CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 19-0007
Study Title:
Exposure-Response Evaluation of IV Artesunate in Children with Severe Malaria

NCT05750459

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RESTRICTED

STUDY TITLE

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Form/Route:	IV injection
Indication Studied:	Severe Malaria
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	November 27, 2023
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This study was performed in compliance with Good Clinical Practice.

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LIST OF ABBREVIATIONS

ACT	Artemisinin Combination Therapy
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	Area Under Curve
BCS	Blantyre coma score
BUN	Blood Urea Nitrogen
C	Celsius
CI	Confidence Interval
C_{max}	Maximum Concentration
CROMS	Clinical Research Operations and Management Support
CSR	Clinical Study Report
DAIDS	Division of AIDS
DHA	Dihydroartemisinin
DMID	Division of Microbiology and Infectious Diseases
eCRF	Electronic Case Report Form
FDA	U.S. Food and Drug Administration
ICH	International Conference on Harmonisation
IDES	Internet Data Entry System
IDI	Infectious Diseases Institute
IDRC	Infectious Disease Research Collaboration
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MedDRA	Medical Dictionary for Regulatory Activities
N	Number (typically refers to participants)
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
PCE	Parasite Clearance Estimator
PCT_{50}	Parasite Clearance Half-life
PCT_{90}	Time to 90% Reduction in Parasitemia

List of Abbreviations *(continued)*

PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetics
PT	Preferred Term
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDCC	Statistical and Data Coordinating Center
SOC	System Organ Class
SOCS	Safety Oversight Committee Support
$t_{1/2}$	Half-life
T_{max}	Time to Maximum Concentration
WBC	White Blood Cell
WHO	World Health Organization
WWARN	WorldWide Antimalarial Resistance Network

1. PREFACE

The Statistical Analysis Plan (SAP) for "Exposure-Response Evaluation of IV Artesunate in Children with Severe Malaria" (DMID Protocol 19-0007) describes and expands upon the statistical information presented in the protocol.

This document describes all planned analyses, excluding planned pharmacokinetics (PK) analyses and planned analyses of exploratory outcome measures, and provides reasons and justifications for these analyses. Planned PK analyses will be described in a separate Pharmacometrics Analysis Plan, and exploratory analyses will be described in an addendum(s) to this SAP. This SAP also includes sample tables, listings, and figures planned for the final analyses, which will be presented in the interim Clinical Study Report (CSR). Regarding the final analyses and interim CSR, this SAP follows the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, as indicated in Topic E3 (Structure and Content of Clinical Study Reports), and more generally is consistent with Topic E8 (General Considerations for Clinical Trials) and Topic E9 (Statistical Principles for Clinical Trials). The structure and content of the SAP provides sufficient detail to meet the requirements identified by the FDA and ICH, and all work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association and the Royal Statistical Society for statistical practice.

This document contains four sections: (1) a review of the study design, (2) general statistical considerations, (3) comprehensive statistical analysis methods for efficacy and safety outcomes, and (4) a list of proposed tables, figures, and listings. Within the table, figure, and listing mock-ups (Appendices 1, 2, and 3), references to interim CSR sections are included. Any deviation from this SAP will be described and justified in protocol amendments and/or in the interim CSR, as appropriate. The reader of this SAP is encouraged to also review the study protocol for details on conduct of the study and the operational aspects of clinical assessments and the Pharmacometrics Analysis Plan for details on the planned population PK modeling analyses for the study.

2. INTRODUCTION

This is a phase 4, single-site, open-label study to evaluate the PK and pharmacodynamics (PD) of the standard of care IV artesunate in Ugandan children 6 months-14 years of age diagnosed with severe malaria according to standardized World Health Organization (WHO) criteria (any *P. falciparum* parasitemia and the presence of danger signs). Up to 100 participants living in or near Tororo District, Uganda will be enrolled and will receive the standard of care IV artesunate dosed according to weight per WHO guidelines for at least 24 hours. After at least 24 hours of IV artesunate and when they can tolerate oral antimalarial therapy, participants will transition to a 3-day course of oral artemisinin-combination therapy (ACT) per national guidelines.

The study is designed and powered to assess the relationship between Dihydroartemisinin (DHA) exposures after IV artesunate dosing and markers of physiologic dysfunction associated with severe malaria in Ugandan children. Current dosing regimens for IV artesunate are based on time to parasite clearance and not clinical endpoints related to physiologic changes that occur with parasitemia. Other measures of physiologic dysfunction, when quantified alone or in a weighted algorithmic score, may more accurately reflect successful treatment and may be more important to quantify and relate to pharmacologic dosing of antimalarial therapy. Biomarkers of physiologic dysfunction will be quantified at regular intervals, including temperature, blood pressure, serum lactate, serum glucose, total and direct bilirubin, serum bicarbonate levels, Blantyre Coma Score (BCS), creatinine and hemoglobin. Participants will be followed for approximately 6 months.

2.1. Purpose of the Analyses

This is a phase 4 open-label study to assess the PK and PD of the standard of care IV artesunate in Ugandan children 6 months-14 years of age diagnosed with severe malaria. The study is intended to inform dosing regimens of IV artesunate by evaluating the relationships between DHA exposures after IV artesunate and markers of physiologic dysfunction associated with severe malaria. This study will also secondarily and exploratorily assess the relationships between *P. falciparum* parasitemia and DHA exposures for comparison with historical studies and between DHA exposures and other clinically relevant measures of successful treatment, including time to hospital discharge and neurodevelopmental outcomes associated with severe malaria.

3. STUDY OBJECTIVES AND OUTCOME MEASURES

3.1. Study Objectives

3.1.1. Primary Study Objective

- To determine the relationship between DHA exposures following IV artesunate dosing and markers of physiologic dysfunction associated with severe malaria in Ugandan children

See Section 3.3 for the definition of severe malaria.

3.1.2. Secondary Study Objectives

- To determine the relationship between DHA exposures and time to hospital discharge
- To determine the relationship between DHA exposures and parasite clearance associated with treatment of severe malaria

3.1.3. Exploratory Study Objectives

- To determine the relationship between DHA exposures and neurodevelopmental outcomes associated with treatment of severe malaria outcomes and explore predictors that may affect this relationship
- To evaluate the role of parasite clearance as a mediator of the relationship between DHA exposures and markers of physiologic dysfunction associated with severe malaria
- To develop a score comprised of markers of physiologic dysfunction and describe its relationship to clinical outcomes
- To assess *P. falciparum* infections for markers of artemisinin resistance
- To store blood for future use, such as identification and characterization of parasite gene expression

3.2. Outcome Measures

3.2.1. Primary Outcome Measures

- DHA PK following the first dose of IV artesunate after enrollment, including C_{max}, area under the curve over hours 0-12 (AUC_{0-12}) and $t_{1/2}$ and time to C_{max} (T_{max})
- Physiologic measures such as temperature, blood pressure, venous serum lactate and bicarbonate levels, serum glucose, BCS, total and direct bilirubin, hemoglobin and creatinine

3.2.2. Secondary Outcome Measures

- Time to hospital discharge
- Measures of parasite clearance calculated from parasite density, as measured by thick blood smear such as parasite clearance $t_{1/2}$, parasite clearance by Day 2, and time to 90% reduction in parasitemia

3.2.3. Exploratory Outcome Measures

- Neurodevelopmental outcomes at 1 and 6 months after severe malaria diagnosis
- The proportion of the effect of DHA exposure on markers of physiologic dysfunction attributable to parasite clearance
- The association between the physiologic dysfunction score, resolution of symptoms, time to hospital discharge, and return to normal range in markers of physiologic dysfunction
- Presence of known K13 mutations associated with artemisinin resistance

3.3. Study Definitions and Derived Variables

Severe Malaria

Severe malaria is defined as presence or history of fever plus a positive blood film for *P. falciparum* malaria with at least one of the following symptoms and signs:

- Repeated convulsions: More than two episodes within 24 h
- Impaired consciousness: A Blantyre coma score < 3 in children
- Coma
- Hyperpyrexia: Axillary temperature ≥ 40˚C
- Respiratory distress: Acidotic breathing
- Inability to tolerate oral therapy and vomiting all oral intake
- Circulatory collapse or shock: Systolic blood pressure < 50 mmHg in children
- Spontaneous bleeding
- Hemoglobinuria: Hemoglobinuria presents as tea colored urine
- Jaundice
- Prostration: Extreme weakness so that the person is unable to sit, stand or walk without assistance
- Severe normocytic anaemia: Hemoglobin concentration < 5 g/dL
- Hypoglycemia: Blood or plasma glucose < 2.2 mmol/L (< 40 mg/dL)
- Renal impairment: Plasma or serum creatinine > 265 µmol/L
- Hyperparasitemia: *P. falciparum* parasitemia > 10%

Whether participants meet this definition of severe malaria will be evaluated in the process of determining enrollment eligibility. Participant history of fever, indication of positive blood film for *P. falciparum* malaria, and the presence of additional assessed symptoms and signs of severe malaria will be documented in the appropriate electronic case report form (eCRF). Only one additional sign or symptom of severe malaria must be present along with history of fever and positive blood film for *P. falciparum* malaria for a participant to meet the definition of severe malaria. Once a participant meets the definition of severe malaria, investigators may opt not to assess the participant for additional signs and symptoms. Reported symptoms and signs of severe malaria at enrollment will be summarized in Table 6.

Baseline

Baseline values of primary outcome measures of physiological dysfunction, laboratory parameters, and vital signs will be defined as the most recent measurement before first dose of IV artesunate. If these measurements are not collected before first dose, such as for participants who received IV artesunate before enrollment, baseline values will be defined as either the screening measurement or the earliest measurement after first dose of IV artesunate, whichever is closest to time of first dose of IV artesunate.

Weight-for-Age and Height-for-Age Z-Scores

Weight-for-age and height-for-age Z-scores at screening will be calculated for participants younger than 60 months using the R package "anthro" [1] which calculates Z-scores based on the WHO Child Growth Standards [2].

Pharmacokinetic Exposure Parameters

PK exposure parameters that will be used in the primary pharmacodynamics analysis include the following.

- **C_{max}**: C_{max} is defined as the maximum DHA concentration observed in plasma after the first on-study dose of IV artesunate over all PK sample concentrations.
- **AUC_{0-12}**: AUC_{0-12} is defined as the area under the concentration-time curve from first on-study dosing of IV artesunate (time 0 hours) to 12 hours post-first on-study dose of IV artesunate.
- **$t_{1/2}$**: $t_{1/2}$ is defined as the time post-first on-study dose of IV artesunate required for the DHA concentration to decrease by a factor of one half in the terminal phase.
- **T_{max}**: Time of maximum concentration (T_{max}) is defined as the time at which the C_{max} occurs.

Details of how these exposure parameters are calculated are provided in a separate Pharmacometrics Analysis Plan.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a phase 4, single-site, open-label PK and PD study of IV artesunate in Ugandan children 6 months-14 years of age diagnosed with severe malaria according to standardized WHO criteria (any *P. falciparum* parasitemia and the presence of danger signs). Up to 100 participants from the Tororo District will be enrolled and administered standard of care IV artesunate for initial treatment of malaria with doses assigned according to WHO guidelines based on child weight [3]. Children weighing <20 kg will receive 3.0 mg/kg/dose and children weighing ≥20 kg will receive 2.4 mg/kg/dose for at least 24 hours. After this initial 24 hours, patients will be evaluated clinically and assessed for ability for oral intake of antimalarials. If unable to take oral medication, IV artesunate will continue at 48 and 72 hours. Children able to transition to oral antimalarial therapy after a minimum of 24 hours or later will initiate a 3-day course of oral ACT per national guidelines.

Participants will be screened up to 24 hours before enrollment and may be enrolled up to 24 hours after their first dose of IV artesunate. Participants will be enrolled and receive their first on-study dose of IV artesunate on study Day 1. All dosing times will be relative to first dose, whether this first dose occurs before enrollment or is administered on-study. The follow-up period, which will include additional dosing of IV artesunate and/or oral ACT according to WHO and national guidelines, will be approximately six months with scheduled visits on Day 2, Day 3, Day 4, Day 5, Day 6, Day 7 (± 2), Day 14 (± 2), Day 28 (± 4), and Day 183 (± 14). If a participant is discharged before study Day 7, the required follow-up visits will be on Day 7 (± 2), Day 14 (± 2), Day 28 (± 4), and Day 183 (± 14). Safety data will be monitored throughout the study by the independent safety monitor (ISM).

The overall study design is presented in Table 1 and the schematic of the study design is presented in Figure 1.

4.2. Discussion of Study Design, Including the Choice of Control Groups

This study is designed to assess the PD of the standard of care regimen of IV artesunate for Ugandan children 6 months – 14 years of age diagnosed with severe malaria. All study participants will be dosed with IV artesunate and may be administered oral ACT based on standard WHO and national guidelines. There is no formal control planned for this study.

4.3. Selection of Study Population

This study will enroll up to 100 participants. Eligible participants for enrollment include children 6 months-14 years of age living in or near Tororo District, Uganda, diagnosed with severe malaria and who meet inclusion and exclusion criteria.

4.3.1. Inclusion Criteria

1. Children ages 6 months – 14 years at the time of severe malaria diagnosis, inclusive
2. Meet the case definition for severe malaria, per WHO standardized guidelines (see Section 3.3)
3. Parent/guardian willing to provide informed consent
4. Assent for children between 8 and 14 years who are conscious and otherwise able to provide assent, inclusive

4.3.2. Exclusion Criteria

1. Receipt of >24 hours of artemisinin therapy

4.3.3. Reasons for Withdrawal

The following criteria will be checked before IV artesunate administration:

- Grade 3 hypersensitivity to IV artesunate
- Severe side effects after IV artesunate administration

If either of these criteria become applicable before completion of study product administration regimen, then further IV artesunate will not be administrated but the participant will be followed for the duration of the study. If any criteria become applicable during the study but after IV artesunate administration regimen is completed, the participant will not be required to discontinue the study.

Additionally, a child between 8 and 14 years or a parent/guardian of a study participant may voluntarily withdraw a participant from continuing study follow-up upon request for any reason.

Every effort will be made to collect data on any participant discontinued from receipt of additional IV artesunate for any reason. If possible, participants who leave the study area will be traced and visited by clinical investigators to collect safety follow-up data.

4.3.4. Termination of Study

The trial may be suspended or terminated by DMID or by the principal investigator (PI) due to any major safety concern identified by the ISM. The trial may also be suspended by the institutional review boards (IRBs) if deemed necessary.

4.4. Treatments

4.4.1. Treatments Administered

Participants will receive the standard of care IV artesunate (Guilin Pharmaceutical Factory, Guangxi, People's Republic of China) for treatment of severe malaria per WHO guidelines, with dosage determined according to participant's weight. Additionally, participants who recover after at least 24 hours of IV artesunate administration and are able to transition to oral antimalarial therapy will initiate a 3-day course of oral artemether-lumefantrine, an artemisinin-combination therapy (ACT), per national guidelines.

4.4.2. Identity of Investigational Product(s)

Artesunate for Injection

Artesunate for injection that is WHO-prequalified, procured by the Infectious Diseases Institute (IDI), and kept under the proper storage conditions at the clinical sites will be used. Artesunate for injection appears as a white, crystalline powder.

Sodium Bicarbonate and Sodium Chloride

Artesunate powder will be dissolved first in sodium bicarbonate and then mixed with sodium chloride to form a solvent for injection that appears as a clear, colorless liquid.

Artesunate for injection will be reconstituted as follows:

- 30 mg vial of artesunate powder will be dissolved in 0.5 mL of 5% sodium bicarbonate (50 mg/mL solution for injection) to form sodium artesunate and then mixed with 2.5 mL of sodium chloride (9mg/ml for injection).
- 60 mg vial of artesunate powder will be dissolved in 1 mL of 5% sodium bicarbonate (50 mg/ml for injection) to form sodium artesunate and then mixed with 5 mL of sodium chloride (9mg/ml for injection).
- 120 mg vial of artesunate powder will be dissolved in 2 mL of 5% sodium bicarbonate to form sodium artesunate (50 mg/mL for injection) and then mixed with 10 mL of sodium chloride (9mg/ml for injection).

IV artesunate will be injected as a bolus into an indwelling IV cannula.

4.4.3. Method of Assigning Participants to Treatment Groups (Randomization)

This is a non-randomized study in which all participants, once consent is obtained and eligibility is confirmed, will receive IV artesunate. Dosage will be assigned based on participant weight. Enrollment will be done online using the enrollment module of the Statistical Data Coordinating Center's (SDCC) Internet Data Entry System (IDES).

4.4.4. Selection of Doses in the Study

Participants will receive the standard of care IV artesunate for initial treatment of severe malaria per WHO guidelines [3].

4.4.5. Selection and Timing of Dose for Each Participant

Children weighing <20 kg will receive IV artesunate at a dose of 3.0 mg/kg/dose and children weighing ≥20 kg will receive 2.4 mg/kg/dose at times 0, 12, and 24 hours relative to time of first dose.

After the initial 24 hours of IV artesunate administration, children will be assessed clinically and for ability to take oral medications. If a participant is unable to take oral medication at this assessment, study nursing staff will continue administering IV artesunate at 48 and 72 hours [3]. Children who recover and are able to transition to oral antimalarial therapy after receiving IV artesunate for a minimum of 24 hours will initiate a 3-day course of oral ACT per national guidelines. Participants will be given standardized instructions by a nurse on how to take the artemether-lumefantrine regimen according to standard practice.

Dosing of IV artesunate will not be adjusted due to toxicity or other reasons. If a participant experiences toxicity related to IV artesunate, then the investigators will follow Ministry of Health Uganda guidelines for alternative treatment of severe malaria.

4.4.6. Blinding

This is an open-label, unblinded study. Blinding (masking) is not needed.

4.4.7. Prior and Concomitant Therapy

At screening and enrollment and at subsequent study visits, investigators will question the participant's parent/guardian about any medication taken, including traditional, herbal, supplements and over-the-counter medicines. Concomitant medication, including any administered during the period starting from 7 days before enrollment and ending at the end of the study follow-up period will be recorded with trade name and/or generic name of the medication, medical indication, start and end dates of treatment.

The study team will procure a supply of medications for treatment of common concurrent ailments that patients with severe malaria may develop such as paracetamol for fever and antibiotics for sepsis, but these should not have any antimalarial effects. Antibiotics such as cotrimoxazole, which are known to have some antimalarial effects will not be administered for such ailments; however, participants taking concomitant medications that have some antimalarial effect for conditions in which the medication is standard of care may be continued, including but not limited to Septrin (cotrimoxazole) in HIV coinfected children. This stock of concomitant medications will ensure that study participants do not buy or receive additional medications outside the study or without the knowledge of the study physicians. The site PI will ensure that this additional study stock of concomitant medications is stored in a temperature-controlled area at the Infectious Disease Research Collaboration (IDRC) Pharmacy, with daily temperature monitoring. The Site PI is responsible for the distribution and disposition of the study stock of concomitant medications and has ultimate responsibility for accountability. The Site PI may delegate to the study coordinator responsibility for study concomitant drug accountability. The study coordinator will be responsible for maintaining complete records and documentation of study concomitant drug receipt, accountability, dispensation, temperature monitoring, storage conditions, and final disposition of drugs. All drugs, whether administered or not, will be documented on the appropriate study concomitant drug accountability record or dispensing log. Unused study drug will be retained as per DMID requirements.

4.4.8. Treatment Compliance

On-study IV artesunate will be administered under the supervision of investigative site personnel, and reconstitution time, infusion date and infusion time will be documented in the eCRF for all administrations. The number of doses of IV artesunate, if any, received before enrollment will also be documented in the eCRF. If able to transition to oral ACT, participants will be given standardized instructions by a nurse on how to take the artemether-lumefantrine regimen according to standard practice. If administration of ACT is not successful (e.g., due to vomiting, etc.), re-dosing may be attempted. If able to transition to oral ACT, the name of the oral ACT administered, administration date and time, and whether the administration was successful will be recorded on the eCRF for all administrations. If unable to transition to oral ACT, the reason the participant was unable to transition will be recorded on the eCRF. If any treatment administration was not performed according to guidelines, a protocol deviation will be submitted.

4.5. Pharmacodynamics, Pharmacokinetics, Immunogenicity, and Safety Variables

4.5.1. Pharmacodynamics Variables

The primary PD outcome response variables are temperature, blood pressure, serum lactate, serum bicarbonate, serum glucose, total and direct bilirubin, hemoglobin, creatinine, and BCS.

BCS is an ordinal scale designed to assess malarial coma in children. Eye movement, best motor response, and best verbal response are assessed and scored according to the evaluation criteria presented in the table below. The BCS is then calculated as the sum of the scores for these three assessments, with possible values of 0, 1, 2, 3, 4, or 5. Lower BCS values are indicative of impaired consciousness.

Assessment	Evaluation Criteria	Score
Eye Movement	Watches or follows – 1 Fails to watch or follow – 0	0 or 1
Best Motor Response	Localizes painful stimulus – 2 Withdraws limb from painful stimulus – 1 No response or inappropriate response – 0	0, 1, or 2
Best Verbal Response	Cries appropriately with pain, or, if verbal, speaks – 2 Moan or abnormal cry with pain – 1 No vocal response to pain – 0	0, 1, or 2
Total Score		**0, 1, 2, 3, 4, or 5**

Primary PD outcome response variables will be recorded at least daily for each patient while hospitalized and at scheduled follow-up visits according to the schedule in Table 2.

Dates and times of hospital admittance and discharge for each participant will be collected on the appropriate eCRF for calculation of time to hospital discharge. Time to hospital discharge is defined as the time in days from initial participant admission to the time of first discharge. Time to hospital discharge will be calculated using the actual dates and times of initial participant admission and first discharge and will be rounded to the nearest tenths place.

Thick and thin blood smears will be performed for quantification of *P. falciparum* parasitemia. Thick blood smears will be used for diagnosis and thin blood smears for typing the species of malaria parasites. Thick and thin blood smears for malaria diagnosis will be stained with Giemsa stain and read at 100X power light microscope. Parasites will be quantitated by counting the number of asexual *P. falciparum* parasites per 200 WBC using the patient's WBC count per µL of blood. Samples for malaria diagnostics will be collected according to the following schedule post-first on-study dose of IV artesunate in hours: 0 (0-2 hour acceptable window), 6 (4-8 hour acceptable window), 12 (10-14 hour acceptable window), 24 (22-26 hour acceptable window), 36 (34-38 hour acceptable window) and 48 (46-50 hour acceptable window), and then parasitemia should be measured at least every 24 hours through Study Day 5 and until clearance. Measures of parasite clearance will be calculated from quantified parasite density.

Total parasite clearance is defined as having a thick blood smear that is negative for *P. falciparum*, i.e. a thick blood smear for which there are no detectable *P. falciparum* parasites per 200 WBC. The date and time of total parasite clearance will be defined as the collection date and time of the first thick blood smear to meet the definition of parasite clearance. Total parasite clearance by Day 2 will be defined as the indicator of whether total parasite clearance occurred within the first 50 hours post-first dose of IV artesunate. Further details of how total parasite clearance by Day 2 is determined are given in Section 8.2.2.

Additionally, parasite clearance half-life (PCT_{50}) and time to 90% reduction in parasitemia (PCT_{90}) will be estimated using the WorldWide Antimalarial Resistance Network (WWARN) parasite clearance estimator (PCE) algorithm [4]. Details of how PCT_{50} and PCT_{90} are calculated are given in Section 8.2.2.

Additional variables that will be used in exploratory PD analyses will be defined in an addendum(s) to this SAP.

4.5.2. Pharmacokinetics Variables

Blood (plasma) samples will be collected for PK analysis and estimation of DHA exposure parameters. Approximately 10mLs (~2 mL/timepoint) of venous blood will be collected into fluoride-oxalate tubes from the arm opposite of that used for drug administration at pre- and 4 times after the first on-study dose in the hospital during different sampling windows. Sampling windows are defined as 0 (pre-dose), 0-1 hour, 1-2.5, 2.5-4, 4-6 and 6-24 hours post the first on-study dose of IV artesunate. Participants will be randomly assigned to either the 4-6 hour or the 6-24 hour collection timepoint via the Screening and Enrollment Log. All blood samples will be chilled immediately to prevent artesunate degradation by plasma esterases. Samples will be centrifuged within 30 minutes to minimize hemolysis, and aliquots of plasma will be stored at -80°C Plasma aliquots will be shipped intermittently to the DMID-CMS (i.e., Fisher BioServices) for storage before quantification. Backup samples will be stored at the IDI Core Laboratory. Plasma samples will be analyzed by a validated liquid chromatographic-tandem mass spectrometry (LC-MS/MS) assay with measurement ranging from 1 to 3500 ng/mL (lower limit of quantification [LLOQ] to upper limit of quantification [ULOQ]).

