threatening consequences
Glucose (Hyperglycemia)	None	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	life-threatening consequences; urgent intervention indicated
Glucose (Hypoglycemia)	None	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures
LDH	None	>3 x ULN	-	-
Potassium (Hyperkalemia)	None	>5.5 - 6.0 mmol/L; intervention initiated	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences
Potassium (Hypokalemia)	None	Symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences

Creatinine	None	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
Urea* **(Blood Nitrogen Urea [BUN])**	None	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN

* Ranges for BUN taken from Division Of Microbiology And Infectious Diseases (DMID) as not available in CTCAE v5

Laboratory values and grading:

Table 6 Hematology Values and Grading

	Haematology (modified CTCAE v5)			
Variable	**Grade 1**	**Moderate Grade 2**	**Severe Grade 3**	**Potentially Life Threatening Grade 4**
Haemoglobin	None		< 8.0 g/dL; < 4.9 mmol/L; < 80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated
Leukocytes (WBC) [decreased]	None	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L
Leukocytes (WBC) [increased]	None	-	>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated
Lymphocytes [decreased]	None	<800 - 500/mm3; <0.8 - 0.5 x 10e9/L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L
Lymphocytes [increased]	None	>4000/mm3 - 20,000/mm3	>20,000/mm3	-

Neutrophils [decreased]	None	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L
Platelet count [decreased]	None		<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L