Concentrations of DHA will be measured and used in estimating DHA exposure parameters, including maximum concentration (C_{max}), area under the curve over hours 0-12 (AUC_{0-12}), half-life ($t_{1/2}$) and time to C_{max} (T_{max}).

4.5.3. Safety Variables

Although no safety outcome measures are planned for this trial, the following safety variables will be collected according to the schedule in Table 2:

- The type, incidence, relatedness, and severity of AEs and SAEs will be recorded after study drug administration through the final visit on Day 183 (± 14) or ET on the appropriate data collection form and eCRF.

  All AEs will be assessed by the PI or appropriate sub-investigator using the Division of AIDS (DAIDS) Table for Grading of Severity of Adults and Pediatric Adverse Events. For unsolicited events not included in the DAIDS Table, the following guidelines will be used to quantify intensity:

  - Mild (Grade 1) – events require minimal or no treatment and do not interfere with the participant's daily activities.
  - Moderate (Grade 2) – events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning and daily activities.
  - Severe (Grade 3) – events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

- Blood samples for biochemistry and hematology assays will be collected according to the schedule in Table 2.
  - Serum biochemistries will be examined on site using a COBAS C111 Analyzer. Biochemistry variables will include serum lactate, serum bicarbonate, creatinine, blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), direct bilirubin, total bilirubin, calcium, sodium, potassium, and glucose. Note that some biochemistry variables will be utilized in the PD analysis.

  - Full blood count will be measured with a Haematology – Mindray Shenzhen analyzer. Hematology variables will include hemoglobin, platelets, white blood cell (WBC) count, neutrophil count, and neutrophil %. Note that some hematology variables will be utilized in the PD analysis.

- Dipstick urinalysis will be performed according to the schedule in Table 2. A variety of analytes will be measured, including urine protein, urine glucose, pH, urobilinogen, bilirubin, nitrites, leukocyte esterase, ketones, and hemolyzed and non-hemolyzed blood.
- Vital signs will be collected approximately every 6 hours until parasite clearance, and will include axillary temperature, respiratory rate, systolic and diastolic blood pressure, and pulse.
- Complete physical examinations will be performed at Screening, Enrollment, and Day 2, Day 3, Day 4, Day 5, Day 6, Day 7 (±2), and Day 183 (±14). Targeted physical examinations will be performed as needed on Day 14 (±2) and Day 28 (±4) and at early termination visits.

5. SAMPLE SIZE CONSIDERATIONS

A maximum of 100 participants will be enrolled in the study. This maximum of 100 participants would provide sufficient sample size to achieve precision on PK parameters following the FDA pediatric precision criteria for conducting PK studies (achieving a 95% confidence interval (CI) within 60% and 140% of the geometric mean).

Simulations in R version 3.4.2 were used to explore power to detect simple linear relationships between exposure and response in the analysis of the primary objective with the planned sample size. The primary objective of this study is to determine the relationship between DHA exposures after IV dosing and markers of physiologic dysfunction associated with severe malaria. This objective can be framed as a series of statistical hypothesis tests, each evaluating the effect of the DHA exposure parameter on the marker of physiologic dysfunction measured at a specific timepoint, adjusting for covariates. The null hypothesis is that there is no effect of exposure on response, and the alternative hypothesis is that there is an effect.

Because the primary objective of this study encompasses multiple exposure and response variables, and the response variables are measured at multiple timepoints, there are multiple exposure-response relationships that are of interest (one for each unique combination of exposure variable, response variable, and timepoint). Thus, there is a need to control type I error. As this study is exploratory (hypothesis-generating) rather than confirmatory, Benjamini-Hochberg procedure is used to control the false discovery rate at 0.05 [Table 5].

For a multiple hypothesis test, average power is defined as the proportion of false null hypotheses correctly rejected [6]. Table 3 provides the average power computed from 5000 simulations, varying the following quantities:

- Number of total statistical tests, representing the number of combinations of exposure variable, response variable, and timepoint to be tested in support of the primary objective
- Value of R^2 for the true, non-null exposure-response relationships
- Proportion of tests with true, non-null exposure-response relationships with the specified R^2
- Sample size

Sample sizes considered in these simulations included 100 or 80 participants. These original simulation results indicate that the target sample size of 100 participants provides >90% power for detecting simple linear relationships for 24 or 48 tests with an underlying R^2 of at least 0.2, if the proportion of non-null relationships among those tested is at least 5%. If at least 80 participants complete follow-up for the primary outcome measure, power for the same scenario is approximately 88%.

However, at the end of the planned enrollment period of 6 months, only 46 participants had been enrolled in the study. Further simulations were performed under the same settings described above with smaller sample sizes considered. These results are also provided in Table 3. These simulation results indicate that if at least 70 participants complete follow-up for the primary outcome measure, power for detecting simple linear relationships for 24 or 48 tests with an underlying R^2 of at least 0.2, if the proportion of non-null relationships among those tested is at least 5%, is $\geq$80%.

Additionally, given that there are eleven markers of physiological dysfunction, four exposure parameters, and four timepoints (see Section 8.1) of interest, the total number of possible hypothesis tests for all of these relationships is 176. Further simulations were performed under the same settings described above with 176 tests and sample sizes of 75, 80, or 90 participants considered. These results are also provided in Table 3. These simulation results indicate that if at least 75 participants complete follow-up for the primary outcome

measure, power for detecting simple linear relationships for 176 tests with an underlying R^2 of at least 0.2, if the proportion of non-null relationships among those tested is at least 5%, is greater than 80%.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

Unless otherwise specified, continuous variables will be summarized by the following descriptive statistics: the number of participants with non-missing data included in the analysis (n), mean, standard deviation (SD), median, minimum value (Min), and maximum value (Max). Summary statistics for discrete data will include frequencies and proportions.

6.2. Timing of Analyses

The primary data analysis will occur after all primary and secondary outcome measure data is collected, with time of hospital discharge response outcome measures censored at Day 183 (±14). Results of this primary data analysis will be available for public release. Results of the primary and secondary data analyses will be included in an interim CSR once all primary and secondary study outcome measures are reached at Day 183 (±14). Available results of exploratory analyses may be included in the interim CSR provided the SAP addendum including these analyses is finalized at the time of the interim CSR, and all other exploratory analyses will be included in a CSR addendum(s).

6.3. Analysis Populations

All analysis populations to be used in the final analysis are described in this section. The primary analysis will be performed using the PD Analysis Population. Estimation of population PK parameters included in the primary analysis will be performed using the Population PK Analysis Population. Other analyses may use the Safety Population, PD Analysis Population, or Population PK Analysis Population.

6.3.1. Safety Population

The Safety Population will include all participants who received at least one dose of IV artesunate.

6.3.2. Population Pharmacokinetic Analysis Population

The Population PK Analysis Population will consist of all participants who received at least one on-study dose of IV artesunate and for whom DHA concentration data are available.

6.3.3. Pharmacodynamic Analysis Population

The PD Analysis Population will include all participants meeting the definition of severe malaria at enrollment for which exposure parameters can be estimated from the final population PK model and for which post-baseline response data are available.

6.4. Covariates and Subgroups

Sensitivity analyses for the primary and both secondary analysis outcome measures will be conducted to assess the effect of receipt of IV artesunate or other artemisinin-based therapies before enrollment on results of the primary and secondary analyses. This sensitivity analysis will be conducted on the subset of the PD Analysis Population who did not receive any IV artesunate or other artemisinin-based therapy before enrollment.

Otherwise, the protocol does not define any formal subgroup analyses, and the study is not adequately powered to perform subgroup analyses. However, primary and secondary analyses will be adjusted for

possible confounding factors. The following baseline covariates will be considered for inclusion in all primary and secondary analyses:

- Sex (male or female),
- Weight group (<20 kg or ≥20 kg),
- Receipt of IV artesunate or artemisinin-based therapy before study enrollment (received no IV artesunate or artemisinin-based therapy before study enrollment or received any IV artesunate or artemisinin-based therapy before study enrollment), and
- Receipt of antimalarial concomitant medications or other concomitant medications with antimalarial properties (received no such concomitant medications or received any such concomitant medications).

Receipt of oral ACT post-enrollment (received no oral ACT or received any oral ACT) will also be considered for inclusion as a covariate in primary analyses at timepoints at which there are participants receiving oral ACT and in secondary analyses. The number of doses of oral ACT received may also be considered for inclusion in these analyses.

Inclusion of covariates in each primary and secondary analysis will be informed by exploratory boxplots and stacked bar graphs of response variables by covariate values, and by timepoint when appropriate (see Section 8 for further details).

6.5. Missing Data

Every effort will be made to minimize missing data and collect all outcome measures specified in this protocol. Participants who discontinue treatment will be followed after treatment discontinuation for collection of all scheduled follow-up data with their consent.

Missing dose data (dosing time, or dosing date) will be imputed to maximize the inclusion of observations subsequent to doses with missing information. Missing dosing time will be imputed if the dose date and amount are available:

- If dosing times are missing, the pre-dose sample time combined with the dose number and dosing timeline will be used to determine the pre-study and on-study dosing times.
- Dosing time will be imputed as the mean of the time from pre-dose draw to dosing for those not missing the given sampling window.

Missing covariate data for analyses that incorporate confounding covariate variables will be handled in the following manner. The covariate will be excluded from the analysis if more than 20% of the covariate values are missing. Baseline individual covariates, including sex and weight group, will be determined from the Day 1 visit. If an individual's baseline covariate is missing at the Day 1 visit, the baseline covariate value will be taken from either the pre-study (screening) visit or from the earliest post-dose visit, whichever is closest to the baseline visit. Receipt of IV artesunate or artemisinin-based therapy before enrollment will be determined from treatment administration records with dates and times before the first on-study dose and/or concomitant medication records with dates up to the Day 1 visit. Receipt of oral ACT, which has planned collection occurring after baseline, will be determined from all visits up to and including the visit at which the analysis timepoint occurs.

No imputation will be performed for missing primary or secondary PD outcome response variables. Rather, only participants in the PD Analysis Population with the PD outcome response variable measured at the timepoint of interest will be included in PD analyses of that PD outcome response variable measured at the timepoint of interest.

Please refer to the Pharmacometrics Analysis Plan for details pertaining to methods for missing concentration data and other missing data that would affect the PK analysis.

6.6. Interim Analyses and Data Monitoring

An Independent Safety Monitor (ISM) will be utilized for study. The ISM is a physician with relevant expertise whose primary responsibility is to provide to DMID an independent safety assessment in a timely fashion. Participation is for the duration of the DMID study and is a voluntary position that does not receive payment.

The ISM is near the study site and has the authority and ability to readily access study participant records in real time. The ISM may be a member of the participating institution's staff but preferably be from a different organizational group within the institution. The ISM should not be in a direct supervisory relationship with the investigator and have no direct involvement in the conduct of the study.

The ISM will receive reports of SAEs from the site investigator and will be notified by email when the Infectious Diseases Institute (IDI) Research Ethics Committee (REC) and DMID are notified of the SAE. The ISM will then evaluate the SAE and report their clinical assessment to the REC and DMID, through DMID-Clinical Research Operations and Management Support (CROMS) Safety Oversight Committee Support (SOCS) and via email. The ISM will also communicate with the investigator at the participating site as needed, review additional safety related events at the request of the REC and DMID, and provide additional information to REC and DMID by teleconference as requested.

Results of the primary and secondary data analyses will be included in an interim CSR once the primary study outcome measure is reached at Day 183 (±14). No other formal interim analyses are planned for this study.

6.7. Multicenter Studies

This is a single-site study.

6.8. Multiple Comparisons/Multiplicity

The primary analysis involves assessing multiple exposure-response relationships measured at multiple timepoints, which can be framed as a series of hypothesis tests to evaluate these potential relationships. To accommodate the multiple hypothesis tests in the primary analysis, the set of p-values corresponding to tests of the effect of exposure on response at each timepoint will be adjusted using the Benjamini-Hochberg procedure to preserve the false discovery rate for the primary outcome at 0.05. There are no adjustments for multiple comparisons planned for secondary or exploratory analyses.

7. STUDY PARTICIPANTS

7.1. Disposition of Participants

Table 9 will present a summary of the reasons participants were screened but not enrolled. Enrolled participants who were ineligible for inclusion in analysis populations will be summarized by reason for participant exclusion in Table 7. A listing of participants that received investigational product will be provided in Listing 1. Individual listings of participants who were excluded from the Safety Population, the Population PK Analysis Population, or the PD Analysis Population will be listed (Listing 5).

The disposition of participants in the study will be tabulated in Table 5. The table shows the total number of participants screened, enrolled, receiving IV artesunate or other artemisinin-based therapy before enrollment, receiving IV artesunate before enrollment, receiving on-study IV artesunate, receiving oral artemisinin-combination therapy, discharged from the hospital, having at least one measurable DHA concentration, having at least one estimable PK exposure parameter, having post-baseline PD response data collected, completing all blood draws, and completing the study. A flowchart showing the disposition of study participants will be included (Figure 1). This figure will present the number of participants screened, enrolled, lost to follow-up, and analyzed. Additionally, the number of participants with reported assessed signs and symptoms contributing to the definition of severe malaria at enrollment will be presented in Table 6. A summary of dosing of IV artesunate and on-study oral ACT is presented in Table 8. A listing of participants who discontinued treatment or terminated early from study follow-up with the reason for discontinuation or termination will be included in Listing 2. Listings of the actual dosages of IV artesunate and on-study oral ACT administered for each participant are provided in Listing 8 and Listing 9, respectively.

7.2. Protocol Deviations

A summary of participant-specific protocol deviations will be presented by deviation category and deviation type for all enrolled participants in Table 4. Deviations will be reviewed by the Sponsor for possible participant exclusion from the per protocol population and will be classified as either major or minor. This table will provide both the number of participants and the number of deviations for each deviation category and deviation type. All participant-specific protocol deviations and non-participant-specific protocol deviations will be listed in Listing 3 and Listing 4, respectively.

8. PHARMACODYNAMICS EVALUATION

All model-based primary and secondary PD analyses will adjust for a subset of the following covariates: sex, weight group (<20 kg or ≥20 kg), receipt of IV artesunate or artemisinin-based therapy before enrollment, and receipt of concomitant medications. Where appropriate, primary and secondary PD analyses may also adjust for receipt of oral ACT. Exploratory boxplots and stacked bar graphs of response variables by covariate values, and by timepoint when appropriate, will inform covariate selection for each model.

Primary and secondary analyses will be performed using the Pharmacodynamics Analysis Population, and a sensitivity analysis will be performed for each primary and secondary analysis including only participants who did not receive IV artesunate or other artemisinin-based therapy before enrollment.

8.1. Primary Pharmacodynamics Analysis

The primary PD analysis will be performed to assess the relationship between DHA PK exposure parameters, including $AUC_{0\text{-}12}$, C_{max}, $t_{1/2}$, and T_{max}, and markers of physiological dysfunction known to be associated with severe malaria. These markers of physiological dysfunction measured at planned follow-up times will be the primary outcome response variables, and will include temperature, systolic and diastolic blood pressure, serum lactate, serum bicarbonate, serum glucose, BCS, total and direct bilirubin, hemoglobin, and creatinine. Values of $AUC_{0\text{-}12}$, C_{max}, $t_{1/2}$, and T_{max} for each participant will be treated as fixed in all PD analyses. Details of the calculation of $AUC_{0\text{-}12}$, C_{max}, T_{max}, and $t_{1/2}$ can be found in the Pharmacometrics Analysis Plan.

Planned follow-up times at which the relationships between each marker of physiological dysfunction and exposure parameter will be assessed include:

- Approximately 24 hours post-first dose, for which the most recent measurement of each physiological dysfunction variable before 24 hours post-first dose will be utilized as the response;
- Approximately 48 hours post-first dose, for which the most recent measurement of each physiological dysfunction variable before 48 hours post-first dose will be utilized as the response;
- Time of completion of the final planned dose of IV artesunate, for which the first measurement of each physiological dysfunction variable after completion of the final planned dose of IV artesunate will be utilized as the response; and
- Time of first hospital discharge, for which the most recent measurement of each physiological dysfunction variable before the time of first hospital discharge will be used as the response.

Exploratory scatterplots of each continuous primary outcome response variable will be presented by exposure parameter and timepoint beginning in Figure 2 and continuing through Figure 11 for the PD Analysis Population. Exploratory box plots of BCS will be presented by exposure parameter and timepoint in Figure 12. Summary statistics for each continuous marker of physiological dysfunction and its change from baseline will also be presented by parameter and timepoint in Table 13 for participants in the PD Analysis Population and in Table 14 for the subset of the PD Analysis Population with no IV artesunate or other artemisinin-based therapy before enrollment. Proportions of participants with each BCS value will be presented by timepoint in Table 15 for participants in the PD Analysis Population and in Table 16 for the subset of the PD Analysis Population with no IV artesunate or other artemisinin-based therapy before enrollment.

Regression models will be fit to characterize the relationship between each primary outcome response and each exposure parameter at each of the above timepoints, controlling for covariates (given in Section 6.4). Note that receipt of oral ACT will only be considered for inclusion in analyses of the primary outcome

response variables at time of first hospital discharge. Exploratory boxplots of each continuous primary outcome response variable will be presented by covariate and timepoint beginning in Figure 13 and continuing through Figure 22. Exploratory stacked bar charts of BCS will be presented by covariate and timepoint in Figure 23. These exploratory plots, presented for the PD Analysis Population, will be used to inform what subset of covariates will be included in each model.

Proportional odds mixed effects models will be used to assess the relationship between each exposure parameter and ordinal BCS at each timepoint. The proportional odds mixed effect model for BCS at any one of the four timepoints considered is defined as follows:

$$logit\{\tau_k(P_i, t_i, BCS_{0,i}, X_i)\} = \alpha_k + \beta_1 P_i + \beta_2 t_i + \eta^T X_i + BCS_{0,i} + b_i.$$

In the above model, $\tau_k(P_i, \boldsymbol{t}_i, BCS_{0,i}, X_i) = \Pr(BCS \leq k | P_i, \boldsymbol{t}_i, BCS_{0,i}, X_i)$ represents the cumulative probability that BCS will be less than or equal to $k \in \{0,1,2,3,4,5\}$ given the covariates. The BCS level-specific intercept is represented by α_k, P_i is the exposure parameter value for the ith participant, t_j is the actual response measurement time post-first dose, $BCS_{0,i}$ is the baseline BCS for the ith participant, and X_i are the values for the ith participant of the additional covariates included in the model. The β_1, β_2, and η are model parameters associated with the above covariates. The term b_i represents a participant-specific random intercept, where it is assumed that b_i follow a normal distribution with mean zero and nonzero variance. For 24 hours and 48 hours post-first dose timepoints, t_i will be measured in hours post-first dose rounded to the nearest tenths place. For time of completion of the final planned dose of IV artesunate and time of first hospital discharge timepoints, t_i will be measured in days post-first dose rounded to the nearest tenths place.

The following pseudocode will be used to fit the proportional odds mixed effects models for BCS and to extract the p-value for the exposure model parameter.

```
/* Proportional odds model fit and output p-values */
proc glimmix data=dataset(where=(population=p and response=r));
*catvar = any categorical covariates included in the model;
*refvalues = the value(s) to be used as the reference level for categorical
covariate(s);
class catvar(ref=refvalues);
*baseresp = response at baseline;
*othercovars = any other covariates (including those specified in the class statement)
included in the model;
model resp = baseresp exposure time othercovars / dist=multinomial link=cumlogit;
random intercept;
by timepoint;
ods output Tests3=tests3;
run;
data tests3; set tests3(where=(effect='EXPOSURE'));
rename ProbF=pval;
run;
```

For the continuous primary outcome response variables, if model assumptions hold, Emax models will be fit for each primary outcome effect and each exposure parameter at each timepoint. The Emax model for primary outcome effect, E_i, is defined as follows:

$$E_i = E_{0,i} + \frac{E_{max} \times {P_i}^{\gamma}}{{EC_{50}}^{\gamma} + {P_i}^{\gamma}} + e_i,$$

where E_i represents the given response outcome measure for the ith participant at the given timepoint, $E_{0,i}$ is the baseline response outcome effect for participant i, E_{max} is the maximum effect, EC_{50} is the exposure at half-maximal effect, P_i is the exposure parameter value for participant i, γ is the Hill parameter [7, 8] or slope coefficient, and e_i are the measurement errors for participant i. These measurement errors are assumed to be independent and normally distributed with mean zero and nonzero variance. E_{max}, EC_{50}, and $E_{0,i}$ may be modeled with fixed covariate effects, i.e., $E_{max} \sim X_i$ where X_i are the subset of covariates included for E_{max}. The subset of covariates included may differ between E_{max}, EC_{50}, and $E_{0,i}$. Alternatively, E_{max}, EC_{50}, and $E_{0,i}$ may be considered random effects if fixed effects are not included. For example, $E_{0,i}$ may also be modeled instead with a random effect, whereby an additive random component with mean-zero normal distribution will be assumed for $E_{0,i}$ such that $E_{0,i} = E_0 + b_{1i}$, where E_0, is the population-level quantity and b_{1i} are independently normally distributed random effects with mean zero and nonzero variance. Model selection will proceed in a forward direction from least complex model (no fixed covariates included on any of the above parameters) to more complex. Estimated log-likelihood statistics or other convergence criteria will be used to assist in Emax model selection.

If Emax models are fit for a primary outcome effect, the following pseudocode will be used for model fitting and to extract p-values for the exposure model parameter

```
### Fitting Emax Model in R ###
library(rstanemax)
#load any other packages needed to run Emax model fit in parallel, for example:
library(rstudioapi)
dataset <- data[which(data$timepoint==t & data$population==p & data$response==r),]
## Emax Model Fit Using Stan ##
model_fit <- stan_emax(
formula = resp ~ exposure, data = dataset,
# include param.cov if any parameter is fitted on named fixed covariate(s)
# omit parameter arguments from param.cov if being treated as random
param.cov = list(emax = "covar_emax", ec50= "covar_ec50", e0 = "covar_e0"),
# cores option included to run in parallel
# chains will be set to a constant low integer (1, 2, or 3) multiple of the number of
cores, which will be the same for all Emax models fit (e.g., chains = 8)
chains = XX, iter = 2000, cores = parallel::detectCores(logical=FALSE), seed = SEED#
)
print(model_fit)

## Extract Posterior Draws of Model Parameters ##
fit_param <- extract_param(model_fit)

## Mean and Standard Deviation of EC50, for example ##
mean(fit_param$ec50)
sd(fit_param$ec50)
```

Exploratory scatterplots for the response outcome measure at each timepoint given the exposure measure will be utilized to assess whether a log-transformation of the response variable may be necessary. These exploratory scatterplots as well as goodness of fit diagnostic plots will be used to assess reasonableness of model assumptions. If Emax model assumptions seem unlikely to hold, linear or polynomial models will be considered as informed by the exploratory scatterplots.

A linear model for primary outcome effect, E_i, is defined as follows:

$$E_i = E_{0,i} + \beta P_i + \eta^T X_i + e_i,$$

where E_i represents the given response outcome measure for the ith participant at the given timepoint, $E_{0,i}$ is the baseline response outcome measure for participant i, P_i is the exposure parameter value for participant i, X_i are the values of the additional covariates included in the model, and e_i are the measurement errors for participant i. These measurement errors are assumed to be independent and normally distributed with mean zero and nonzero variance. In addition to the covariates listed in Section 6.4, actual time of response measurement post-first dose will also be considered for inclusion in the model.

If linear models are fit for a primary outcome effect, the following pseudocode will be used for model fitting and to extract p-values for the exposure model parameter.

```
/* Linear model fit and output p-values */
proc glm data=dataset(where=(population=p and response=r));
*catvar = any categorical covariates included in the model;
*refvalues = the value(s) to be used as the reference level for categorical
covariate(s);
class catvar(ref=refvalues);
*baseresp = response at baseline;
*othercovars = any other covariates (including those specified in the class statement)
included in the model;
model resp = baseresp exposure othercovars / noint ss3;
by timepoint;
ods output ModelAnova=tests3;
run;
data tests3; set tests3(where=(source='EXPOSURE'));
rename ProbF=pval;
run;
```

A polynomial model for primary outcome effect, E_i, is defined as follows:

$$E_i = E_{0,i} + \sum_{j=1}^{a} \beta_j P_i^j + \eta^T X_i + e_i,$$

where E_i represents the given response outcome measure for the ith participant at the given timepoint, $E_{0,i}$ is the baseline response outcome measure for participant i, P_i is the exposure parameter value for participant i, a is the highest order exponent included in the model with its selection informed by exploratory data plots, X_i are the values of the additional covariates included in the model, and e_i are the measurement errors for participant i. These measurement errors are assumed to be independent and normally distributed with mean zero and nonzero variance. Again, in addition to the covariates listed in Section 6.4, actual time of response measurement post-first dose will also be considered for inclusion in the model. Estimated log-likelihood statistics or other model fit statistics may be used to assist in covariate selection for linear or polynomial models.

If linear models are fit for a primary outcome effect, the following pseudocode will be used for model fitting and to extract p-values for the exposure model parameter.

```
/* Polynomial model fit and output p-values */
data dataset; set dataset;
```

```
*exposure^j from 2 up to a will be calculated;
exposurea=exposure**a;
exposurea_1=exposure**(a-1);…
run;
proc glm data=dataset(where=(population=p and response=r));
*catvar = any categorical covariates included in the model;
*refvalues = the value(s) to be used as the reference level for categorical
covariate(s);
class catvar(ref=refvalues);
*exposure… exposurea: exposure raised to the powers 1 up to a will be included as
covariates in the model;
*baseresp = response at baseline;
*othercovars = any other covariates (including those specified in the class statement)
included in the model;
model resp = baseresp exposure… exposurea othercovars / noint ss3;
by timepoint;
ods output ModelAnova=tests3;
run;
data tests3; set tests3(where=(source='exposurea'));
rename ProbF=pval;
run;
```

Model assumptions, including normality of participant-specific measurement errors, will be assessed via exploratory scatterplots and residual plots, which will also inform whether a log-transformation of the response variable may be necessary. In the event that model assumptions are not met, additional models or transformations of the response variables will be assessed, and any changes from the analyses described in this SAP will be fully described in the interim CSR.

Models fit for the sensitivity analysis of the primary analysis using the subset of the PD Analysis Population who did not receive IV artesunate or other artemisinin-based therapy before enrollment will be of the same form as those fit in the primary analysis for the respective PD response variable, exposure parameter, and timepoint. Covariates included in each model fit for this sensitivity analysis will be those included in the respective primary analysis model with effects that remain estimable in the sensitivity analysis subset. The type of model, covariates included, and any transformations applied to the response outcome measure for each final primary analysis model will be presented in Table 19 by marker of physiological dysfunction, PK exposure parameter, and timepoint for the PD Analysis Population and the subset of the PD Analysis Population that did not receive IV artesunate or other artemisinin-based therapy before enrollment.

For each model fit, the relationship between the response outcome measure at the given timepoint and the exposure measure will be assessed via a hypothesis test. If an Emax model is fit for the response outcome measure and exposure parameter, the following null hypothesis will be tested:

$$H_0: EC_{50} = 0.$$

Post-hoc distributional assessments will be performed for EC_{50}, and EC_{50} will be transformed if necessary to have an approximately normal distribution for inference. Possible transformations may include log-transformations. Point estimates and CIs for EC_{50} will be presented after their transformation back to their original scale. If any transformation is applied for the EC_{50}, the transformation will be presented in Table 19.

Otherwise, if a linear model is fit for the response outcome measure and exposure parameter, the following null hypothesis will be tested:

$$H_0: \beta = 0.$$

Furthermore, if a polynomial model is fit for the response outcome measure and exposure parameter, then the following null hypothesis will be tested:

$$H_0: \beta_a = 0.$$

To adjust for multiple testing, the set of p-values for the exposure effect parameters, which correspond to tests of the effect of exposure on response at each timepoint, will be adjusted using the Benjamini-Hochberg procedure to preserve the false discovery rate for the primary outcome at 0.05 in both the primary analysis and the sensitivity analysis of the primary outcome measures. The corresponding point estimates of the parameters being tested will be presented with 95% CIs and p-values for each marker of physiological dysfunction and exposure parameter in Table 17 for participants in the PD Analysis Population and in Table 18 for the subset of the PD Analysis Population with no IV artesunate or other artemisinin-based therapy before enrollment. Significant p-values after the Benjamini-Hochberg procedure has been performed will be indicated.

Individual trend plots for each marker of physiological dysfunction over time will be presented by sex and weight group beginning in Figure 24 and continuing through Figure 34. Graphical displays of each marker of physiological dysfunction by exposure will be presented by planned timepoint beginning in Figure 35 and continuing through Figure 210 for participants in the PD Analysis population and in the subset of the PD Analysis Population that did not receive any IV artesunate or other artemisinin-based therapy before enrollment. These figures will show individual measurements alongside model estimates.

Individual listings of BCS assessments will be presented in Listing 11. Individual listings of temperature are included in Listing 20. Individual listings of biochemistry and hematology markers of physiological dysfunction are given in Listing 17 and Listing 18, respectively. Individual listings of exposure parameters by weight group will be presented in Listing 13.

8.2. Secondary Pharmacodynamics Analyses

8.2.1. Time to Hospital Discharge

We will perform secondary PD analyses to assess the relationship between measures of DHA exposure, including $AUC_{0\text{-}12}$, C_{max}, $t_{1/2}$ and T_{max}, and time to first hospital discharge. We will utilize Cox proportional hazards regression models for time to first hospital discharge and each DHA exposure parameter. Covariate selection (see Section 6.4 for a list of covariates that will be considered) for these models will be aided by exploratory boxplots of time to first hospital discharge by covariate, presented in Figure 211 for participants in the PD Analysis Population.

The Cox proportional hazards regression model for time to hospital discharge and $AUC_{0\text{-}12}$, for example, would have cumulative hazard function

$$\Lambda(T_{HD}|AUC_{0-12,i}, X_i) = \lambda(T_{HD}) \times \exp\{\beta \mathrm{AUC}_{0-12,\mathrm{i}} + \eta^{\mathrm{T}} \mathrm{X}_{\mathrm{i}}\},$$

where T_{HD} represents time to hospital discharge, $\lambda(T_{HD})$ is the baseline hazard function, X_i are the additional covariates included in the model, β is the expected change in the log hazard ratio relative to a one unit change in AUC_{0-12} holding the other covariates constant, and η is the vector of expected changes in the log hazard ratio comparing levels of the included covariates holding AUC_{0-12} and other covariates constant. The Cox

proportional cumulative hazard function for time to first hospital discharge and C_{max}, $t_{1/2}$, or T_{max} would be of the same form.

Models fit for the sensitivity analysis of the secondary analysis for time to hospital discharge using the subset of the PD Analysis Population who did not receive IV artesunate or other artemisinin-based therapy before enrollment will be of the same form as those fit in the secondary analysis for time to hospital discharge and the respective exposure parameter. Covariates included in each model fit for this sensitivity analysis will be those included in the respective secondary analysis model with effects that remain estimable in the sensitivity analysis subset. The type of model and covariates included for each analysis model will be presented in Table 22 by PK exposure parameter for the PD Analysis Population and the subset of the PD Analysis Population that did not receive IV artesunate or other artemisinin-based therapy before enrollment.

Summary statistics, including mean, SD, median, minimum, and maximum, for time to hospital discharge will be presented in Table 20. Hazard ratios for time to hospital discharge corresponding to a one-unit change in exposure parameters adjusted for other covariates included in the models will be presented with corresponding 95% confidence intervals in Table 21. Forest plots of hazard ratios and 95% CIs by exposure parameter will be presented for time to hospital discharge in Figure 215.

The following pseudocode will be used to fit a Cox proportional hazard model for time to hospital discharge and estimate the hazard ratio for a one-unit increase in exposure along with its Wald confidence interval after adjusting for other covariates.

```
/* Fit Cox PH Model and Estimate Hazard Ratio for Exposure Parameter */
proc phreg data=dataset(where=(population=p));
*catvars = any categorical covariates included in the model;
*refvalues = the value(s) to be used as the reference level for categorical
covariate(s);
class catvars(ref=refvalues);
*othercovars = any other covariates (including those specified in the class statement)
included in the model;
model dischtime * censoringvar(1) = exposure othercovars / ties=breslow;
by timepoint;
hazardratio exposure / cl=wald;
ods output hazardratios = hrest;
run;
```

8.2.2. Parasite Clearance

We will additionally perform secondary analyses to assess the relationship between measures of DHA exposure, again including $AUC_{0\text{-}12}$, C_{max}, $t_{1/2}$ and T_{max}, and measures of parasitemia clearance. The outcome response variables for these analyses are measures of parasite clearance calculated from parasite density, as measured by thick blood smear, including parasite clearance half-life (PCT_{50}), total parasite clearance by Day 2, and time to 90% reduction in parasitemia (PCT_{90}).

PCT_{50} and PCT_{90} will be estimated using the WWARN PCE algorithm [4]. PCT_{50} is the time from first on-study dose needed for parasitemia to be reduced by half during the log-linear phase of parasite clearance, and can be calculated by $PCT_{50} = \log_e(2)/K,$ where K is the first-order clearance rate constant. PCT_{90} is the time from first on-study dose needed for parasitemia to be reduced by 90% during the log-linear phase of parasite clearance, and can be calculated by $PCT_{90} = \log_e(10)/K$. The first-order clearance rate constant K is typically equal to the negative slope of the log-parasitemia-time linear relationship during the log-linear phase of parasite clearance.

PCT_{50} and PCT_{90} will be estimated using the parasite density per µL. The parasite density per µL will be calculated using the formula: Number of parasites per 200 WBCs × 40 = asexual parasites /µL. The clearance rate constant K will be calculated using the following steps according to the WWARN PCE algorithm [4] for each participant separately.

1. Perform data cleaning. Data cleaning will proceed in order as follows:
    a. Removal of data from recurrences of parasitemia including any measurements after 7 days, measurements after a time when 2 measurements are >24 h apart, and data after the last measured zero parasitemia if the positive measurements before and after this measurement are separated by >24 h are removed.
    b. Removal of all trailing zeros after the last nonzero parasitemia except the first zero.
    c. Removal of repeated parasitemia measurements <100/µL and data that fall between them.
    d. Replacement of the first zero parasitemia measurement directly after the last positive parasitemia with the limit of detection (40 /µL [4]).
    e. Removal of extreme values outside of the range $(0, 3 \times 10^6)$ or measurements with times below zero.
    f. Removal of outliers based on the normalized slope between each set of neighboring measurements, calculated by dividing the rate of change between each set of 2 consecutive measurements by the average rate of change over the whole profile, according to the following rules:
        i. Remove data points in the first 12 hours associated with the condition: $NormSlope_i < -20$ and $NormSlope_{i+1} > 10$, where $NormSlope_i$ denotes the normalized slope between the i^{th} and $(i+1)^{th}$ data points.
        ii. Remove data points after the first 12 hours associated with either condition: $NormSlope_i < -7.5$ and $NormSlope_{i+1} > 10$, or $NormSlope_i < -40$ and $NormSlope_{i+1} > 3.75$.
        iii. Remove any data points at any time that are associated with any of the following 4 conditions: $NormSlope_i > 2$ and $NormSlope_{i+1} < -10$, $NormSlope_i > 10$ and $NormSlope_{i+1} < -2$, $NormSlope_i > 1$ and $NormSlope_{i+1} < -20$, or $NormSlope_i > 50$ and $NormSlope_{i+1} < 0.4$.
        iv. Remove the last parasitemia measurement if the penultimate parasitemia measurement is <200 and the last is >3 times the penultimate measurement and >100.
2. Perform checks to determine whether the clearance rate constant cannot be estimated:
    a. The number of nonzero parasitemia measurements (including a zero replaced by the detection limit) < 3
    b. Initial parasitemia <1000 parasites/µL.
    c. Final parasitemia ≥1000 parasites/µL.
    d. Zero parasitemia measurement is recorded, but the last nonzero parasitemia ≥1000 parasites/µL and the normal linear regression fitted to all datapoints excluding the zero yields a CI for the time that parasitemia is below the limit of detection includes the timepoint for when the zero was recorded.

3. Perform checks to determine if there are not enough data to estimate a lag phase.
    a. There are <3 measurements or there is a time difference of >14 h between measurements in the first 24 h
4. Perform model fitting.

    Models that will be considered include linear, quadratic, or cubic tobit or normal regression for the log-parasitemia of the form:

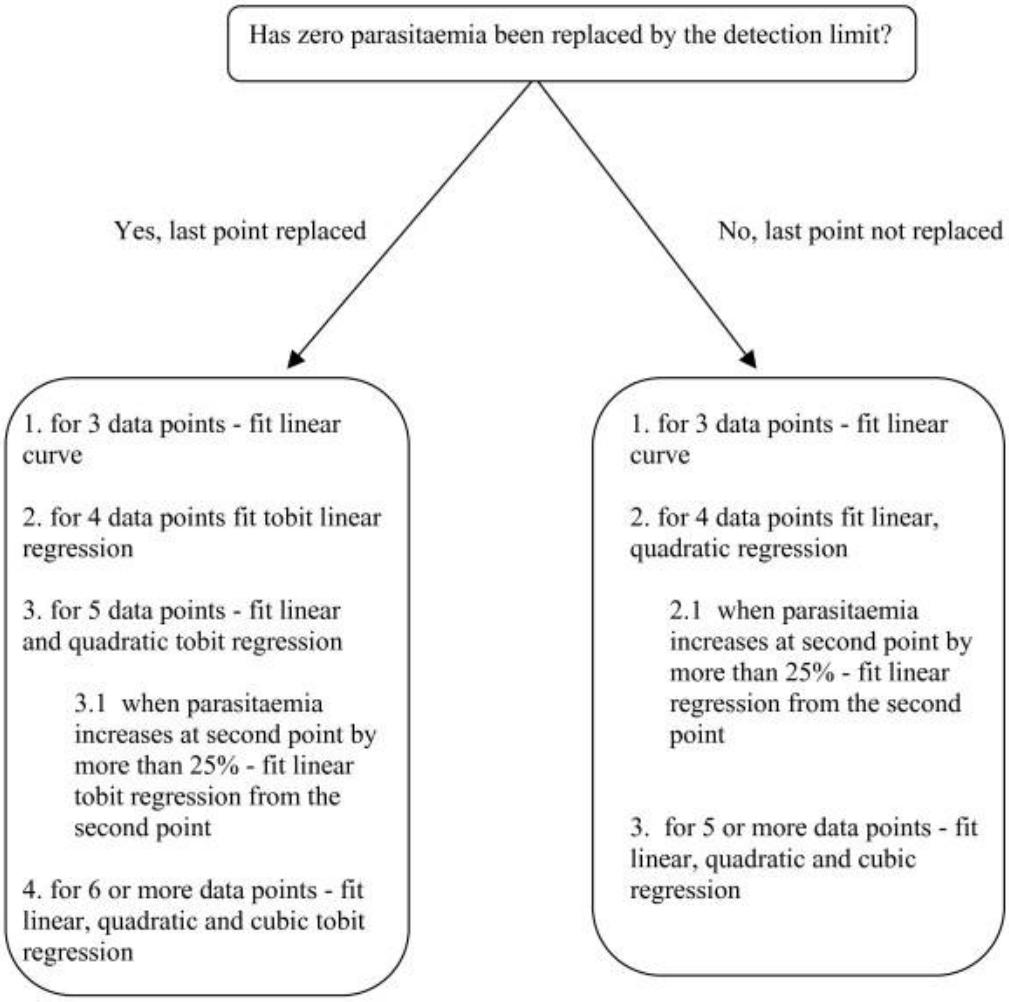
    Linear: $\log(P_i|t_i) = \beta_0 + t_i\beta_1 + e_i$

    Quadratic: $\log(P_i|t_i) = \beta_0 + t_i\beta_1 + t_i^2\beta_2 + e_i$

    Cubic: $\log(P_i|t_i) = \beta_0 + t_i\beta_1 + t_i^2\beta_2 + t_i^3\beta_3 + e_i$,

    where $P_i$is the participant's parasitemia at the ith time, t_i is the ith time, and e_i is the measurement error term for the ith measurement.

a. If none of the conditions in Steps 2 or 3 are met, then fit models to the natural log-parasitemia versus time data as described in the following figure provided in [4].



b. If none of the criteria in Step 2 are met but the criteria in Step 3 is met, fit tobit linear regression if a zero parasitemia measurement has been recorded for the participant or normal linear regression otherwise.

c. If any of the criteria in Step 2 are met, K and the duration of the lag phase (t_{lag}) cannot be estimated, so proceed to Step 6 below.

5. Estimate K and t_{lag} according to the following figure given in [4].

Step 1: Find *Best* model

Best model is defined as the model with the smallest AIC or RSS_{shared} among fitted models, where appropriate.

Step 2: Identify *possibly convex* models

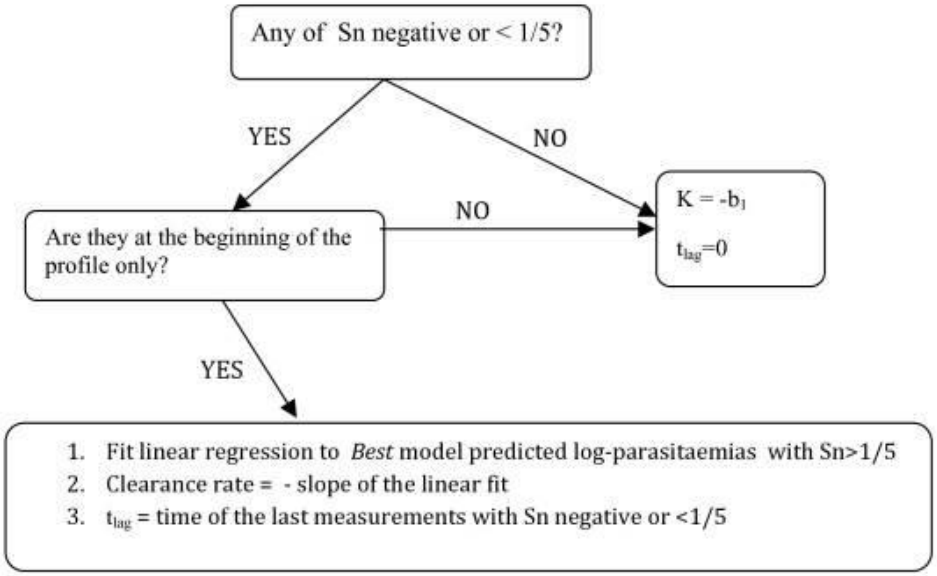
Possibly convex models are quadratic or cubic models with negative concavity somewhere over the time domain.

Step 3: If model is NOT *possibly convex*:

$K = -b_1$; $t_{lag}=0$; GO TO **Step 5**

Step 4: If model is *possibly convex*

4.1 For each log-parasitaemia predicted by the *Best* model y_i (but excluding any measured zero parasitaemias), calculate slope S_i between this point and the preceding predicted value
4.2 Find the most negative slope, Smax
4.3 Calculate normalised slopes Sn = S / Smax
4.4 Find clearance rate constant using the chart below



Step 5: END

6. End.

PCT_{50} and PCT_{90} for each participant will then be estimated using the formulas described previously in this section. Individual estimates of K and t_{lag} will be presented in Listing 15. The following pseudocode will be used to fit cubic normal and tobit regression models and to calculate model-predicted values for each participant's log-parasite density data.

```
/* Cubic Regression with Predicted Values by Participant ID */
data clearance; set clearance;
time2=time**2; time3=time**3;
log_density=log(density);
run;
proc reg data=clearance;
   model log_density=time time2 time3 / p;
```

```
   by partid;
   ods output OutputStatistics=predicted;
run;

/* Cubic Tobit Regression with Predicted Values by Participant ID */
data clearance; set clearance;
time2=time**2; time3=time**3;
log_density=log(density);
/*replace parasite density values = the lower limit for the variable with .*/
if density=LOD then lower=.;
else lower=log_density;
run;
proc lifereg data=clearance outest=OUTEST(keep=partid _scale_);
   model (lower, log_density) = time time2 time3 / d=normal;
   by partid;
   /*output mean of uncensored variable*/
   output out=OUT xbeta=Xbeta;
run;
data predict; merge out outest; by partid;
   lambda = pdf('NORMAL',Xbeta/_scale_)
            / cdf('NORMAL',Xbeta/_scale_);
   /*calculate mean of censored variable*/
   predict = cdf('NORMAL', Xbeta/_scale_)
             * (Xbeta + _scale_*lambda);
run;
```

Total parasite clearance by Day 2 will be a binary variable indicating whether total parasite clearance has occurred within the first 50 hours post-first dose of IV artesunate. Total parasite clearance will be determined using all thick blood smears collected within the 50 hours from the first dose of IV artesunate. Total parasite clearance by Day 2 will be determined for participants in the PD Analysis Population with any results of thick blood smears available within 50 hours after the first dose of IV artesunate.

The relationship between $AUC_{0\text{-}12}$, C_{max}, $t_{1/2}$ and T_{max}, and the time-to-event response variables of PCT_{50} and PCT_{90} will be analyzed using Cox proportional hazards regression. One Cox proportional hazards regression model will be fit for each response variable and DHA exposure parameter. Covariates in these models will include the appropriate exposure parameter as well as a subset of the covariates given in Section 6.4. Covariate selection for these models will be aided by exploratory boxplots of PCT_{50} and PCT_{90} by covariate in Figure 212 and Figure 213, respectively.

Models fit for the sensitivity analysis of the secondary analysis for PCT_{50} and PCT_{90} using the subset of the PD Analysis Population who did not receive IV artesunate or other artemisinin-based therapy before enrollment will be of the same form as those fit in the secondary analysis for the respective time to percent reduction parameter and exposure parameter. Covariates included in each model fit for this sensitivity analysis will be those included in the respective secondary analysis model with effects that remain estimable in the sensitivity analysis subset. The type of model and covariates included for each analysis model will be presented in Table 26 by parameter (PCT_{50} or PCT_{90}) and PK exposure parameter for the PD Analysis Population and the subset of the PD Analysis Population that did not receive IV artesunate or other artemisinin-based therapy before enrollment.

The Cox proportional hazards regression cumulative hazard function for PCT_{50} and PCT_{90} given $AUC_{0\text{-}12}$, C_{max}, $t_{1/2}$, or T_{max} will have the same form as that given in Section 8.2.1.

Hazard ratios for PCT_{50} and PCT_{90} corresponding to a one-unit change in exposure parameters adjusted for other covariates included in the models will be presented with corresponding 95% confidence intervals in

Table 25. Forest plots of hazard ratios and 95% CIs by exposure parameter will be presented for PCT_{50} and PCT_{90} in Figure 216 and Figure 217, respectively.

The relationship between exposure parameters ($AUC_{0\text{-}12}$, C_{max}, $t_{1/2}$, and T_{max}) and the binary variable of total parasite clearance by Day 2 will each be analyzed using logistic regression models. Covariate selection (see Section 6.4 for a list of covariates that will be considered) for these models will be aided by exploratory stacked bar charts of total parasite clearance by Day 2 by covariate, presented in Figure 214 for participants in the PD Analysis Population.

The logistic regression model for total parasite clearance by Day 2 (Y) and $AUC_{0\text{-}12}$, for example, would be

$$logit(\pi) = \alpha + \beta \mathrm{AUC}_{0-12,\mathrm{i}} + \eta^{\mathrm{T}} \mathrm{X}_{\mathrm{i}},$$

where $\pi = \Pr\left(Y = 1 \middle| AUC_{0-12,i}, X_i\right)$ is the probability of total parasite clearance by Day 2 adjusted for covariates X_i and $AUC_{0-12,i}$, α is the model intercept, β corresponds to the log odds ratio for a one unit increase in AUC_{0-12} adjusted for other covariates, and η is a vector with components corresponding to the log odds ratio comparing levels of each additional included covariate holding AUC_{0-12} and any other covariates constant. The logistic regression function for total parasite clearance by Day 2 and C_{max}, $t_{1/2}$, or T_{max} would be of the same form.

Models fit for the sensitivity analysis of the secondary analysis for total parasite clearance by Day 2 using the subset of the PD Analysis Population who did not receive IV artesunate or other artemisinin-based therapy before enrollment will be of the same form as those fit in the secondary analysis for total parasite clearance by Day 2 and the respective PK exposure parameter. Covariates included in each model fit for this sensitivity analysis will be those included in the respective secondary analysis model with effects that remain estimable in the sensitivity analysis subset. The type of model and covariates included for each analysis model will be presented in Table 28 by PK exposure parameter for the PD Analysis Population and the subset of the PD Analysis Population that did not receive IV artesunate or other artemisinin-based therapy before enrollment.

Parasite density will be summarized by timepoint in Table 23. The proportion of participants with total parasite clearance will be presented by timepoint in Table 24. Individual parasite densities and parasite species identified from thick and thin blood smears, respectively, will be listed in Listing 14.

Odds ratios for total parasite clearance by Day 2 corresponding to a one-unit change in exposure parameters adjusted for the confounding variable will be presented with corresponding 95% confidence intervals in Table 27. Forest plots of odds ratios and 95% CIs for total parasite clearance by Day 2 by exposure parameter will be presented in Figure 218.

The following pseudocode will be used to fit a logistic regression model for total parasite clearance by Day 2 and estimate the odds ratio for a one-unit increase in exposure along with its Wald confidence interval after adjusting for other covariates.

```
/* Fit Logistic Regression and Estimate Odds Ratio for Exposure Parameter */
proc logistic data=dataset(where=(population=p));
*catvars = any categorical covariates included in the model;
*refvalues = the value(s) to be used as the reference level for categorical
covariate(s);
class catvars(param=ref ref=refvalues);
*othercovars = any other covariates (including those specified in the class statement)
included in the model;
model D2totcl (event='Yes') = exposure othercovars;
by timepoint;
oddsratio exposure;
```

```
ods output oddsratioswald = orest;
run;
```

8.3. Exploratory Pharmacodynamics Analyses

Details of planned analyses for exploratory PD outcome measures will be provided in an addendum to this SAP.

9. SAFETY EVALUATION

9.1. Demographic and Other Baseline Characteristics

Sex, ethnicity, race, and town/village of residence will be summarized for all participants in the Safety Population (Table 10). Ethnicity will be categorized "Hispanic or Latino," or "Not Hispanic or Latino," "Unknown," or "Not Reported." In accordance with National Institutes of Health (NIH) reporting policies, participants may self-designate as belonging to more than one race or may refuse to identify a race.

Weight-for-age and height-for-age z-scores will be determined for participants younger than 60 months based on WHO Child Growth Standards [2]. Age at enrollment, weight, height, weight-for-age z-score, and height-for-age z-score will be summarized by sex (Table 11).

Individual participant listings will be presented for all demographic and baseline characteristics (Listing 6).

9.1.1. Prior and Concurrent Medical Conditions

Number and percentage of participants' pre-existing and concurrent medical conditions will be summarized by MedDRA® System Organ Class (SOC) for the Safety Population (Table 12).

Individual participant listings will be presented for all pre-existing and concurrent medical conditions (Listing 7).

9.1.2. Prior and Concomitant Medications

Concomitant medications include any traditional, herbal, supplement, and over-the-counter medicine administered during the period starting from 7 days before enrollment and ending at the end of the study follow-up period.

All concomitant medications will be coded to the Anatomical Therapeutic Classification (ATC) using the current WHO Drug Dictionary. The use of concomitant medications taken during the study will be summarized by ATC 1 and ATC 2 in Table 45. If a participant took a specific medication multiple times or took multiple medications within a specific therapeutic class, that participant would be counted only once for the coded drug name or therapeutic class. Individual participant listings will be presented for all concomitant medications (Listing 22).

9.2. Measurements of Treatment Compliance

Participants may have received IV artesunate before enrollment in the study. The number of participants who received IV artesunate before enrollment will be given in Table 5.

Date and time of IV artesunate administrations including any administered before enrollment will be included in Listing 8. Date and time of oral ACT administration will be included with the name of treatment received in Listing 9.

The number and proportion of enrolled participants receiving IV artesunate and oral ACT will be summarized by dose and timing of dosing (pre-enrollment or on-study) in Table 8. Overall individual compliance data for IV artesunate administered before enrollment and on-study and oral ACT will be presented, including the treatments and numbers of doses received and whether participants were able to transition to oral antimalarial therapy per guidelines with the reason if not (Listing 10).

9.3. Adverse Events

An overall summary of adverse events for participants in the Safety Population will be presented in Table 29. This summary will include the numbers of participants with at least one AE, at least one related AE, at least one SAE, at least one AE leading to early termination.

9.3.1. Solicited Events and Symptoms

There are no solicited events or symptoms collected for this study.

9.3.2. Unsolicited Adverse Events

A listing of all unsolicited AEs will be presented (Listing 16) with information regarding onset, duration, severity, relationship to study product or study procedures, and outcome. A participant listing of non-serious AEs of moderate or greater severity will also be reported in Table 32.

The number and proportion of participants experiencing unsolicited AEs will be summarized by MedDRA SOC and PT, severity, and relationship to study product or study procedures in Table 30. The percentage of participants reporting unsolicited AEs related to IV artesunate, related to oral ACT, and related to study procedures will be summarized graphically by MedDRA SOC and maximum severity in Figure 220. The number of related AEs reported will be presented graphically by whether related to IV artesunate, oral ACT, or study procedures, as well as by MedDRA SOC and maximum severity in Figure 219.

9.4. Deaths, Serious Adverse Events and other Significant Adverse Events

Individual data listings of deaths and other SAEs will be provided (Table 31). The listing will include participant ID, AE description, onset, duration, MedDRA SOC and PT, reason reported as an SAE, severity, relationship to study treatment or procedures, alternate etiology if not related, action taken with study treatment, whether the participant discontinued due to the AE, and AE outcome.

9.5. Pregnancies

This is a study of IV artesunate in Ugandan children 6 months-14 years of age diagnosed with severe malaria according to standardized WHO criteria. Given the age range of the study population, pregnancies are not expected to occur, and pregnancy information was not collected.

9.6. Clinical Laboratory Evaluations

Biochemistry laboratory evaluations, hematology laboratory evaluations, and dipstick urinalysis will be performed at Screening and on Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, and Day 7 (±2), with serum bicarbonate additionally assessed on Day 14 (±2) and hemoglobin additionally assessed on Day 14 (±2) and Day 28 (±4). Hematology laboratory evaluations will also be performed at the final study visit on Day 183 (±14). Baseline for laboratory evaluations will be defined as given in Section 3.3.

For tables, listings, and figures, the sort order for biochemistry parameters will be: alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), calcium, creatinine, direct bilirubin, glucose, potassium, serum bicarbonate, serum lactate, sodium, and total bilirubin. The sort order for hematology parameters will be: hemoglobin, neutrophil count, neutrophil %, platelets, and white blood cell count (WBC). The sort order for urinalysis parameters will be: hemolyzed and non-hemolyzed blood, bilirubin, ketones, leukocyte esterase, nitrites, pH, urine glucose, urine protein and urobilinogen.

Abnormalities in clinical laboratories after the baseline visit will be captured as AEs on the appropriate data collection form and eCRF. Abnormalities that are present at baseline will only be reported as AEs after the baseline visit if they have worsened (increased in severity/grade).

All biochemistry results will be presented in Listing 17, all hematology laboratory results will be presented in Listing 18, and all urinalysis results will be presented in Listing 19. Abnormal laboratory results will be recorded as unsolicited AEs in Listing 16.

Summary statistics of measurements and their change from baseline will be presented by continuous laboratory parameter and timepoint for biochemistry (Table 33) and hematology (Table 34) parameters. Boxplots of change from baseline at scheduled collection days will be presented by weight group, sex, and timepoint for continuous chemistry parameters beginning at Figure 221 and continuing through Figure 232, and for continuous hematology parameters beginning at Figure 233 and continuing through Figure 237. Urinalysis results will be summarized by scheduled timepoint and parameter beginning in Table 35 and continuing through Table 43.

9.7. Vital Signs and Physical Evaluations

Vital signs will be collected at Screening, baseline on Day 1, and continuing approximately every 6 hours until 6 hours post-parasite clearance. Vital sign measurements will include axillary temperature, systolic and diastolic blood pressure, respiratory rate, and pulse. All vital signs measurements will be presented in Listing 20.

Summaries of vital signs will utilize participants' average vital signs on each study day and their respective average change from baseline. Descriptive statistics for each average vital sign parameter and its average change from baseline, including mean, SD, median, minimum, and maximum, will be presented by study day in Table 44. Boxplots of average change from baseline will be presented by study day for each vital sign beginning at Figure 238 and continuing through Figure 242.

Physical examinations will be performed at Screening and on Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, Day 7 (±2), and Day 183 (±14), and targeted physical examinations will be performed as needed on Day 14 (±2) and Day 28 (±4). Abnormal physical exam findings will be presented in Listing 21.

9.8. Other Safety Measures

There are no other planned safety measures collected for this study.

10. PHARMACOKINETICS

Planned PK analyses, including those planned for the estimation of exposure parameters to be used in PD analyses, will be described in a separate Pharmacometrics Analysis Plan.

Individual DHA concentrations will be listed by weight group in Listing 12.

11. IMMUNOGENICITY

There are no immunogenicity analyses planned for this study.

12. OTHER ANALYSES

Not applicable

13. REPORTING CONVENTIONS

P-values ≥0.001 and ≤0.999 will be reported to 3 decimal places, p-values less than 0.001 will be reported as "<0.001", and p-values greater than 0.999 will be reported as ">0.999". The mean, median, standard deviation, and other statistics will be reported to 1 decimal place greater than the original data. The minimum and maximum will use the same number of decimal places as the original data. Proportions will be presented as 2 decimal places; values greater than zero but <0.01 will be presented as "<0.01", and values less than one but >0.99 will be presented as ">0.99". Percentages will be reported to the nearest whole number; values greater than zero but < 1% will be presented as "<1"; values greater than 99% but less than 100% will be reported as ">99". Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

14. TECHNICAL DETAILS

SAS version 9.4 or above and R versions 3.2 or above will be used to generate tables, figures, and listings.

15. SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Section 11.3.1 of the Protocol Version 6.0 indicates that demographic characteristics including town/village of residence will be tabulated. Participants included in the study were to be drawn from the population of children aged 6 months to 14 years residing in Tororo District, Uganda, and were seen at Tororo Hospital. As participant town or village of residence, which was collected using a free text field, within Tororo District may vary greatly, town/village of residence will not be included in summary demographics tables but will be listed in the listing of demographic information.

Section 11.3.5 of the Protocol Version 6.0 indicates that timepoint and an interaction term between exposure and timepoint will be included in all models for the primary analysis. However, because we plan to assess the relationship of interest between the primary outcome measures using separate models for each timepoint, such terms will not be included in the primary analysis models and specification of covariance structures for repeated measures will not be necessary. Actual time of response measurement may be considered for inclusion in linear and polynomial models. Section 11.3.5 of the Protocol Version 6.0 also indicates that random effects will be included in all models for the primary analysis; while random effects will be considered for inclusion in Emax models, they are not planned for linear and polynomial models.

Expanded power simulations beyond what is presented in Protocol Version 6.0 are included in this SAP.

16. REFERENCES

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17. LISTING OF TABLES, FIGURES, AND LISTINGS

Table, figure, and listing shells are presented in Appendices 1, 2, and 3.

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APPENDIX 1. TABLE MOCK-UPS

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9.1 Overall Study Design and Plan Description

Table 1: Study Design

Weight Groups to Determine Dosing	Study Treatment Dosing		Number of Participants
	IV Artesunate	Oral ACT	
< 20 kg	3.0 mg/kg/dose for at least 0, 12, and 24 hours	3-day course if able to transition	≤100
≥ 20 kg	2.4 mg/kg/dose for at least 0, 12, and 24 hours		

9.5.1 Pharmacodynamic, Pharmacokinetic, and Safety Measurements Assessed

Table 2: Schedule of Study Procedures

Procedures	*Screening Day -1 to 1*	*Enrollment Day 1*	*Day 2*	*Day 3*	*Day 4*	*Day 5*	*Day 6*	*Day 7 (±2 days)*	*Day 14 (±2 days)*	*Day 28 (±4 days)*	*Final Study Visit, Day 183 (±14 days)*	*Early termination (ET) Visit*
Informed consent	X											
Demographics	X											
Inclusion/Exclusion criteria	X											
Enrollment		X										
Administer IV artesunate		X	X	X								
Administer oral ACT					X	X	X					
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X	X	X	X*	X*	X	X*
Medical History	X	X									X	
*Vital signs****	X	X	X	X	X	X	X	X	X	X	X	X
Height	X									X	X	
Weight	X									X	X	
Thick blood smear for Pf parasitemia (per parasitemia sampling plan)	X	X	X	X	X	X						
Dried blood spot for artemisinin resistance	X											
PAXgene tube for mRNA	X											
Hematology	X	X	X	X	X	X	X	X	X**	X**	X	X^
Serum bicarbonate	X	X	X	X	X	X	X	X	X			X^
Serum lactate	X	X	X	X	X	X	X	X				X^
Serum sodium	X	X	X	X	X	X	X	X				X^
Serum potassium	X	X	X	X	X	X	X	X				X^
Serum creatinine	X	X	X	X	X	X	X	X				X^
Serum glucose	X	X	X	X	X	X	X	X				X^
Serum bilirubin, ALT and AST	X	X	X	X	X	X	X	X				X^
Urinalysis	X	X	X	X	X	X	X	X				
Blantyre coma score	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetic assessments (per PK sampling plan)	X	X										
Neurodevelopmental assessments (parent or caregiver interview, standardized developmental, cognitive & behavioral measures)								X	X	X	X	

* Targeted physical exam, if needed
**Only hemoglobin
*** approximately every 6 h until 6 h post parasite clearance
^ If ET is before D7, collect D7 blood samples; if D8 to D14 may collect serum bicarbonate, hemoglobin, platelets, WBC count, and neutrophil count. If >D14 blood for hemoglobin, platelets, WBC count, and neutrophil count.

9.7.1 Sample Size

Table 3: Sample Size/Probability Estimates

Number of Tests	R^2	Proportion of Tests with Specified R^2	Power									
			N=100	N=90	N=80	N=75	N=70	N=65	N=60	N=55	N=50	N=45
24	0.2	0.05	0.95	-	0.88	0.84	0.80	0.78	0.72	0.66	0.6	0.52
48	0.2	0.05	0.95	-	0.88	0.84	0.81	0.76	0.69	0.63	0.56	0.49
176	0.2	0.05	-	0.93	0.88	0.85	-	-	-	-	-	-
24	0.2	0.10	0.97	-	0.92	0.89	0.86	0.83	0.77	0.72	0.65	0.58
48	0.2	0.10	0.98	-	0.92	0.90	0.87	0.84	0.79	0.73	0.66	0.58
176	0.2	0.10	-	0.96	0.92	0.90	-	-	-	-	-	-

10.2 Protocol Deviations

Table 4: Distribution of Participant-Specific Protocol Deviations by Category and Type

Category	Deviation Type	All Enrolled Participants (N=X)	
		No. of Part.	No. of Dev.
Major Deviations			
Eligibility/enrollment	Any type		
	Did not meet inclusion criterion	x	x
	Met exclusion criterion		
	ICF not signed prior to study procedures		
	Assent not obtained prior to study procedures (if participant able)		
	Other		
Treatment administration schedule	Any type		
	Out of window visit		
	Missed visit/visit not conducted		
	Missed treatment administration		
	Delayed treatment administration		
	Other		
Follow-up visit schedule	Any type		
	Out of window visit		
	Missed visit/visit not conducted		
	Other		
Protocol procedure/assessment	Any type		
	Incorrect version of ICF signed		
	Blood not collected		
	Urine not collected		
	Too few aliquots obtained		
	Specimen result not obtained		
	Required procedure not conducted		
	Required procedure done incorrectly		
	Study product temperature excursion		
	Specimen temperature excursion		
	Other		
Treatment administration	Any type		

Table 4: Distribution of Protocol Deviations by Category and Type *(continued)*

Category	Deviation Type	All Enrolled Participants (N=X)	
		No. of Part.	No. of Dev.
	Required procedure done incorrectly		
	Study product temperature excursion		
	Other		
Minor Deviations			
[Repeat for all minor deviations]			
All Deviations			
[Repeat for all deviations]			
Note: N = Number of enrolled participants.			

12.2.2 Displays of Adverse Events

12.4.1 Individual Laboratory Measurements and Abnormal Laboratory Values

There is no toxicity grading table for this protocol.

14.1 Description of Study Participants

14.1.1 Disposition of Participants

Table 5: Participant Disposition

Participant Disposition	All Participants (N=X)	
	n	%
Screened	--	--
Enrolled	x	100
Met the Definition of Severe Malaria[b]		
Received Any IV Artesunate or Other Artemisinin-Based Therapy Before Enrollment		
Received Any IV Artesunate[b]		
Received Any IV Artesunate Before Enrollment		
Received On-Study IV Artesunate	x	xx
Received All Scheduled IV Artesunate (Initial 24 hours, Including Any IV Artesunate Administered Before Enrollment)[a]		
Transitioned to Oral ACT	x	xx
Successfully Administered Oral ACT		
Completed 3-Day Course of Oral ACT		
Resumed IV Artesunate After Receiving Oral ACT		
Discharged from Hospital		
Had at Least One Measurable DHA Concentration[b]		
Had at Least One Estimable PK Exposure Parameter[b]		
Had at Least One Post-baseline PD Response Collected[b]		
Had at Least One Post-Baseline Temperature Measurement		
Had at Least One Post-Baseline Systolic Blood Pressure Measurement		
Had at Least One Post-Baseline Diastolic Blood Pressure Measurement		
Had at Least One Post-Baseline Serum Lactate Measurement		
Had at Least One Post-Baseline Serum Bicarbonate Measurement		
Had at Least One Post-Baseline Serum Glucose Measurement		
Had at Least One Post-Baseline BCS Assessment		
Had at Least One Post-Baseline Total Bilirubin Measurement		
Had at Least One Post-Baseline Direct Bilirubin Measurement		
Had at Least One Post-Baseline Hemoglobin Measurement		
Had at Least One Post-Baseline Creatinine Measurement		
Completed Final Clinical Laboratory Blood Draw		

Table 5: Participant Disposition *(continued)*

Participant Disposition	All Participants (N=X)	
	n	%
Completed Final PK Blood Draw		
Completed All Clinical Laboratory Blood Draws		
Completed All PK Blood Draws		
Completed All Planned BCS Assessments		
Completed Follow-up (Study Day 183)[a]		

Note: N = Number of enrolled participants.
[a] Refer to Listing 16.2.1 for reasons participants discontinued or terminated early.
[b] Refer to Listing 16.2.3 for reasons participants are excluded from the Analysis populations.

Table 6: Reported Severe Malaria Signs and Symptoms at Enrollment

Severe Malaria Signs and Symptoms	All Participants (N=X)	
	n[a]	%
Presence or history of fever	x	xx
Positive blood film for *P. falciparum malaria*	x	xx
Additional Signs and Symptoms		
Repeated convulsions (more than 2 in 24 hours)	x	xx
Impaired consciousness (BCS <3)	x	xx
Coma	x	xx
Hyperpyrexia (axillary temperature ≥40˚C)	x	xx
Respiratory distress (acidotic breathing)	x	xx
Inability to tolerate oral therapy and vomiting all oral intake	x	xx
Circulatory collapse or shock (systolic blood pressure <50 mmHg)	x	xx
Spontaneous bleeding	x	xx
Hemoglobinuria (tea colored urine)	x	xx
Jaundice	x	xx
Prostration (extreme weakness with inability to sit, stand, or walk without assistance)	x	xx
Severe normocytic anemia (hemoglobin <5 g/dL)	x	xx
Hypoglycemia (blood sugar <2.2 mmol/L or 40 mg/dL)	x	xx
Renal impairment (serum creatinine >265 µmol/L)	x	xx
Hyperparasitemia (>10%)	x	xx

Note: N = Number of enrolled participants.
[a] The symptoms are listed in the order they are given on the enrollment data collection form. Only one additional sign or symptom of severe malaria must be present to meet the definition of severe malaria. Once a participant meets the definition of severe malaria, investigators may opt not to assess the participant for other signs and symptoms of severe malaria.

Table 7: Analysis Populations

Analysis Populations	Reason Participants Excluded	All Enrolled Participants (N=X)	
		n	%
Safety Population	Did not receive at least one dose of IV artesunate	x	xx
Population PK Analysis Population	Any Reason		
	Did not receive at least one on-study dose of IV artesunate		
	Did not have at least one measurable DHA concentration		
PD Analysis Population	Any Reason		
	Did not have exposure parameters obtained from the final population PK model		
	Did not have any post-baseline response data available		

Note: N = Number of enrolled participants.

Table 8: Summary of Dosing

[Implementation Note: If any participant receives additional IV Artesunate beyond the 72 hours dose, additional IV Artesunate Dose rows will be added as needed (e.g., Sixth Dose, etc.). If any participant receives additional oral ACT doses after the planned 3 dose regimen, more rows will be added as needed (e.g. Fourth Dose, etc.).]

Treatment	Dose	Timing of Dose	All Participants (N=X)	
			n	%
IV Artesunate	Any Dose	Any Time	x	xx
		Pre-Enrollment	x	xx
		On-Study	x	xx
	First Dose (0 hours)	Any Time	x	xx
		Pre-Enrollment	x	xx
		On-Study	x	xx
	Second Dose (12 hours)	Any Time	x	xx
		Pre-Enrollment	x	xx
		On-Study	x	xx
	Third Dose (24 hours)	Any Time	x	xx
		Pre-Enrollment	x	xx
		On-Study	x	xx
	Fourth Dose (48 hours)	On-Study	x	xx
	Fifth Dose (72 hours)	On-Study	x	xx
Oral ACT[a]	Any Dose	On-Study	x	xx
	First Dose	On-Study	x	xx
	Second Dose	On-Study	x	xx
	Third Dose	On-Study	x	xx

Note: N = Number of enrolled participants.
[a] Only on-study oral ACT is summarized in this table. Refer to Listing 16.2.10 for possible oral ACT received before enrollment.

Table 9: Ineligibility Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
Any Category	Number of participants failing any eligibility criterion or eligible but not enrolled	x	100
Eligible but Not Enrolled	Any reason eligible but not enrolled	x	xx
	[reason eligible but not enrolled 1]	x	xx
	[reason eligible but not enrolled 2]	x	xx
	[reason eligible but not enrolled 3]	x	xx
Inclusion	Any inclusion criterion	x	xx
	[inclusion criterion 1]	x	xx
	[inclusion criterion 2]	x	xx
	[inclusion criterion 3]	x	xx
Exclusion	Any exclusion criterion	x	xx
	[exclusion criterion 1]	x	xx
	[exclusion criterion 2]	x	xx
	[exclusion criterion 3]	x	xx

[a] More than one criterion may be marked per participant.
[b] Denominator for percentages is the total number of screen failures.

14.1.2 Demographic Data

Table 10: Summary of Categorical Demographic and Baseline Characteristics

Variable	Characteristic	All Participants (N=X)	
		n	%
Sex	Male	x	xx
	Female		
Ethnicity	Not Hispanic or Latino	x	xx
	Hispanic or Latino		
	Not Reported		
	Unknown		
Race	American Indian or Alaska Native	x	xx
	Asian		
	Native Hawaiian or Other Pacific Islander		
	Black or African American		
	White		
	Multi-Racial		
	Unknown		
Note: N = Number of participants in the Safety Population.			

Table 11: Summary of Continuous Demographic and Baseline Characteristics by Sex

Variable	Statistic	Male (N=X)	Female (N=X)	All Participants (N=X)
Age (years)	n	x	x	x
	Mean	xx	xx	xx
	Standard Deviation	xx	xx	xx
	Median	xx	xx	xx
	Minimum	x	x	x
	Maximum	x	x	x
Weight (kg)	n	x	x	x
	Mean	xx	xx	xx
	Standard Deviation	xx	xx	xx
	Median	xx	xx	xx
	Minimum	x	x	x
	Maximum	x	x	x
Height (cm)	n	x	x	x
	Mean	xx	xx	xx
	Standard Deviation	xx	xx	xx
	Median	xx	xx	xx
	Minimum	x	x	x
	Maximum	x	x	x
Weight-for-Age Z-Score	n	x	x	x
	Mean	xx	xx	xx
	Standard Deviation	xx	xx	xx
	Median	xx	xx	xx
	Minimum	x	x	x
	Maximum	x	x	x
Height-for-Age Z-Score	n	x	x	x
	Mean	xx	xx	xx
	Standard Deviation	xx	xx	xx
	Median	xx	xx	xx
	Minimum	x	x	x
	Maximum	x	x	x

Note: N = Number of participants in the Safety Population. n = Number of participants in the Safety Population with the demographic variable available.
Weight-for-age and height-for-age Z-scores are calculated for participants younger than 60 months according to the WHO Child Growth Standards (2006).

14.1.3 Prior and Concurrent Medical Conditions

Table 12: Summary of Participants with Pre-Existing and Concurrent Medical Conditions by MedDRA System Organ Class

MedDRA System Organ Class	All Participants (N=X)	
	n	%
Any SOC	x	xx
[SOC 1]		
[SOC 2]		

Note: N = Number of participants in the Safety Population; n = Number of participants reporting medical history within the specified SOC. A participant is only counted once per SOC.

14.2 Pharmacodynamic Data

Table 13: Continuous Markers of Physiological Dysfunction Summary Statistics for Measurement and Change from Baseline by Parameter and Timepoint – PD Analysis Population

[Implementation Note:

Parameter sort order: temperature, systolic blood pressure, diastolic blood pressure, serum lactate, serum bicarbonate, serum glucose, total bilirubin, direct bilirubin, hemoglobin, and creatinine.]

Timepoint	N	Measurement				Change from Baseline			
		Mean	SD	Median	Min, Max	Mean	SD	Median	Min, Max
Temperature (˚C)									
Baseline	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
24 hours post-first IV artesunate dose	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
48 hours post-first IV artesunate dose	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Time of completion of planned IV artesunate dosing	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Time of first hospital discharge	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
[Repeat for all parameters]									
Note: N = Number of participants in the PD Analysis Population with the result assessed at the respective timepoint.									

Tables with similar format:

Table 14: Continuous Markers of Physiological Dysfunction Summary Statistics for Measurement and Change from Baseline by Parameter and Timepoint – PD Analysis Population, No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset

[Implementation Note: The footnote will be updated to "N = Number of participants in the PD Analysis Population who did not receive any IV artesunate or other artemisinin-based therapy before enrollment with the result assessed at the respective timepoint."]

Table 15: Blantyre Coma Score by Timepoint – PD Analysis Population

Timepoint	N	0		1		2		3		4		5	
		n	%	n	%	n	%	n	%	n	%	n	%
Baseline	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
24 hours post-first IV artesunate dose													
48 hours post-first IV artesunate dose													
Time of completion of planned IV artesunate dosing													
Time of first hospital discharge													
Note: N = Number of participants in the PD Analysis Population with BCS assessed at the given timepoint.													

Tables with similar format:

Table 16: Blantyre Coma Score by Timepoint – PD Analysis Population, No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset

[Implementation Note: The footnote will be updated to "N = Number of participants in the PD Analysis Population who did not receive any IV artesunate or other artemisinin-based therapy before enrollment with BCS assessed at the given timepoint."]

Table 17: Assessment of Relationships between Markers of Physiological Dysfunction and Exposure Parameters by Marker of Physiological Dysfunction, Exposure Parameter, and Timepoint – PD Analysis Population

[Implementation Note: Significant p-values after the Benjamini-Hochberg procedure has been performed will be indicated with "***" after the p-value, e.g. "0.008***". Marker of Physiological Dysfunction sort order: temperature, systolic blood pressure, diastolic blood pressure, serum lactate, serum bicarbonate, serum glucose, total bilirubin, direct bilirubin, hemoglobin, and creatinine.

The model parameter included in the case when a polynomial model was fit is that corresponding to the exposure parameter raised to the highest power included in the model (i.e., β_a).]

Marker of Physiological Dysfunction	Timepoint	PK Exposure Parameter											
		AUC_{0-12} (ng*h/mL)			C_{max} (ng/mL)			T_{max} (h)			$t_{1/2}$ (h)		
		N*	Model Parameter Estimate[a] (95% CI)	P-Value[b]	N*	Model Parameter Estimate[a] (95% CI)	P-Value[b]	N*	Model Parameter Estimate[a] (95% CI)	P-Value[b]	N*	Model Parameter Estimate[a] (95% CI)	P-Value[b]
PD Analysis Population													
Temperature (˚C)	24 hours post-first IV artesunate dose (N=X)	x	xx.x (xx.x,xx.x)	x.xxx	x	xx.x (xx.x,xx.x)	x.xxx	x	xx.x (xx.x,xx.x)	x.xxx	x	xx.x (xx.x,xx.x)	x.xxx
	48 hours post-first IV artesunate dose (N=X)	x	xx.x (xx.x,xx.x)	x.xxx	x	xx.x (xx.x,xx.x)	x.xxx	x	xx.x (xx.x,xx.x)	x.xxx	x	xx.x (xx.x,xx.x)	x.xxx
	Time of completion of planned IV artesunate dosing (N=X)	x	xx.x (xx.x,xx.x)	x.xxx	x	xx.x (xx.x,xx.x)	x.xxx	x	xx.x (xx.x,xx.x)	x.xxx	x	xx.x (xx.x,xx.x)	x.xxx
	Time of first hospital discharge (N=X)	x	xx.x (xx.x,xx.x)	x.xxx	x	xx.x (xx.x,xx.x)	x.xxx	x	xx.x (xx.x,xx.x)	x.xxx	x	xx.x (xx.x,xx.x)	x.xxx
Repeat for all markers of physiological dysfunction													

Notes: N = Number of participants in the PD Analysis Population with the marker of physiological dysfunction assessed at the given timepoint. N* = Number of participants in the PD Analysis Population with estimable PK exposure parameter and the marker of physiological dysfunction assessed at the given timepoint. CI = Confidence interval.

[a] Model parameter estimates and 95% CIs are estimated using an Emax, linear, polynomial, or proportional odds model adjusted for the PK exposure parameter and other covariates. If a polynomial model was fit, the model parameter estimate and 95% CI displayed are those corresponding to the coefficient for the exposure parameter raised to the highest power included in the model. See Table 19 for the type of model and covariates included for each analysis. See Figure 35 through Figure 210 for the full models fit with all model coefficient estimates.

[b] P-values are compared to an adjusted significance threshold using the Benjamini-Hochberg procedure to control the false discovery rate at 0.05, and significant p-values are indicated by ***.

Tables with similar format:

Table 18: Assessment of Relationships between Markers of Physiological Dysfunction and Exposure Parameters by Marker of Physiological Dysfunction, Exposure Parameter, and Timepoint – PD Analysis Population, No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset

[Implementation Note: The "PD Analysis Population" row will be updated to "No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset". The first footnote will be updated to "N = Number of participants in the PD Analysis Population who did not receive any IV artesunate or other artemisinin-based therapy before enrollment with the marker of physiological dysfunction assessed at the given timepoint. N* = Number of participants in the PD Analysis Population who did not receive any IV artesunate or other artemisinin-based therapy before enrollment with estimable PK exposure parameter and the marker of physiological dysfunction assessed at the given timepoint."]

Table 19: Model Specifications for Assessments of Relationships between Markers of Physiological Dysfunction and Exposure Parameters by Marker of Physiological Dysfunction, Exposure Parameter, Timepoint, and Analysis Population

[Implementation Note: Model Type will be either Emax, Linear, Polynomial, or Proportional Odds (for BCS only). Covariates Included in the Model will at minimum include Exposure Parameter, but may also include Sex, Weight Group, Receipt of IV Artesunate or Other Artemisinin-Based Therapy Before Enrollment, Receipt of Concomitant Medications, Receipt of Oral ACT, and Actual Time of Response Measurement. If a polynomial model is fit, all powers included in the model will be listed (e.g., Exposure, $Exposure^2$, $Exposure^3$). If an Emax model is fit, Covariates Included in the Model will list any covariates included for each model parameter, e.g. "Exposure; Emax: Sex, Weight).

Response Transformations Performed will display any transformations to the response variable, such as "Log-transformation". If no response variable transformation was necessary for the model, Response Transformations Performed will be displayed as "-".

Parameter Transformations for Inference is only applicable for Emax models. All other model types will have "NA" for this column. For Emax models, this will either be displayed as "-" if no transformation was necessary, or the parameter and transformation will be displayed, e.g., "EC_{50}: log-transformation".]

Marker of Physiological Dysfunction	PK Exposure Parameter	Timepoint	Model Type	Covariates Included in the Model	Response Transformations Performed	Parameter Transformations for Inference
PD Analysis Population						
Temperature (˚C)	AUC_{0-12}	24 hours post-first IV artesunate dose (N=X)				
		48 hours post-first IV artesunate dose (N=X)				
		Time of completion of planned IV artesunate dosing (N=X)				
		Time of first hospital discharge (N=X)				
	C_{max}	24 hours post-first IV artesunate dose (N=X)				
		48 hours post-first IV artesunate dose (N=X)				
		Time of completion of planned IV artesunate dosing (N=X)				

Table 19: Model Specifications for Assessments of Relationships between Markers of Physiological Dysfunction and Exposure Parameters by Marker of Physiological Dysfunction, Exposure Parameter, Timepoint, and Analysis Population *(continued)*

		Time of first hospital discharge (N=X)				
	T_{max}	24 hours post-first IV artesunate dose (N=X)				
		48 hours post-first IV artesunate dose (N=X)				
		Time of completion of planned IV artesunate dosing (N=X)				
		Time of first hospital discharge (N=X)				
	$t_{1/2}$	24 hours post-first IV artesunate dose (N=X)				
		48 hours post-first IV artesunate dose (N=X)				
		Time of completion of planned IV artesunate dosing (N=X)				
		Time of first hospital discharge (N=X)				
[Repeat for all markers of physiological dysfunction]						
PD Analysis Population, No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset						
[Repeat for PD Analysis Population, No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset]						
Note: N = Number of participants in the analysis population or subset with estimable PK exposure parameter and the marker of physiological dysfunction assessed at the given timepoint.						

Table 20: Time to Hospital Discharge Summary Statistics by Analysis Population

Analysis Population	N	Time to Hospital Discharge (Days)			
		Mean	SD	Median	Min, Max
PD Analysis Population	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
PD Analysis Population, No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Note: N = Number of participants in each analysis population or subset for which time to first hospital discharge can be calculated.					

Table 21: Assessment of Relationships between Time to Hospital Discharge and Exposure Parameters by Exposure Parameter and Analysis Population

Analysis Population	PK Exposure Parameter											
	AUC_{0-12} (ng*h/mL)			C_{max} (ng/mL)			T_{max} (h)			$t_{1/2}$ (h)		
	N*	Hazard Ratio[a]	95% CI	N*	Hazard Ratio[a]	95% CI	N*	Hazard Ratio[a]	95% CI	N*	Hazard Ratio[a]	95% CI
PD Analysis Population (N=X)	x	xx.x	(xx.x, xx.x)	x	xx.x	(xx.x, xx.x)	x	xx.x	(xx.x, xx.x)	x	xx.x	(xx.x, xx.x)
PD Analysis Population, No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset (N=X)	x	xx.x	(xx.x, xx.x)	x	xx.x	(xx.x, xx.x)	x	xx.x	(xx.x, xx.x)	x	xx.x	(xx.x, xx.x)

Notes: N = Number of participants in each analysis population or subset for which time to first hospital discharge can be calculated. N* = Number of participants in each analysis population or subset with estimable PK exposure parameter and for which time to first hospital discharge can be calculated. CI = Confidence interval.
Time of hospital discharge is calculated as the time in days from time of initial participant admission to the time of first discharge.
[a] Hazard ratios and 95% CIs are estimated using a Cox proportional hazard model adjusted for the PK exposure parameter and other covariates. See Table 22 for covariates included in each model.

Table 22: Model Specifications for Assessments of Relationships between Time to Hospital Discharge and Exposure Parameters by Exposure Parameter and Analysis Population

[Implementation Note: Model Type will Cox Proportional Hazard. Covariates Included in the Model will at minimum include Exposure Parameter and Actual Time of Collection, but may also include Sex, Weight Group, Receipt of IV Artesunate or Other Artemisinin-Based Therapy Before Enrollment, Receipt of Concomitant Medications, and Receipt of Oral ACT.]

Analysis Population	PK Exposure Parameter	Model Type	Covariates Included in the Model
PD Analysis Population (N=X)	AUC_{0-12} (N*=X)		
	C_{max} (N*=X)		
	T_{max} (N*=X)		
	$t_{1/2}$ (N*=X)		
PD Analysis Population, No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset (N=X)	AUC_{0-12} (N*=X)		
	C_{max} (N*=X)		
	T_{max} (N*=X)		
	$t_{1/2}$ (N*=X)		
Notes: N = Number of participants in each analysis population or subset for which time to first hospital discharge can be calculated. N* = Number of participants in each analysis population or subset with estimable PK exposure parameter and for which time to first hospital discharge can be calculated. Time of hospital discharge is calculated as the time in days from time of initial participant admission to the time of first discharge.			

Table 23: Parasite Density Summary Statistics by Timepoint and Analysis Population

Analysis Population	Planned Timepoint[a]	N	Parasite Density (# Parasites per 200 WBC)			
			Mean	SD	Median	Min, Max
PD Analysis Population	0 (0-2) h	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	6 (4-8) h	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	12 (10-14) h	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	24 (22-26) h	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	36 (34-38) h	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	48 (46-50) h	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Day 3	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Day 4	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Day 5	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
PD Analysis Population, No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset	0 (0-2) h	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	…					

Notes: N = Number of participants in the analysis population or subset with parasite density results available at the respective timepoint.
[a] Timepoints are given post-first on-study dose of IV artesunate.

Table 24: Proportions of Total Parasite Clearance by Timepoint and Analysis Population

Planned Timepoint[a]	PD Analysis Population (N=X)			PD Analysis Population, No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset (N=X)		
	N*	n	%	N*	n	%
0 (0-2) h	x	x	xx	x	x	xx
6 (4-8) h	x	x	xx	x	x	xx
12 (10-14) h	x	x	xx	x	x	xx
24 (22-26) h	x	x	xx	x	x	xx
36 (34-38) h	x	x	xx	x	x	xx
48 (46-50) h	x	x	xx	x	x	xx
Day 3	x	x	xx	x	x	xx
Day 4	x	x	xx	x	x	xx
Day 5	x	x	xx	x	x	xx

Notes: N = Number of participants in the analysis population or subset. N* = Number of participants in the analysis population or subset with parasitemia results available at the respective timepoint.
Proportion (%) cleared is calculated using N* as the denominator.
[a] Timepoints are given post-first on-study dose of IV artesunate.

Table 25: Assessment of Relationships between Time to Percent Reduction of Parasitemia and Exposure Parameters by Parasite Clearance Parameter, Exposure Parameter, and Analysis Population

		PK Exposure Parameter											
		AUC_{0-12} (ng*h/mL)			C_{max} (ng/mL)			T_{max} (h)			$t_{1/2}$ (h)		
Analysis Population	**Parameter**	**N***	**Hazard Ratio[a]**	**95% CI**	**N***	**Hazard Ratio[a]**	**95% CI**	**N***	**Hazard Ratio[a]**	**95% CI**	**N***	**Hazard Ratio[a]**	**95% CI**
PD Analysis Population (N=X)	PCT_{50} (hours)	x	xx.x	(xx.x, xx.x)	x	xx.x	(xx.x, xx.x)	x	xx.x	(xx.x, xx.x)	x	xx.x	(xx.x, xx.x)
	PCT_{90} (hours)	x	xx.x	(xx.x, xx.x)	x	xx.x	(xx.x, xx.x)	x	xx.x	(xx.x, xx.x)	x	xx.x	(xx.x, xx.x)
PD Analysis Population, No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset (N=X)	PCT_{50} (hours)	x	xx.x	(xx.x, xx.x)	x	xx.x	(xx.x, xx.x)	x	xx.x	(xx.x, xx.x)	x	xx.x	(xx.x, xx.x)
	PCT_{90} (hours)	x	xx.x	(xx.x, xx.x)	x	xx.x	(xx.x, xx.x)	x	xx.x	(xx.x, xx.x)	x	xx.x	(xx.x, xx.x)

Notes: N = Number of participants in each analysis population or subset. N* = Number of participants in each analysis population or subset with estimable PK parameter and for which the parasite clearance and PK exposure parameters can be calculated. CI = Confidence interval. PCT_{50} = Half-life of parasite clearance from time of first on-study IV artesunate dose. PCT_{90} = Time to 90% reduction in parasitemia from first on-study IV artesunate dose.

[a] Hazard ratios and 95% CIs are estimated using a Cox proportional hazard model adjusted for the PK exposure parameter and other covariates. See Table 26 for covariates included in each analysis model.

Table 26: Model Specifications for Assessments of Relationships between Time to Percent Reduction of Parasitemia and Exposure Parameters by Parasite Clearance Parameter, Exposure Parameter, and Analysis Population

[Implementation Note: Model Type will be Cox Proportional Hazard. Covariates Included in the Model will at minimum include Exposure Parameter and Actual Time of Collection, but may also include Sex, Weight Group, Receipt of IV Artesunate or Other Artemisinin-Based Therapy Before Enrollment, Receipt of Concomitant Medications, and Receipt of Oral ACT included as covariates.]

Analysis Population	Parameter	PK Exposure Parameter	Model Type	Covariates Included in the Model
PD Analysis Population (N=X)	PCT_{50} (hours)	AUC_{0-12} (N*=X)		
		C_{max} (N*=X)		
		T_{max} (N*=X)		
		$t_{1/2}$ (N*=X)		
	PCT_{90} (hours)	AUC_{0-12} (N*=X)		
		C_{max} (N*=X)		
		T_{max} (N*=X)		
		$t_{1/2}$ (N*=X)		
PD Analysis Population, No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset (N=X)	PCT_{50} (hours)	AUC_{0-12} (N*=X)		
		C_{max} (N*=X)		
		T_{max} (N*=X)		
		$t_{1/2}$ (N*=X)		
	PCT_{90} (hours)	AUC_{0-12} (N*=X)		
		C_{max} (N*=X)		
		T_{max} (N*=X)		
		$t_{1/2}$ (N*=X)		

Notes: N = Number of participants in each analysis population or subset. N* = Number of participants in each analysis population or subset with estimable PK parameter and for which the parameter can be calculated. PCT_{50} = Half-life of parasite clearance from time of first on-study IV artesunate dose. PCT_{90} = Time to 90% reduction in parasitemia from first on-study IV artesunate dose.

Table 27: Assessment of Relationships between Total Parasite Clearance by Day 2 and Exposure Parameters by Exposure Parameter and Analysis Population

Analysis Population	PK Exposure Parameter											
	AUC_{0-12} (ng*h/mL)			C_{max} (ng/mL)			T_{max} (h)			$t_{1/2}$ (h)		
	N*	Odds Ratio[a]	95% CI	N*	Odds Ratio[a]	95% CI	N*	Odds Ratio[a]	95% CI	N*	Odds Ratio[a]	95% CI
PD Analysis Population (N=X)	x	xx.x	(xx.x,xx.x)	x	xx.x	(xx.x,xx.x)	x	xx.x	(xx.x,xx.x)	x	xx.x	(xx.x,xx.x)
PD Analysis Population, No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset (N=X)	x	xx.x	(xx.x,xx.x)	x	xx.x	(xx.x,xx.x)	x	xx.x	(xx.x,xx.x)	x	xx.x	(xx.x,xx.x)

Notes: N = Number of participants in each analysis population or subset for which thick blood smear results are available within 50 hours after the first dose of IV artesunate. N* = Number of participants in each analysis population or subset with estimable PK exposure parameter and for which thick blood smear results are available within 50 hours after the first dose of IV artesunate.
CI = Confidence interval.
Total parasite clearance by day 2 is determined using blood smears collected within 50 hours post-first dose of IV artesunate.
[a] Odds ratios and 95% CIs are estimated using a logistic regression model adjusted for the PK exposure parameter and other covariates. See Table 28 for the covariates included in each model.

Table 28: Model Specifications for Assessments of Relationships between Total Parasite Clearance by Day 2 and Exposure Parameters by Exposure Parameter and Analysis Population

[Implementation Note: Model Type will be Logistic Regression. Covariates Included in the Model will at minimum include Exposure Parameter and Actual Time of Collection, but may also include Sex, Weight Group, Receipt of IV Artesunate or Other Artemisinin-Based Therapy Before Enrollment, Receipt of Concomitant Medications, and Receipt of Oral ACT included as covariates.]

Analysis Population	PK Exposure Parameter	Model Type	Covariates Included in the Model
PD Analysis Population (N=X)	AUC_{0-12} (N*=X)		
	C_{max} (N*=X)		
	T_{max} (N*=X)		
	$t_{1/2}$ (N*=X)		
PD Analysis Population, No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset (N=X)	AUC_{0-12} (N*=X)		
	C_{max} (N*=X)		
	T_{max} (N*=X)		
	$t_{1/2}$ (N*=X)		

Notes: N = Number of participants in each analysis population or subset for which thick blood smear results are available within 50 hours after the first dose of IV artesunate. N* = Number of participants in each analysis population or subset with estimable PK exposure parameter and for which thick blood smear results are available within 50 hours after the first dose of IV artesunate.
Total parasite clearance by day 2 is determined using blood smears collected within 50 hours post-first dose of IV artesunate.

14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 29: Overall Summary of Adverse Events

	All Participants (N = xx)	
Participants[a] with	n	%
At least one unsolicited adverse event	x	x
At least one related unsolicited adverse event	x	x
Mild (Grade 1)	x	x
Moderate (Grade 2)	x	x
Severe (Grade 3)	x	x
Not yet assessed	x	x
At least one severe (Grade 3) unsolicited adverse event	x	x
Related	x	x
Related to IV artesunate	x	x
Related to oral ACT	x	x
Related to study procedures	x	x
Unrelated	x	x
At least one serious adverse event[b]	x	x
At least one related, serious adverse event	x	x
At least one serious adverse event related to IV artesunate	x	x
At least one serious adverse event related to oral ACT	x	x
At least one serious adverse event related to study procedures	x	x
At least one adverse event leading to early termination[c]	x	x

N = Number of participants in the Safety Population
[a] Participants are counted once for each category regardless of the number of events.
[b] A listing of Serious Adverse Events is included in Table 31.
[c] As reported on the Adverse Event eCRF.

14.3.1.1 Solicited Adverse Events

(Solicited Adverse Events are not applicable to this study.)

14.3.1.2 Unsolicited Adverse Events

Table 30: Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Severity, and Relationship

MedDRA System Organ Class	Preferred Term	Severity	All Participants (N = X)									
			Related to IV Artesunate		Related to Oral ACT		Related to Study Procedures		Not Related		Total	
			n	%	n	%	n	%	n	%	n	%
Any SOC	Any PT	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx
		Mild	x	xx	x	xx	x	xx	x	xx	x	xx
		Moderate	x	xx	x	xx	x	xx	x	xx	x	xx
		Severe	x	xx	x	xx	x	xx	x	xx	x	xx
SOC 1	PT 1	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx
		Mild	x	xx	x	xx	x	xx	x	xx	x	xx
		Moderate	x	xx	x	xx	x	xx	x	xx	x	xx
		Severe	x	xx	x	xx	x	xx	x	xx	x	xx
	PT 2	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx
		Mild	x	xx	x	xx	x	xx	x	xx	x	xx
		Moderate	x	xx	x	xx	x	xx	x	xx	x	xx
		Severe	x	xx	x	xx	x	xx	x	xx	x	xx

Notes: N = Number of participants in the Safety Population. n = Number of participants reporting adverse events within each MedDRA System Organ Class and Preferred Term. Participants may be counted for more than one severity and relationship.
Percentages are calculated as n/Nx100.

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 31: Listing of Serious Adverse Events

[Implementation Note: If the event is ongoing (no stop date), indicate "ongoing" for the "Duration."

If more than one reason is selected for the reason reported as an SAE, list all reasons in the column, separated by a comma.

If related to study treatment, then in the "Relationship to Study Treatment" column indicate whether the SAE was related to IV Artesunate or Oral ACT (e.g., "Related: IV Artesunate" or "Related: Oral ACT").

In the "If Not Related, Alternate Etiology" column, merge the 2 data fields for collecting alternate etiology, separate by a colon.

Sort order: Participant ID, No. of Days Post Enrollment, AE Number.]

Adverse Event	No. of Days Post Enrollment (Duration)	No. of Days Post Enrollment the Event Became Serious	Reason Reported as an SAE	Severity	Relationship to Study Treatment	Relationship to Study Procedures	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Participant Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Participant ID: , AE Number:												
Comments:												
Participant ID: , AE Number:												
Comments:												

Table 32: Listing of Non-Serious, Unsolicited, Moderate or Severe Adverse Events

[Implementation Note: If the event is ongoing (no stop date), indicate "ongoing" for the "Duration."

If related to study treatment, then in the "Relationship to Study Treatment" column indicate whether the SAE was related to IV Artesunate or Oral ACT (e.g., "Related: IV Artesunate" or "Related: Oral ACT").

In the "If Not Related, Alternate Etiology" column, merge the 2 data fields for collecting alternate etiology, separate by a colon.

Sort order: Participant ID, No. of Days Post Enrollment, AE Number.]

Adverse Event	No. of Days Post Enrollment (Duration)	Severity	Relationship to Study Treatment	Relationship to Study Procedure	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Participant Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Participant ID: , AE Number:										
Comments:										
Participant ID: , AE Number:										
Comments:										

14.3.3 Narratives of Deaths, Other Serious and Significant Adverse Events

(not included in SAP, but this is a placeholder for the interim CSR)

14.3.4 Abnormal Laboratory Value Listings (by Participant)

Abnormal laboratory results will be listed as Unsolicited AEs in Listing 16

14.3.5 Displays of Laboratory Results

14.3.5.1 Chemistry Results

Table 33: Chemistry Summary Statistics for Measurement and Change from Baseline by Parameter and Timepoint

[Implementation Note: For Serum Bicarbonate there will be an additional row for Day 14.
Parameter sort order: alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), calcium, creatinine, direct bilirubin, glucose, potassium, serum bicarbonate, serum lactate, sodium, total bilirubin.
If no participants have post-baseline chemistry data available on Day 1, The Day 1 rows and footnote a will be removed.]

Timepoint	N	Measurement				Change from Baseline			
		Mean	SD	Median	Min, Max	Mean	SD	Median	Min, Max
Alanine Aminotransferase (IU/L)									
Screening	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
Baseline	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
Day 1[a]	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 2	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 3	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 4	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 5	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 6	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 7	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
[Repeat for all parameters]									

Note: N = Number of participants in the Safety Population with the laboratory result assessed at the respective timepoint.
[a] Participants with post-baseline chemistry data available on Day 1 are included in the Day 1 row.

14.3.5.2 Hematology Results

Table 34: Hematology Summary Statistics for Measurement and Change from Baseline by Parameter and Timepoint

[Implementation Note: For all hematology parameters other than hemoglobin, Day 14 and Day 28 will not be included as timepoints.
Parameter sort order: hemoglobin, neutrophil count, neutrophil %, platelets, and white blood cell count (WBC).
If no participants have post-baseline hematology data available on Day 1, The Day 1 rows and footnote a will be removed.]

Timepoint	N	Measurement				Change from Baseline			
		Mean	SD	Median	Min, Max	Mean	SD	Median	Min, Max
Hemoglobin (g/dL)									
Screening	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
Baseline	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
Day 1[a]	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 2	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 3	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 4	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 5	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 6	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 7	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 14	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 28	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 183	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
[Repeat for all parameters]									

Note: N = Number of participants in the Safety Population with the laboratory result assessed at the respective timepoint.
[a] Participants with post-baseline hematology data available on Day 1 are included in the Day 1 row.

14.3.5.3 Urinalysis Results

Table 35: Laboratory Results by Parameter and Timepoint – Hemolyzed and Non-Hemolyzed Blood

[Implementation Note: If no participants have post-baseline hemolyzed and non-hemolyzed blood data available on Day 1, The Day 1 rows and footnote a will be removed.]

Timepoint	N	Not Detected		Trace		1+		2+		3+		4+	
		n	%	n	%	n	%	n	%	n	%	n	%
Screening	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Baseline													
Day 1[a]													
Day 2													
Day 3													
Day 4													
Day 5													
Day 6													
Day 7													

Note: N = Number of participants in the Safety Population with the urinalysis result assessed at the respective timepoint.
[a] Participants with post-baseline data available on Day 1 are included in the Day 1 row.

Tables with Similar Format:

Table 36: Laboratory Results by Parameter and Timepoint – Bilirubin

[Implementation Note: The Bilirubin table will have the following column headers: Not Detected, 1+, 2+, and 3+.]

Table 37: Laboratory Results by Parameter and Timepoint – Ketones

[Implementation Note: The Ketones table will have the following column headers: Not Detected, Trace, 1+, 2+, 3+, and 4+.]

Table 38: Laboratory Results by Parameter and Timepoint – Leukocyte Esterase

[Implementation Note: The Leukocyte Esterase table will have the following column headers: Not Detected, Trace, 1+, 2+, and 3+.]

Table 39: Laboratory Results by Parameter and Timepoint – Nitrites

[Implementation Note: The Nitrites table will have the following column headers: Negative and Positive.]

Table 40: Laboratory Results by Parameter and Timepoint – pH

[Implementation Note: The pH table will have the following column headers: 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, and ≥9.0.]

Table 41: Laboratory Results by Parameter and Timepoint – Urine Glucose

[Implementation Note: The Urine Glucose table will have the following column headers: Not Detected, Trace, 1+, 2+, 3+, and 4+.]

Table 42: Laboratory Results by Parameter and Timepoint – Urine Protein

[Implementation Note: The Urine Protein table will have the following column headers: Not Detected, Trace, 1+, 2+, 3+, and 4+.]

Table 43: Laboratory Results by Parameter and Timepoint – Urobilinogen

[Implementation Note: The Urobilinogen table will have the following column headers: Not Detected, 1+, 2+, and 3+.]

14.3.6 Displays of Vital Signs

Table 44: Vital Signs Summary Statistics for Average Measurement and Average Change from Baseline by Parameter and Timepoint

[Implementation Note: Vital signs collected for each participant on each study day will be averaged over, and summary statistics will be calculated for these mean vital signs and the corresponding average changes from baseline for each participant and timepoint/study day.

Vital signs sort order: Temperature, Systolic Blood Pressure, Diastolic Blood Pressure, Respiratory Rate, and Pulse.]

Timepoint/Study Day	N	Average Measurement				Average Change from Baseline			
		Mean	SD	Median	Min, Max	Mean	SD	Median	Min, Max
Temperature (°C)									
Baseline	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	-	-	-	-
Day 1[a]	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 2	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 3	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 4	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 5	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 6	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 7	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 14	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 28	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
Day 183	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
[Repeat for all vital signs]									

Note: N = Number of participants in the Safety Population with the vital sign assessed at the respective timepoint or on the respective study day.
Vital signs were collected approximately every 6 hours until 6 hours post-parasite clearance. This table displays summary statistics for the average vital signs for each participant at each timepoint or on each study day of collection.
[a] Only average post-baseline vital signs data available on Day 1 are summarized in the Day 1 row.

14.4 Summary of Concomitant Medications

Table 45: Number and Percentage of Participants with Prior and Concurrent Medications by WHO Drug Classification

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	All Participants (N=X)	
		n	%
Any Level 1 Codes	Any Level 2 Codes	x	xx
[ATC Level 1 - 1]	Any [ATC 1 – 1]		
	[ATC 2 - 1]		
	[ATC 2 - 2]		
	[ATC 2 - 3]		
[ATC Level 1 – 2]	[ATC 2 - 1]		
	[ATC 2 - 2]		
	[ATC 2 - 3]		

N = Number of participants in the Safety Population. n=Number of participants reporting taking at least one medication in the specific WHO Drug Class.

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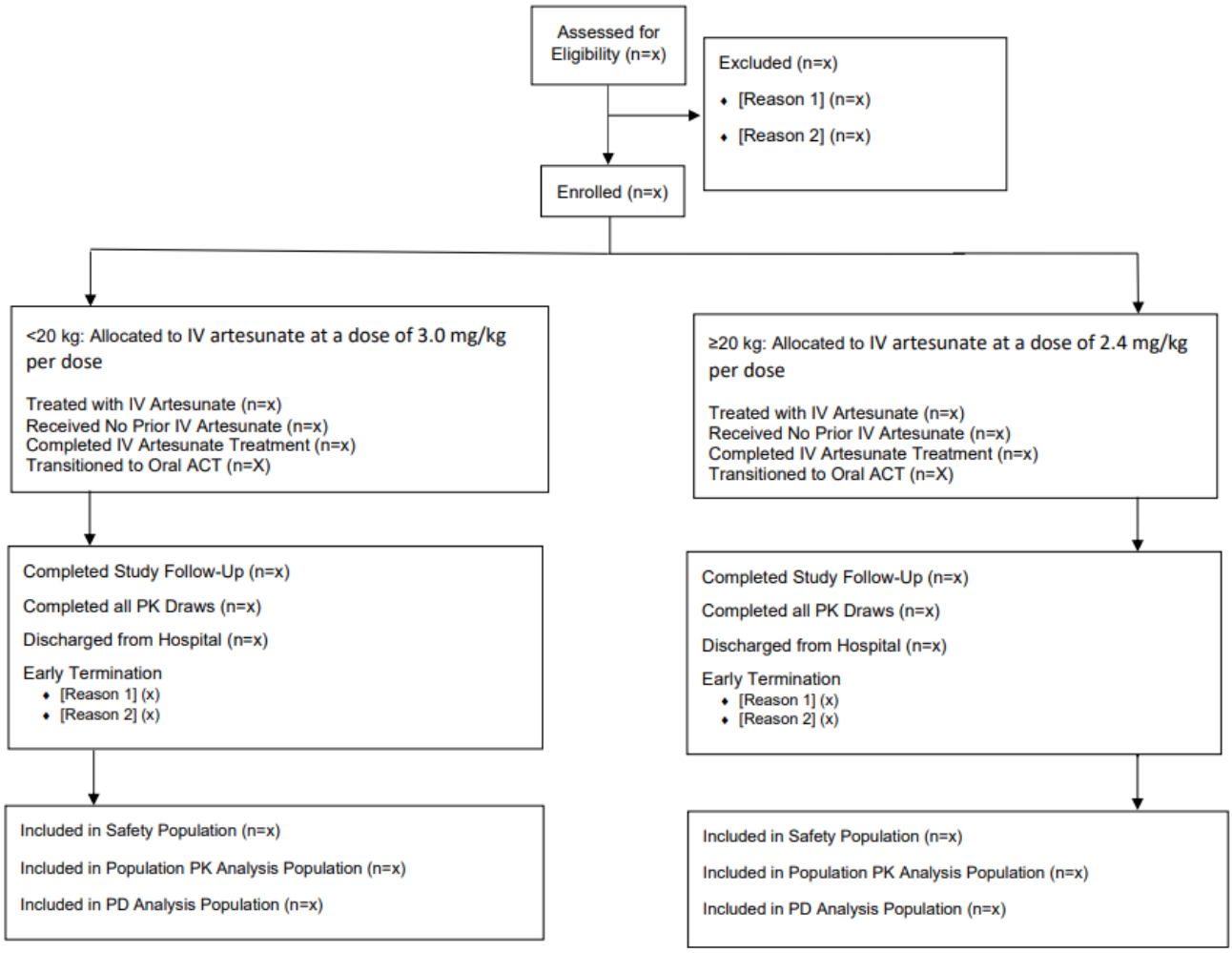
10.1 Disposition of Participants

Figure 1: CONSORT Flow Diagram

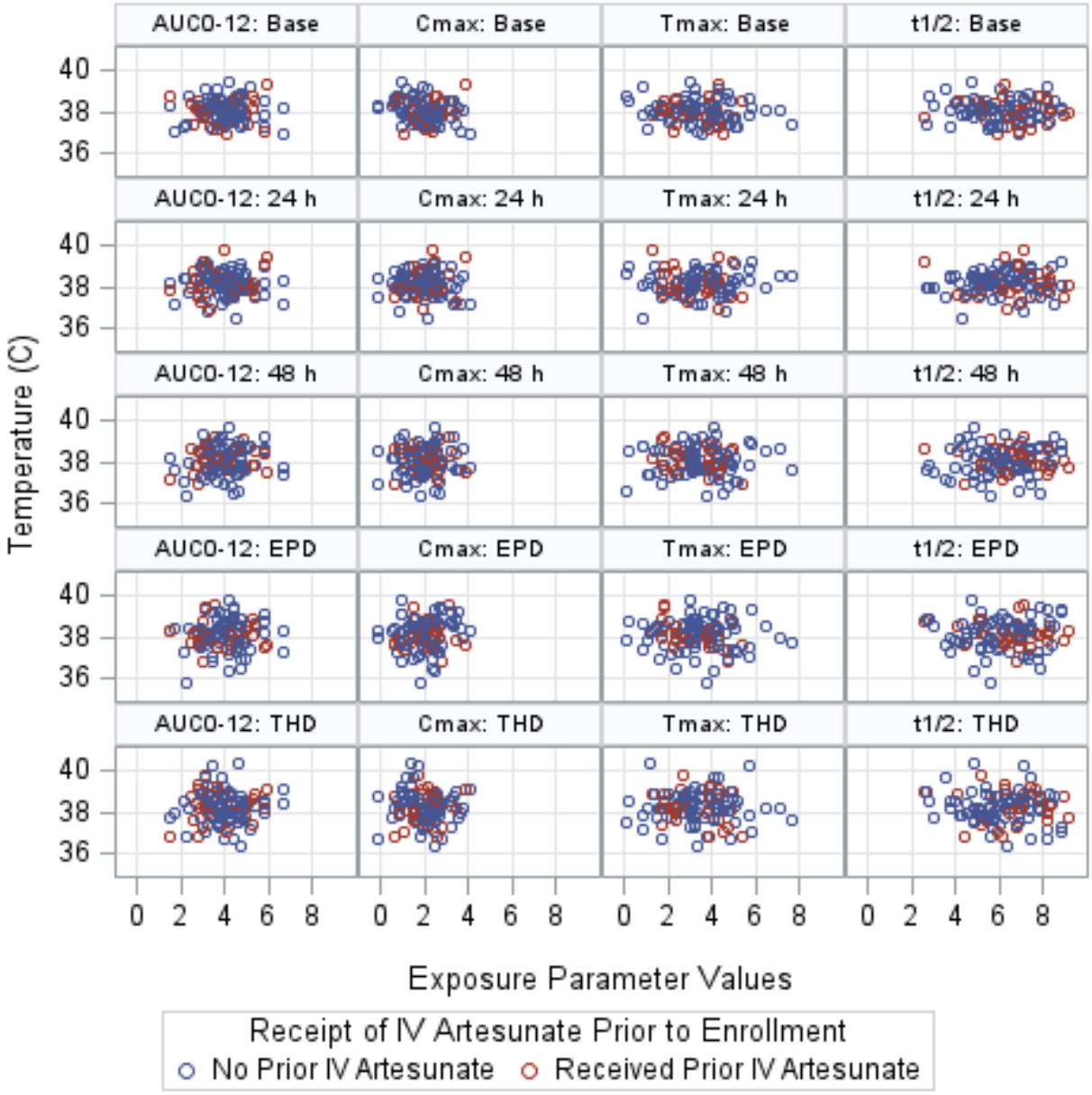


14.2.2 Pharmacokinetic Response Figures by Measure and Timepoint

Figure 2: Scatterplots of Markers of Physiological Dysfunction by Exposure Parameter and Timepoint – PD Analysis Population, Temperature

[Implementation Note: This is a sample figure. This figure will have panels for every exposure parameter (AUC_{0-12}, C_{max}, T_{max}, and $t_{1/2}$) and timepoint combination. The y-axis label will be "Temperature (˚C)".

Points will be color-coded based on receipt of IV artesunate or other artemisinin-based therapy before enrollment. The legend will be updated to have the title "Received IV Artesunate or Other Artemisinin-Based Therapy Before Enrollment?" and the categories "Yes" or "No".]



Notes: Base = Baseline. 24 h and 48 h are measured from time of first dose of IV artesunate. EPD = End of Planned IV artesunate Dosing. THD = Time of first Hospital Discharge.
AUC_{0-12} is measured in ng*h/mL, C_{max} is measured in ng/mL, T_{max} is measured in hours, and $t_{1/2}$ is measured in hours.

Figures with similar format:

Figure 3: Scatterplots of Markers of Physiological Dysfunction by Exposure Parameter and Timepoint – PD Analysis Population, Systolic Blood Pressure

Figure 4: Scatterplots of Markers of Physiological Dysfunction by Exposure Parameter and Timepoint – PD Analysis Population, Diastolic Blood Pressure

Figure 5: Scatterplots of Markers of Physiological Dysfunction by Exposure Parameter and Timepoint – PD Analysis Population, Serum Lactate

Figure 6: Scatterplots of Markers of Physiological Dysfunction by Exposure Parameter and Timepoint – PD Analysis Population, Serum Bicarbonate

Figure 7: Scatterplots of Markers of Physiological Dysfunction by Exposure Parameter and Timepoint – PD Analysis Population, Serum Glucose

Figure 8: Scatterplots of Markers of Physiological Dysfunction by Exposure Parameter and Timepoint – PD Analysis Population, Total Bilirubin

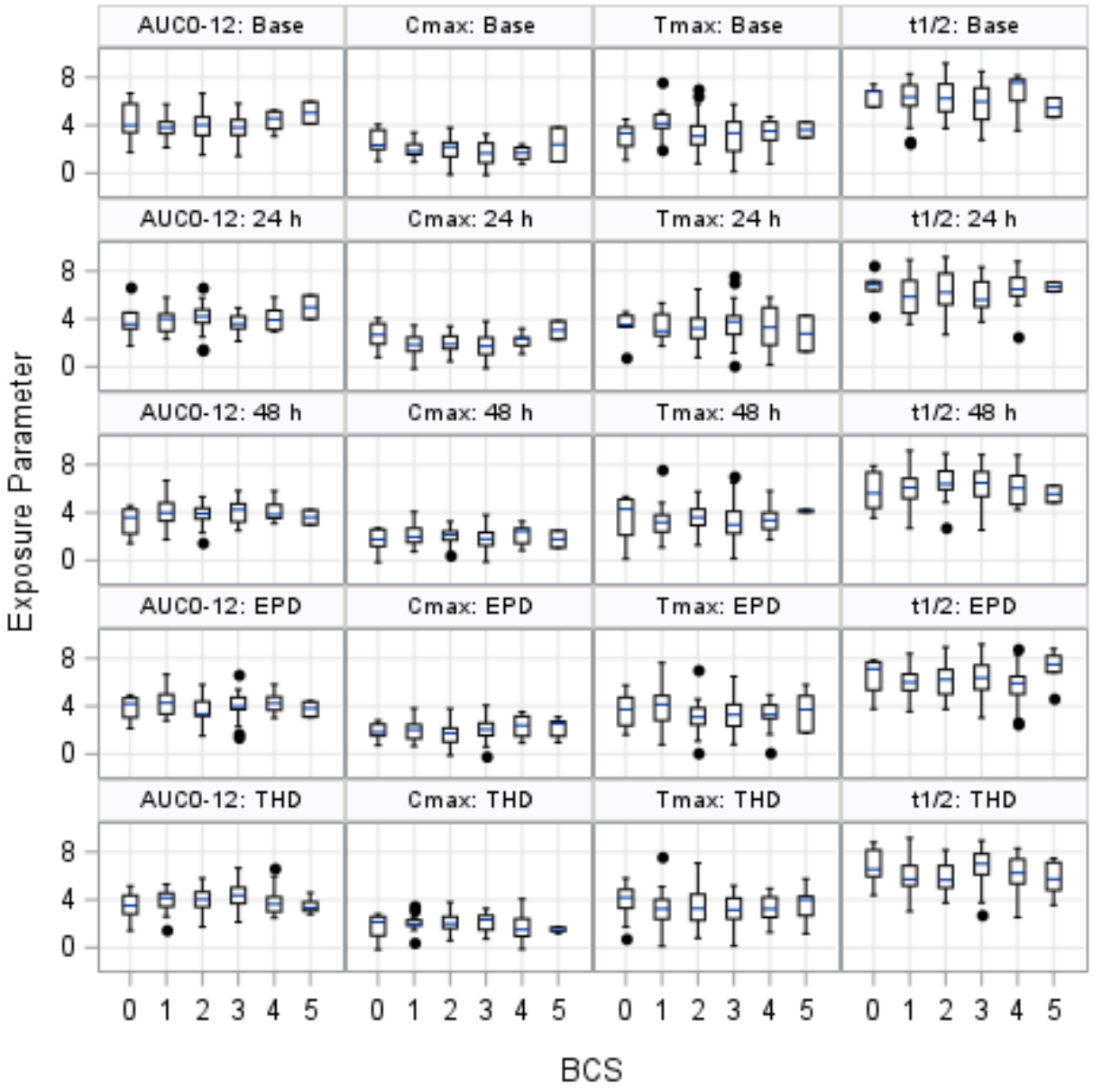
Figure 9: Scatterplots of Markers of Physiological Dysfunction by Exposure Parameter and Timepoint – PD Analysis Population, Direct Bilirubin

Figure 10: Scatterplots of Markers of Physiological Dysfunction by Exposure Parameter and Timepoint – PD Analysis Population, Hemoglobin

Figure 11: Scatterplots of Markers of Physiological Dysfunction by Exposure Parameter and Timepoint – PD Analysis Population, Creatinine

Figure 12: Boxplots of Markers of Physiological Dysfunction by Exposure Parameter and Timepoint – PD Analysis Population, BCS

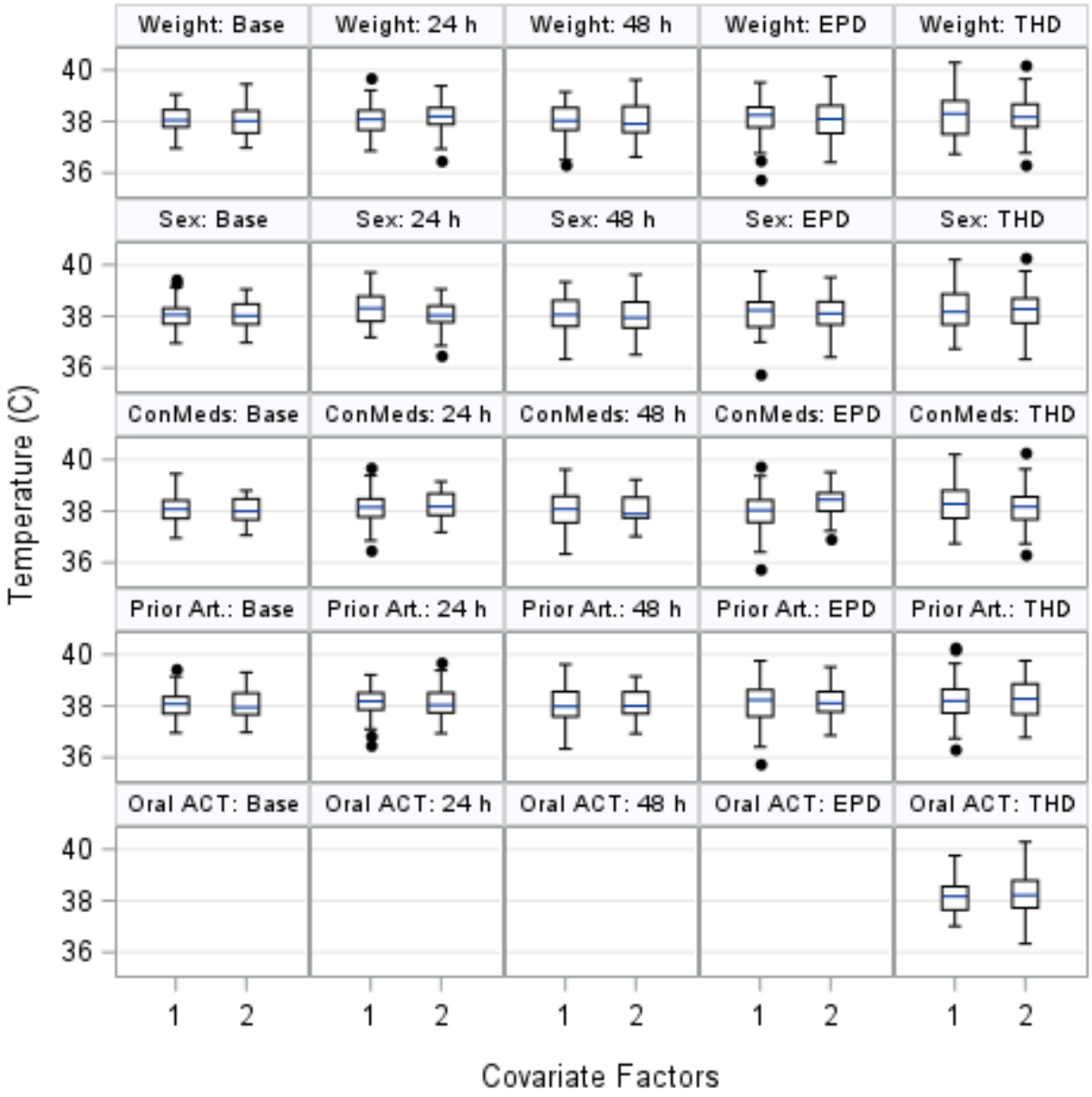
[Implementation Note: This is a sample figure. This figure will have panels for every exposure parameter (AUC_{0-12}, C_{max}, T_{max}, and $t_{1/2}$) and timepoint combination.]



Notes: Base = Baseline. 24 h and 48 h are measured from time of first dose of IV artesunate. EPD = End of Planned IV artesunate Dosing. THD = Time of first Hospital Discharge.
AUC_{0-12} is measured in ng*h/mL, C_{max} is measured in ng/mL, T_{max} is measured in hours, and $t_{1/2}$ is measured in hours.

Figure 13: Boxplots of Markers of Physiological Dysfunction by Covariate and Timepoint – PD Analysis Population, Temperature

[Implementation Note: This is a sample figure. This figure will have panels for every covariate (see Section 8) and timepoint combination. The y-axis label will be "Temperature (˚C)".]



Notes: Base = Baseline. 24 h and 48 h are measured from time of first dose of IV artesunate. EPD = End of Planned IV Artesunate Dosing. THD = Time of first Hospital Discharge. ConMeds = Receipt of Concomitant Medications. Prior Art. = Receipt of IV Artesunate or Other Artemisinin-based Therapy Before Enrollment.
Covariate Factor levels are as follows. Weight: {1 = <20 kg, 2 = ≥20 kg}. Sex: {1 = Male, 2 = Female}. ConMeds: {1 = Did Not Receive Concomitant Medications, 2 = Received Concomitant Medications}. Prior Art.: {1 = No IV Artesunate or Other Artemisinin-Based Therapy Before Enrollment, 2 = Received IV Artesunate or Other Artemisinin-Based Therapy Before Enrollment}. Oral ACT: {1 = Did Not Receive Any Oral ACT, 2 = Received Oral ACT}.

Figures with similar format:

Figure 14: Boxplots of Markers of Physiological Dysfunction by Covariate and Timepoint – PD Analysis Population, Systolic Blood Pressure

Figure 15: Boxplots of Markers of Physiological Dysfunction by Covariate and Timepoint – PD Analysis Population, Diastolic Blood Pressure

Figure 16: Boxplots of Markers of Physiological Dysfunction by Covariate and Timepoint – PD Analysis Population, Serum Lactate

Figure 17: Boxplots of Markers of Physiological Dysfunction by Covariate and Timepoint – PD Analysis Population, Serum Bicarbonate

Figure 18: Boxplots of Markers of Physiological Dysfunction by Covariate and Timepoint – PD Analysis Population, Serum Glucose

Figure 19: Boxplots of Markers of Physiological Dysfunction by Covariate and Timepoint – PD Analysis Population, Total Bilirubin

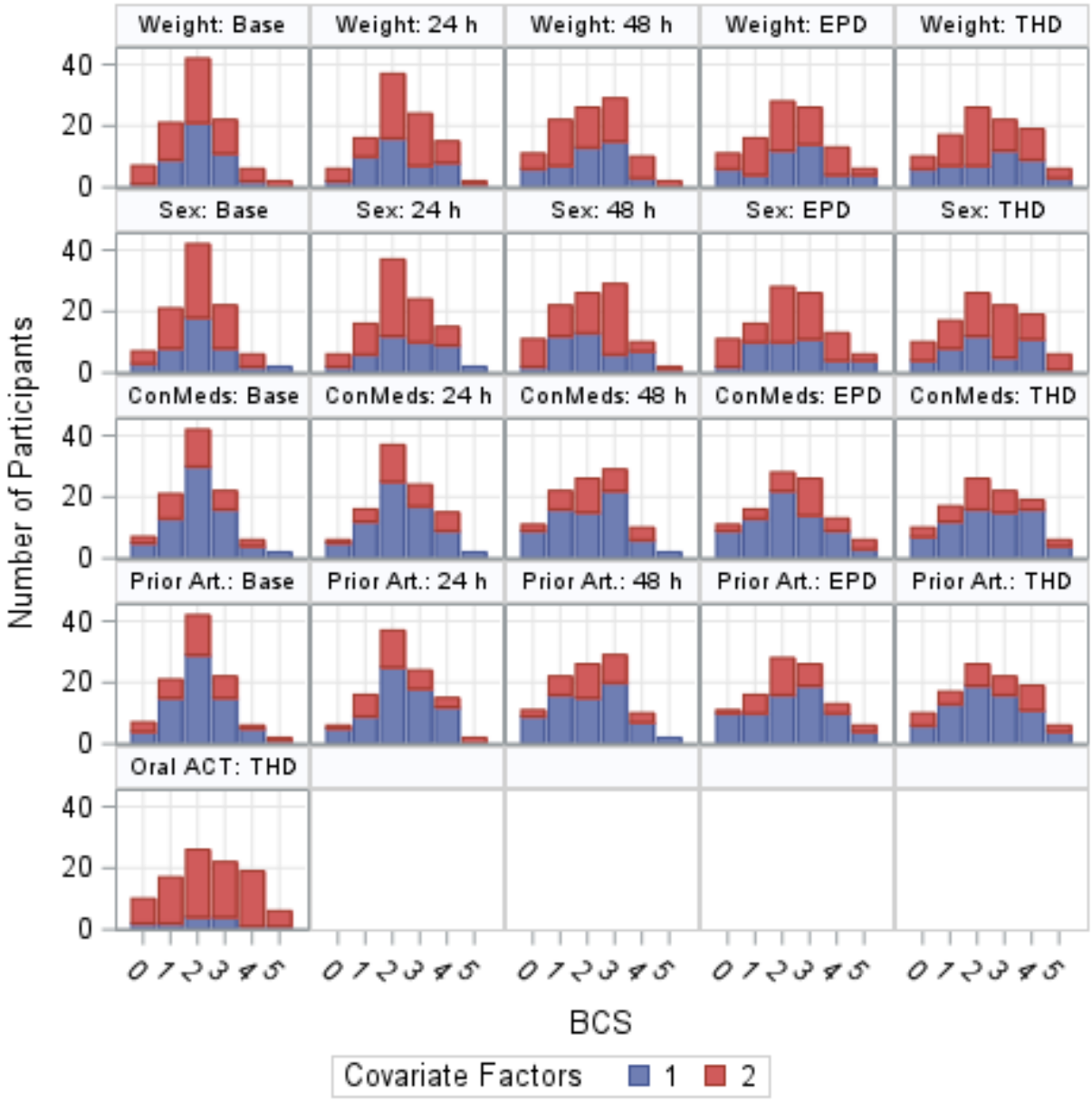
Figure 20: Boxplots of Markers of Physiological Dysfunction by Covariate and Timepoint – PD Analysis Population, Direct Bilirubin

Figure 21: Boxplots of Markers of Physiological Dysfunction by Covariate and Timepoint – PD Analysis Population, Hemoglobin

Figure 22: Boxplots of Markers of Physiological Dysfunction by Covariate and Timepoint – PD Analysis Population, Creatinine

Figure 23: Stacked Bar Charts of Markers of Physiological Dysfunction by Covariate and Timepoint – PD Analysis Population, BCS

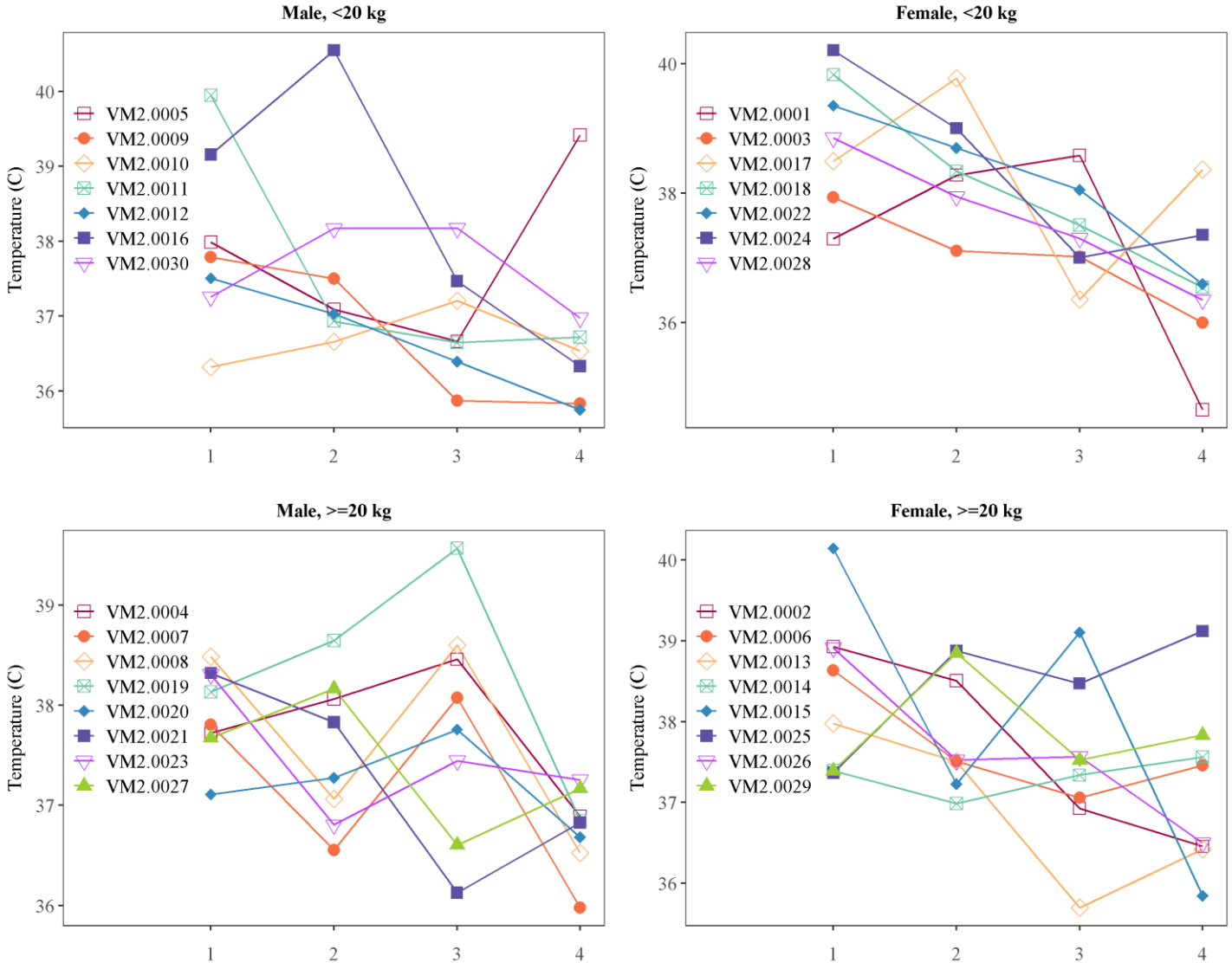
[Implementation Note: This is a sample figure. This figure will have panels for every covariate (see Section 8) and timepoint combination.]



Notes: Base = Baseline. 24 h and 48 h are measured from time of first dose of IV artesunate. EPD = End of Planned IV artesunate Dosing. THD = Time of first Hospital Discharge. ConMeds = Receipt of Concomitant Medications. Prior Art. = Receipt of IV Artesunate or Other Artemisinin-based Therapy Before Enrollment.
Covariate Factor levels are as follows. Weight: {1 = <20 kg, 2 = ≥20 kg}. Sex: {1 = Male, 2 = Female}. ConMeds: {1 = Did Not Receive Concomitant Medications, 2 = Received Concomitant Medications}. Prior Art.: {1 = No IV Artesunate or Other Artemisinin-Based Therapy Before Enrollment, 2 = Received IV Artesunate or Other Artemisinin-Based Therapy Before Enrollment}. Oral ACT: {1 = Did Not Receive Any Oral ACT, 2 = Received Oral ACT}.

Figure 24: Individual Trend Plots for Markers of Physiological Dysfunction by Sex, Weight Group, and Timepoint – PD Analysis Population, Temperature

[Implementation Note: This is a sample figure. This Figure will include x-axis values "24 h", "48 h", "EOD", and "THD" and have x-axis label "Timepoint". The y-axis label will be "Temperature (˚C)".]



Notes: Base = Baseline. 24 h and 48 h are measured from time of first dose of IV artesunate. EPD = End of Planned IV artesunate Dosing. THD = Time of first Hospital Discharge.

Figures with similar format:

Figure 25: Individual Trend Plots for Markers of Physiological Dysfunction by Sex, Weight Group, and Timepoint – PD Analysis Population, Systolic Blood Pressure

Figure 26: Individual Trend Plots for Markers of Physiological Dysfunction by Sex, Weight Group, and Timepoint – PD Analysis Population, Diastolic Blood Pressure

Figure 27: Individual Trend Plots for Markers of Physiological Dysfunction by Sex, Weight Group, and Timepoint – PD Analysis Population, Serum Lactate

Figure 28: Individual Trend Plots for Markers of Physiological Dysfunction by Sex, Weight Group, and Timepoint – PD Analysis Population, Serum Bicarbonate

Figure 29: Individual Trend Plots for Markers of Physiological Dysfunction by Sex, Weight Group, and Timepoint – PD Analysis Population, Serum Glucose

Figure 30: Individual Trend Plots for Markers of Physiological Dysfunction by Sex, Weight Group, and Timepoint – PD Analysis Population, Total Bilirubin

Figure 31: Individual Trend Plots for Markers of Physiological Dysfunction by Sex, Weight Group, and Timepoint – PD Analysis Population, Direct Bilirubin

Figure 32: Individual Trend Plots for Markers of Physiological Dysfunction by Sex, Weight Group, and Timepoint – PD Analysis Population, Hemoglobin

Figure 33: Individual Trend Plots for Markers of Physiological Dysfunction by Sex, Weight Group, and Timepoint – PD Analysis Population, Creatinine

Figure 34: Individual Trend Plots for Markers of Physiological Dysfunction by Sex, Weight Group, and Timepoint – PD Analysis Population, BCS

Figure 35: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Temperature vs AUC_{0-12} at 24 Hours Post-First Dose of IV Artesunate

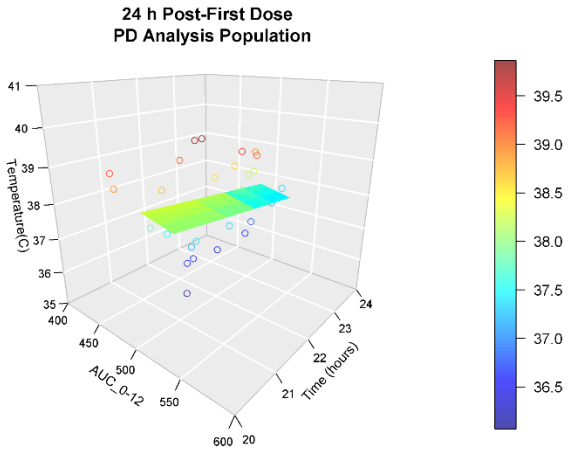
[Implementation Note: This is a sample figure. If actual time of response measurement post-first dose is not included in the model, the "Time (hours)" axes will be removed, and each plot will be two-dimensional with y-axis "Temperature (°C)", x-axis "AUC_{0-12} (ng*h/mL)", and predicted values plotted as a line or curve. In this case, if a linear model is fit, the second sentence in the footnote will be updated to "Actual values of temperature are plotted as points, and predicted values of temperature assuming all categorical values are held constant are plotted as a regression line." The phrase "regression line" in this sentence will be replaced with "regression curve" if a polynomial model is fit and with "exposure-response curve" if an Emax model is fit.

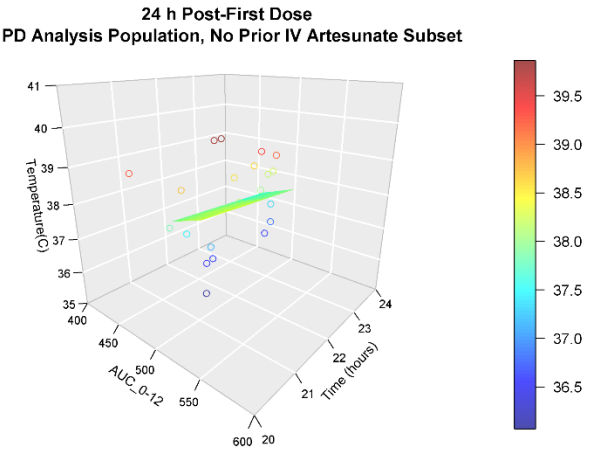
If Emax models with no fixed covariates, linear models, or polynomial models are fit, this figure will have two panels with labels "PD Analysis Population (N=X)" and "PD Analysis Population, No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset (N=X)". If Emax models with fixed covariates on any of the model parameters are fit, then there will be one curve for every combination of fixed covariate levels for each population or subset. These may be displayed in separate panels to facilitate readability, with at most one panel per covariate level combination. For example, if an Emax model is fit with the Emax parameter fit on fixed covariates of sex and weight, the figure could have up to 8 panels with labels "Males <20 kg - PD Analysis Population (N=X)", "Males <20 kg - PD Analysis Population, No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset (N=X)", etc.

If an Emax model is fit for the given response, exposure, and timepoint, similar plots will be displayed with actual values plotted as points and predicted values plotted as a curve for each combination of fixed covariate levels. The fitted model with estimates of Emax, EC50, E0, and the Hill parameter for each grouping of fixed covariates and analysis population or subset will be displayed in the corresponding panel.

Units will be added to all axes. At minimum, the fitted line given below the plot will have covariates for exposure, but may also have sex, weight group, receipt of IV artesunate or other artemisinin-based therapy before enrollment, receipt of concomitant medications, and actual time of measurement included as covariates. The footnote will be updated to reflect which covariates are included.

Note that models for the No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset will be of the same form as that for the PD Analysis Population, but will only include the subset of covariates included in the model for the PD Analysis Population with effects that remain estimable in the No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset. The footnote will be updated to only include the covariates included in the model.]





Note: N = Number of participants in the population or subset with available response data for the timepoint and for which the exposure parameter is estimable. Actual values of temperature are plotted as points, and predicted values of temperature assuming all categorical values are held constant are plotted as a regression plane. In the above fitted model, x represents exposure, t represents actual time of measurement of the marker of physiological dysfunction, s represents sex (Male = 1), w represents weight group (<20 kg = 1), p represents receipt of prior IV artesunate or other artemisinin-based therapy (Receipt of prior IV artesunate or other artemisinin-based therapy = 1), and c represents receipt of concomitant medications (receipt of any concomitant medications = 1).

Figure 36: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Temperature vs AUC_{0-12} at 48 Hours Post-First Dose of IV Artesunate

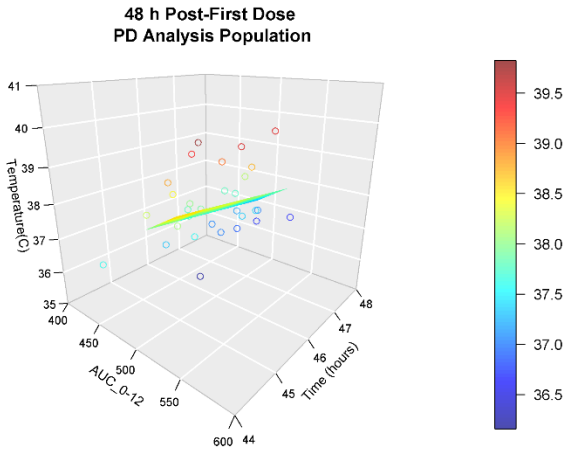
[Implementation Note: This is a sample figure. If actual time of response measurement post-first dose is not included in the model, the "Time (hours)" axes will be removed, and each plot will be two-dimensional with y-axis "Temperature (°C)", x-axis "AUC_{0-12} (ng*h/mL)", and predicted values plotted as a line or curve. In this case, if a linear model is fit, the second sentence in the footnote will be updated to "Actual values of temperature are plotted as points, and predicted values of temperature assuming all categorical values are held constant are plotted as a regression line." The phrase "regression line" in this sentence will be replaced with "regression curve" if a polynomial model is fit and with "exposure-response curve" if an Emax model is fit.

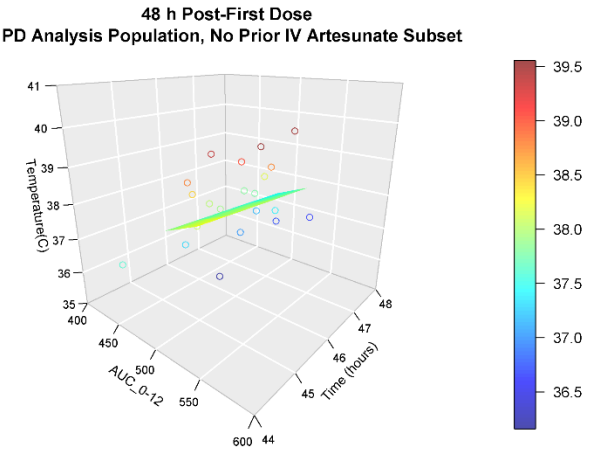
If Emax models with no fixed covariates, linear models, or polynomial models are fit, this figure will have two panels with labels "PD Analysis Population (N=X)" and "PD Analysis Population, No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset (N=X)". If Emax models with fixed covariates on any of the model parameters are fit, then there will be one curve for every combination of fixed covariate levels for each population or subset. These may be displayed in separate panels to facilitate readability, with at most one panel per covariate level combination. For example, if an Emax model is fit with the Emax parameter fit on fixed covariates of sex and weight, the figure could have up to 8 panels with labels "Males <20 kg - PD Analysis Population (N=X)", "Males <20 kg - PD Analysis Population, No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset (N=X)", etc.

If an Emax model is fit for the given response, exposure, and timepoint, similar plots will be displayed with actual values plotted as points and predicted values plotted as a curve for each combination of fixed covariate levels. The fitted model with estimates of Emax, EC50, E0, and the Hill parameter for each grouping of fixed covariates and analysis population or subset will be displayed in the corresponding panel.

Units will be added to all axes. At minimum, the fitted line given below the plot will have covariates for exposure, but may also have sex, weight group, receipt of IV artesunate or other artemisinin-based therapy before enrollment, receipt of concomitant medications, and actual time of measurement included as covariates. The footnote will be updated to reflect which covariates are included.

Note that the model for the No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset will be of the same form as that for the PD Analysis Population, but will only include the subset of covariates included in the model for the PD Analysis Population with effects that remain estimable in the No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset. The footnote will be updated to only include the covariates included in the model.]





Note: N = Number of participants in the population or subset with available response data for the timepoint and for which the exposure parameter is estimable. Actual values of temperature are plotted as points, and predicted values of temperature assuming all categorical values are held constant are plotted as a regression plane. In the above fitted model, x represents exposure, t represents actual time of measurement of the marker of physiological dysfunction, s represents sex (Male = 1), w represents weight group (<20 kg = 1), p represents receipt of prior IV artesunate or other artemisinin-based therapy (Receipt of prior IV artesunate or other artemisinin-based therapy = 1), and c represents receipt of concomitant medications (receipt of any concomitant medications = 1).

Figure 37: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Temperature vs AUC_{0-12} at the End of Planned IV Artesunate Dosing

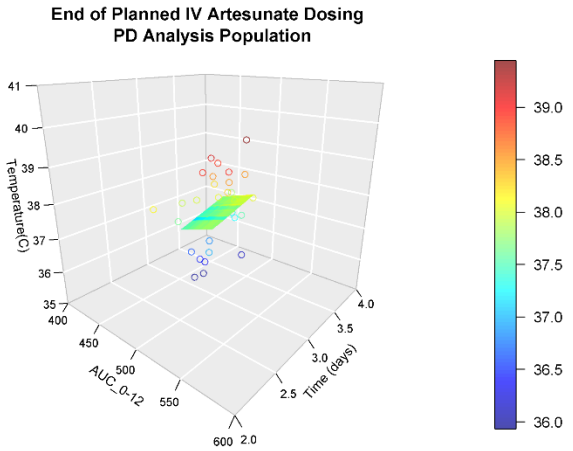
[Implementation Note: This is a sample figure. If actual time of response measurement post-first dose is not included in the model, the "Time (hours)" axes will be removed, and each plot will be two-dimensional with y-axis "Temperature (°C)", x-axis "AUC_{0-12} (ng*h/mL)", and predicted values plotted as a line or curve. In this case, if a linear model is fit, the second sentence in the footnote will be updated to "Actual values of temperature are plotted as points, and predicted values of temperature assuming all categorical values are held constant are plotted as a regression line." The phrase "regression line" in this sentence will be replaced with "regression curve" if a polynomial model is fit and with "exposure-response curve" if an Emax model is fit.

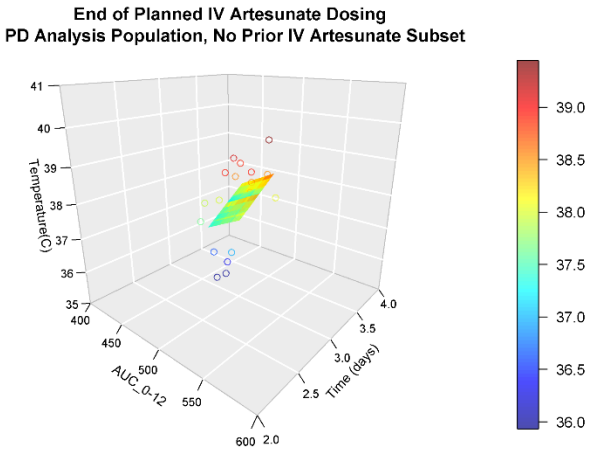
If Emax models with no fixed covariates, linear models, or polynomial models are fit, this figure will have two panels with labels "PD Analysis Population (N=X)" and "PD Analysis Population, No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset (N=X)". If Emax models with fixed covariates on any of the model parameters are fit, then there will be one curve for every combination of fixed covariate levels for each population or subset. These may be displayed in separate panels to facilitate readability, with at most one panel per covariate level combination. For example, if an Emax model is fit with the Emax parameter fit on fixed covariates of sex and weight, the figure could have up to 8 panels with labels "Males <20 kg - PD Analysis Population (N=X)", "Males <20 kg - PD Analysis Population, No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset (N=X)", etc.

If an Emax model is fit for the given response, exposure, and timepoint, similar plots will be displayed with actual values plotted as points and predicted values plotted as a curve for each combination of fixed covariate levels. The fitted model with estimates of Emax, EC50, E0, and the Hill parameter for each grouping of fixed covariates and analysis population or subset will be displayed in the corresponding panel.

Units will be added to all axes. At minimum, the fitted line given below the plot will have covariates for exposure, but may also have sex, weight group, receipt of IV artesunate or other artemisinin-based therapy before enrollment, receipt of concomitant medications, and actual time of measurement included as covariates. The footnote will be updated to reflect which covariates are included.

Note that the model for the No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset will be of the same form as that for the PD Analysis Population, but will only include the subset of covariates included in the model for the PD Analysis Population with effects that remain estimable in the No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset. The footnote will be updated to only include the covariates included in the model.]





Note: N = Number of participants in the population or subset with available response data for the timepoint and for which the exposure parameter is estimable. Actual values of temperature are plotted as points, and predicted values of temperature assuming all categorical values are held constant are plotted as a regression plane. In the above fitted model, x represents exposure, t represents actual time of measurement of the marker of physiological dysfunction, s represents sex (Male = 1), w represents weight group (<20 kg = 1), p represents receipt of prior IV artesunate or other artemisinin-based therapy (Receipt of prior IV artesunate or other artemisinin-based therapy = 1), and c represents receipt of concomitant medications (receipt of any concomitant medications = 1).

Figure 38: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Temperature vs AUC_{0-12} at Time of First Hospital Discharge

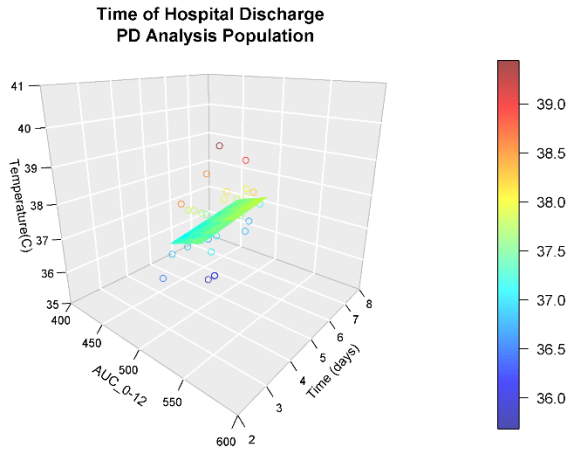
[Implementation Note: This is a sample figure. If actual time of response measurement post-first dose is not included in the model, the "Time (hours)" axes will be removed, and each plot will be two-dimensional with y-axis "Temperature (°C)", x-axis "AUC_{0-12} (ng*h/mL)", and predicted values plotted as a line or curve. In this case, if a linear model is fit, the second sentence in the footnote will be updated to "Actual values of temperature are plotted as points, and predicted values of temperature assuming all categorical values are held constant are plotted as a regression line." The phrase "regression line" in this sentence will be replaced with "regression curve" if a polynomial model is fit and with "exposure-response curve" if an Emax model is fit.

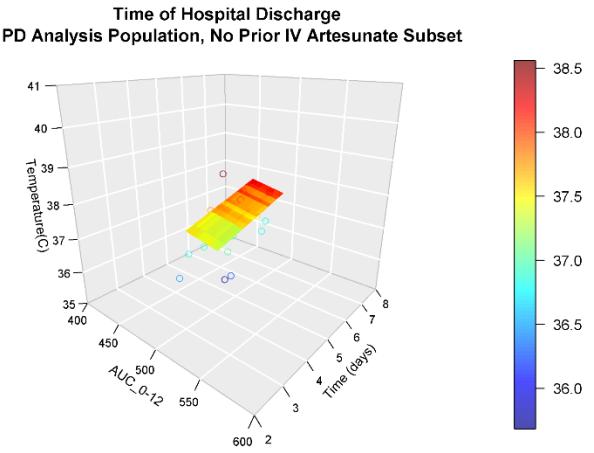
If Emax models with no fixed covariates, linear models, or polynomial models are fit, this figure will have two panels with labels "PD Analysis Population (N=X)" and "PD Analysis Population, No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset (N=X)". If Emax models with fixed covariates on any of the model parameters are fit, then there will be one curve for every combination of fixed covariate levels for each population or subset. These may be displayed in separate panels to facilitate readability, with at most one panel per covariate level combination. For example, if an Emax model is fit with the Emax parameter fit on fixed covariates of sex and weight, the figure could have up to 8 panels with labels "Males <20 kg - PD Analysis Population (N=X)", "Males <20 kg - PD Analysis Population, No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset (N=X)", etc.

If an Emax model is fit for the given response, exposure, and timepoint, similar plots will be displayed with actual values plotted as points and predicted values plotted as a curve for each combination of fixed covariate levels. The fitted model with estimates of Emax, EC50, E0, and the Hill parameter for each grouping of fixed covariates and analysis population or subset will be displayed in the corresponding panel.

Units will be added to all axes. At minimum, the fitted line given below the plot will have covariates for exposure, but may also have sex, weight group, receipt of IV artesunate or other artemisinin-based therapy before enrollment, receipt of concomitant medications, actual time of measurement, and receipt of oral ACT included as covariates. The footnote will be updated to reflect which covariates are included.

Note that the model for the No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset will be of the same form as that for the PD Analysis Population, but will only include the subset of covariates included in the model for the PD Analysis Population with effects that remain estimable in the No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset. The footnote will be updated to only include the covariates included in the model.]





Note: N = Number of participants in the population or subset with available response data for the timepoint and for which the exposure parameter is estimable. Actual values of temperature are plotted as points, and predicted values of temperature assuming all categorical values are held constant are plotted as a regression plane. In the above fitted model, x represents exposure, t represents actual time of measurement of the marker of physiological dysfunction, s represents sex (Male = 1), w represents weight group (<20 kg = 1), p represents receipt of prior IV artesunate or other artemisinin-based therapy (Receipt of prior IV artesunate or other artemisinin-based therapy = 1), c represents receipt of concomitant medications (receipt of any concomitant medications = 1), and a represents receipt of oral ACT (receipt of any oral ACT = 1).

Figures with similar format:

Figure 39: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Temperature vs C_{max} at 24 Hours Post-First Dose of IV Artesunate

Figure 40: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Temperature vs C_{max} at 48 Hours Post-First Dose of IV Artesunate

Figure 41: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Temperature vs C_{max} at the End of Planned IV Artesunate Dosing

Figure 42: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Temperature vs C_{max} at Time of First Hospital Discharge

Figure 43: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Temperature vs T_{max} at 24 Hours Post-First Dose of IV Artesunate

Figure 44: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Temperature vs T_{max} at 48 Hours Post-First Dose of IV Artesunate

Figure 45: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Temperature vs T_{max} at the End of Planned IV Artesunate Dosing

Figure 46: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Temperature vs T_{max} at Time of First Hospital Discharge

Figure 47: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Temperature vs $t_{1/2}$ at 24 Hours Post-First Dose of IV Artesunate

Figure 48: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Temperature vs $t_{1/2}$ at 48 Hours Post-First Dose of IV Artesunate

Figure 49: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Temperature vs $t_{1/2}$ at the End of Planned IV Artesunate Dosing

Figure 50: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Temperature vs $t_{1/2}$ at Time of First Hospital Discharge

Figure 51: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Systolic Blood Pressure vs AUC_{0-12} at 24 Hours Post-First Dose of IV Artesunate

Figure 52: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Systolic Blood Pressure vs AUC_{0-12} at 48 Hours Post-First Dose of IV Artesunate

Figure 53: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Systolic Blood Pressure vs AUC_{0-12} at the End of Planned IV Artesunate Dosing

Figure 54: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Systolic Blood Pressure vs AUC_{0-12} at Time of First Hospital Discharge

Figure 55: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Systolic Blood Pressure vs C_{max} at 24 Hours Post-First Dose of IV Artesunate

Figure 56: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Systolic Blood Pressure vs C_{max} at 48 Hours Post-First Dose of IV Artesunate

Figure 57: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Systolic Blood Pressure vs C_{max} at the End of Planned IV Artesunate Dosing

Figure 58: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Systolic Blood Pressure vs C_{max} at Time of First Hospital Discharge

Figure 59: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Systolic Blood Pressure vs T_{max} at 24 Hours Post-First Dose of IV Artesunate

Figure 60: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Systolic Blood Pressure vs T_{max} at 48 Hours Post-First Dose of IV Artesunate

Figure 61: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Systolic Blood Pressure vs T_{max} at the End of Planned IV Artesunate Dosing

Figure 62: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Systolic Blood Pressure vs T_{max} at Time of First Hospital Discharge

Figure 63: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Systolic Blood Pressure vs $t_{1/2}$ at 24 Hours Post-First Dose of IV Artesunate

Figure 64: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Systolic Blood Pressure vs $t_{1/2}$ at 48 Hours Post-First Dose of IV Artesunate

Figure 65: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Systolic Blood Pressure vs $t_{1/2}$ at the End of Planned IV Artesunate Dosing

Figure 66: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Systolic Blood Pressure vs $t_{1/2}$ at Time of First Hospital Discharge

Figure 67: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Diastolic Blood Pressure vs AUC_{0-12} at 24 Hours Post-First Dose of IV Artesunate

Figure 68: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Diastolic Blood Pressure vs AUC_{0-12} at 48 Hours Post-First Dose of IV Artesunate

Figure 69: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Diastolic Blood Pressure vs AUC_{0-12} at the End of Planned IV Artesunate Dosing

Figure 70: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Diastolic Blood Pressure vs AUC_{0-12} at Time of First Hospital Discharge

Figure 71: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Diastolic Blood Pressure vs C_{max} at 24 Hours Post-First Dose of IV Artesunate

Figure 72: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Diastolic Blood Pressure vs C_{max} at 48 Hours Post-First Dose of IV Artesunate

Figure 73: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Diastolic Blood Pressure vs C_{max} at the End of Planned IV Artesunate Dosing

Figure 74: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Diastolic Blood Pressure vs C_{max} at Time of First Hospital Discharge

Figure 75: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Diastolic Blood Pressure vs T_{max} at 24 Hours Post-First Dose of IV Artesunate

Figure 76: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Diastolic Blood Pressure vs T_{max} at 48 Hours Post-First Dose of IV Artesunate

Figure 77: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Diastolic Blood Pressure vs T_{max} at the End of Planned IV Artesunate Dosing

Figure 78: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Diastolic Blood Pressure vs T_{max} at Time of First Hospital Discharge

Figure 79: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Diastolic Blood Pressure vs $t_{1/2}$ at 24 Hours Post-First Dose of IV Artesunate

Figure 80: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Diastolic Blood Pressure vs $t_{1/2}$ at 48 Hours Post-First Dose of IV Artesunate

Figure 81: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Diastolic Blood Pressure vs $t_{1/2}$ at the End of Planned IV Artesunate Dosing

Figure 82: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Diastolic Blood Pressure vs $t_{1/2}$ at Time of First Hospital Discharge

Figure 83: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Lactate vs AUC_{0-12} at 24 Hours Post-First Dose of IV Artesunate

Figure 84: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Lactate vs AUC_{0-12} at 48 Hours Post-First Dose of IV Artesunate

Figure 85: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Lactate vs AUC_{0-12} at the End of Planned IV Artesunate Dosing

Figure 86: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Lactate vs AUC_{0-12} at Time of First Hospital Discharge

Figure 87: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Lactate vs C_{max} at 24 Hours Post-First Dose of IV Artesunate

Figure 88: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Lactate vs C_{max} at 48 Hours Post-First Dose of IV Artesunate

Figure 89: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Lactate vs C_{max} at the End of Planned IV Artesunate Dosing

Figure 90: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Lactate vs C_{max} at Time of First Hospital Discharge

Figure 91: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Lactate vs T_{max} at 24 Hours Post-First Dose of IV Artesunate

Figure 92: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Lactate vs T_{max} at 48 Hours Post-First Dose of IV Artesunate

Figure 93: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Lactate vs T_{max} at the End of Planned IV Artesunate Dosing

Figure 94: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Lactate vs T_{max} at Time of First Hospital Discharge

Figure 95: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Lactate vs $t_{1/2}$ at 24 Hours Post-First Dose of IV Artesunate

Figure 96: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Lactate vs $t_{1/2}$ at 48 Hours Post-First Dose of IV Artesunate

Figure 97: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Lactate vs $t_{1/2}$ at the End of Planned IV Artesunate Dosing

Figure 98: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Lactate vs $t_{1/2}$ at Time of First Hospital Discharge

Figure 99: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Bicarbonate vs AUC_{0-12} at 24 Hours Post-First Dose of IV Artesunate

Figure 100: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Bicarbonate vs AUC_{0-12} at 48 Hours Post-First Dose of IV Artesunate

Figure 101: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Bicarbonate vs AUC_{0-12} at the End of Planned IV Artesunate Dosing

Figure 102: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Bicarbonate vs AUC_{0-12} at Time of First Hospital Discharge

Figure 103: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Bicarbonate vs C_{max} at 24 Hours Post-First Dose of IV Artesunate

Figure 104: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Bicarbonate vs C_{max} at 48 Hours Post-First Dose of IV Artesunate

Figure 105: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Bicarbonate vs C_{max} at the End of Planned IV Artesunate Dosing

Figure 106: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Bicarbonate vs C_{max} at Time of First Hospital Discharge

Figure 107: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Bicarbonate vs T_{max} at 24 Hours Post-First Dose of IV Artesunate

Figure 108: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Bicarbonate vs T_{max} at 48 Hours Post-First Dose of IV Artesunate

Figure 109: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Bicarbonate vs T_{max} at the End of Planned IV Artesunate Dosing

Figure 110: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Bicarbonate vs T_{max} at Time of First Hospital Discharge

Figure 111: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Bicarbonate vs $t_{1/2}$ at 24 Hours Post-First Dose of IV Artesunate

Figure 112: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Bicarbonate vs $t_{1/2}$ at 48 Hours Post-First Dose of IV Artesunate

Figure 113: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Bicarbonate vs $t_{1/2}$ at the End of Planned IV Artesunate Dosing

Figure 114: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Bicarbonate vs $t_{1/2}$ at Time of First Hospital Discharge

Figure 115: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Glucose vs AUC_{0-12} at 24 Hours Post-First Dose of IV Artesunate

Figure 116: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Glucose vs AUC_{0-12} at 48 Hours Post-First Dose of IV Artesunate

Figure 117: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Glucose vs AUC_{0-12} at the End of Planned IV Artesunate Dosing

Figure 118: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Glucose vs AUC_{0-12} at Time of First Hospital Discharge

Figure 119: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Glucose vs C_{max} at 24 Hours Post-First Dose of IV Artesunate

Figure 120: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Glucose vs C_{max} at 48 Hours Post-First Dose of IV Artesunate

Figure 121: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Glucose vs C_{max} at the End of Planned IV Artesunate Dosing

Figure 122: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Glucose vs C_{max} at Time of First Hospital Discharge

Figure 123: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Glucose vs T_{max} at 24 Hours Post-First Dose of IV Artesunate

Figure 124: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Glucose vs T_{max} at 48 Hours Post-First Dose of IV Artesunate

Figure 125: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Glucose vs T_{max} at the End of Planned IV Artesunate Dosing

Figure 126: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Glucose vs T_{max} at Time of First Hospital Discharge

Figure 127: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Glucose vs $t_{1/2}$ at 24 Hours Post-First Dose of IV Artesunate

Figure 128: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Glucose vs $t_{1/2}$ at 48 Hours Post-First Dose of IV Artesunate

Figure 129: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Glucose vs $t_{1/2}$ at the End of Planned IV Artesunate Dosing

Figure 130: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Serum Glucose vs $t_{1/2}$ at Time of First Hospital Discharge

Figure 131: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Total Bilirubin vs AUC_{0-12} at 24 Hours Post-First Dose of IV Artesunate

Figure 132: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Total Bilirubin vs AUC_{0-12} at 48 Hours Post-First Dose of IV Artesunate

Figure 133: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Total Bilirubin vs AUC_{0-12} at the End of Planned IV Artesunate Dosing

Figure 134: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Total Bilirubin vs AUC_{0-12} at Time of First Hospital Discharge

Figure 135: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Total Bilirubin vs C_{max} at 24 Hours Post-First Dose of IV Artesunate

Figure 136: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Total Bilirubin vs C_{max} at 48 Hours Post-First Dose of IV Artesunate

Figure 137: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Total Bilirubin vs C_{max} at the End of Planned IV Artesunate Dosing

Figure 138: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Total Bilirubin vs C_{max} at Time of First Hospital Discharge

Figure 139: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Total Bilirubin vs T_{max} at 24 Hours Post-First Dose of IV Artesunate

Figure 140: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Total Bilirubin vs T_{max} at 48 Hours Post-First Dose of IV Artesunate

Figure 141: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Total Bilirubin vs T_{max} at the End of Planned IV Artesunate Dosing

Figure 142: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Total Bilirubin vs T_{max} at Time of First Hospital Discharge

Figure 143: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Total Bilirubin vs $t_{1/2}$ at 24 Hours Post-First Dose of IV Artesunate

Figure 144: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Total Bilirubin vs $t_{1/2}$ at 48 Hours Post-First Dose of IV Artesunate

Figure 145: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Total Bilirubin vs $t_{1/2}$ at the End of Planned IV Artesunate Dosing

Figure 146: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Total Bilirubin vs $t_{1/2}$ at Time of First Hospital Discharge

Figure 147: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Direct Bilirubin vs AUC_{0-12} at 24 Hours Post-First Dose of IV Artesunate

Figure 148: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Direct Bilirubin vs AUC_{0-12} at 48 Hours Post-First Dose of IV Artesunate

Figure 149: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Direct Bilirubin vs AUC_{0-12} at the End of Planned IV Artesunate Dosing

Figure 150: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Direct Bilirubin vs AUC_{0-12} at Time of First Hospital Discharge

Figure 151: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Direct Bilirubin vs C_{max} at 24 Hours Post-First Dose of IV Artesunate

Figure 152: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Direct Bilirubin vs C_{max} at 48 Hours Post-First Dose of IV Artesunate

Figure 153: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Direct Bilirubin vs C_{max} at the End of Planned IV Artesunate Dosing

Figure 154: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Direct Bilirubin vs C_{max} at Time of First Hospital Discharge

Figure 155: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Direct Bilirubin vs T_{max} at 24 Hours Post-First Dose of IV Artesunate

Figure 156: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Direct Bilirubin vs T_{max} at 48 Hours Post-First Dose of IV Artesunate

Figure 157: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Direct Bilirubin vs T_{max} at the End of Planned IV Artesunate Dosing

Figure 158: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Direct Bilirubin vs T_{max} at Time of First Hospital Discharge

Figure 159: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Direct Bilirubin vs $t_{1/2}$ at 24 Hours Post-First Dose of IV Artesunate

Figure 160: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Direct Bilirubin vs $t_{1/2}$ at 48 Hours Post-First Dose of IV Artesunate

Figure 161: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Direct Bilirubin vs $t_{1/2}$ at the End of Planned IV Artesunate Dosing

Figure 162: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Direct Bilirubin vs $t_{1/2}$ at Time of First Hospital Discharge

Figure 163: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Hemoglobin vs AUC_{0-12} at 24 Hours Post-First Dose of IV Artesunate

Figure 164: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Hemoglobin vs AUC_{0-12} at 48 Hours Post-First Dose of IV Artesunate

Figure 165: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Hemoglobin vs AUC_{0-12} at the End of Planned IV Artesunate Dosing

Figure 166: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Hemoglobin vs AUC_{0-12} at Time of First Hospital Discharge

Figure 167: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Hemoglobin vs C_{max} at 24 Hours Post-First Dose of IV Artesunate

Figure 168: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Hemoglobin vs C_{max} at 48 Hours Post-First Dose of IV Artesunate

Figure 169: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Hemoglobin vs C_{max} at the End of Planned IV Artesunate Dosing

Figure 170: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Hemoglobin vs C_{max} at Time of First Hospital Discharge

Figure 171: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Hemoglobin vs T_{max} at 24 Hours Post-First Dose of IV Artesunate

Figure 172: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Hemoglobin vs T_{max} at 48 Hours Post-First Dose of IV Artesunate

Figure 173: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Hemoglobin vs T_{max} at the End of Planned IV Artesunate Dosing

Figure 174: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Hemoglobin vs T_{max} at Time of First Hospital Discharge

Figure 175: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Hemoglobin vs $t_{1/2}$ at 24 Hours Post-First Dose of IV Artesunate

Figure 176: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Hemoglobin vs $t_{1/2}$ at 48 Hours Post-First Dose of IV Artesunate

Figure 177: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Hemoglobin vs $t_{1/2}$ at the End of Planned IV Artesunate Dosing

Figure 178: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Hemoglobin vs $t_{1/2}$ at Time of First Hospital Discharge

Figure 179: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Creatinine vs AUC_{0-12} at 24 Hours Post-First Dose of IV Artesunate

Figure 180: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Creatinine vs AUC_{0-12} at 48 Hours Post-First Dose of IV Artesunate

Figure 181: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Creatinine vs AUC_{0-12} at the End of Planned IV Artesunate Dosing

Figure 182: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Creatinine vs AUC_{0-12} at Time of First Hospital Discharge

Figure 183: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Creatinine vs C_{max} at 24 Hours Post-First Dose of IV Artesunate

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Figure 185: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Creatinine vs C_{max} at the End of Planned IV Artesunate Dosing

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Figure 187: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Creatinine vs T_{max} at 24 Hours Post-First Dose of IV Artesunate

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Figure 191: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Creatinine vs $t_{1/2}$ at 24 Hours Post-First Dose of IV Artesunate

Figure 192: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Creatinine vs $t_{1/2}$ at 48 Hours Post-First Dose of IV Artesunate

Figure 193: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Creatinine vs $t_{1/2}$ at the End of Planned IV Artesunate Dosing

Figure 194: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – Creatinine vs $t_{1/2}$ at Time of First Hospital Discharge

Figure 195: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – BCS vs AUC_{0-12} at 24 Hours Post-First Dose of IV Artesunate

Figure 196: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – BCS vs AUC_{0-12} at 48 Hours Post-First Dose of IV Artesunate

Figure 197: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – BCS vs AUC_{0-12} at the End of Planned IV Artesunate Dosing

Figure 198: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – BCS vs AUC_{0-12} at Time of First Hospital Discharge

Figure 199: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – BCS vs C_{max} at 24 Hours Post-First Dose of IV Artesunate

Figure 200: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – BCS vs C_{max} at 48 Hours Post-First Dose of IV Artesunate

Figure 201: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – BCS vs C_{max} at the End of Planned IV Artesunate Dosing

Figure 202: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – BCS vs C_{max} at Time of First Hospital Discharge

Figure 203: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – BCS vs T_{max} at 24 Hours Post-First Dose of IV Artesunate

Figure 204: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – BCS vs T_{max} at 48 Hours Post-First Dose of IV Artesunate

Figure 205: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – BCS vs T_{max} at the End of Planned IV Artesunate Dosing

Figure 206: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – BCS vs T_{max} at Time of First Hospital Discharge

Figure 207: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – BCS vs $t_{1/2}$ at 24 Hours Post-First Dose of IV Artesunate

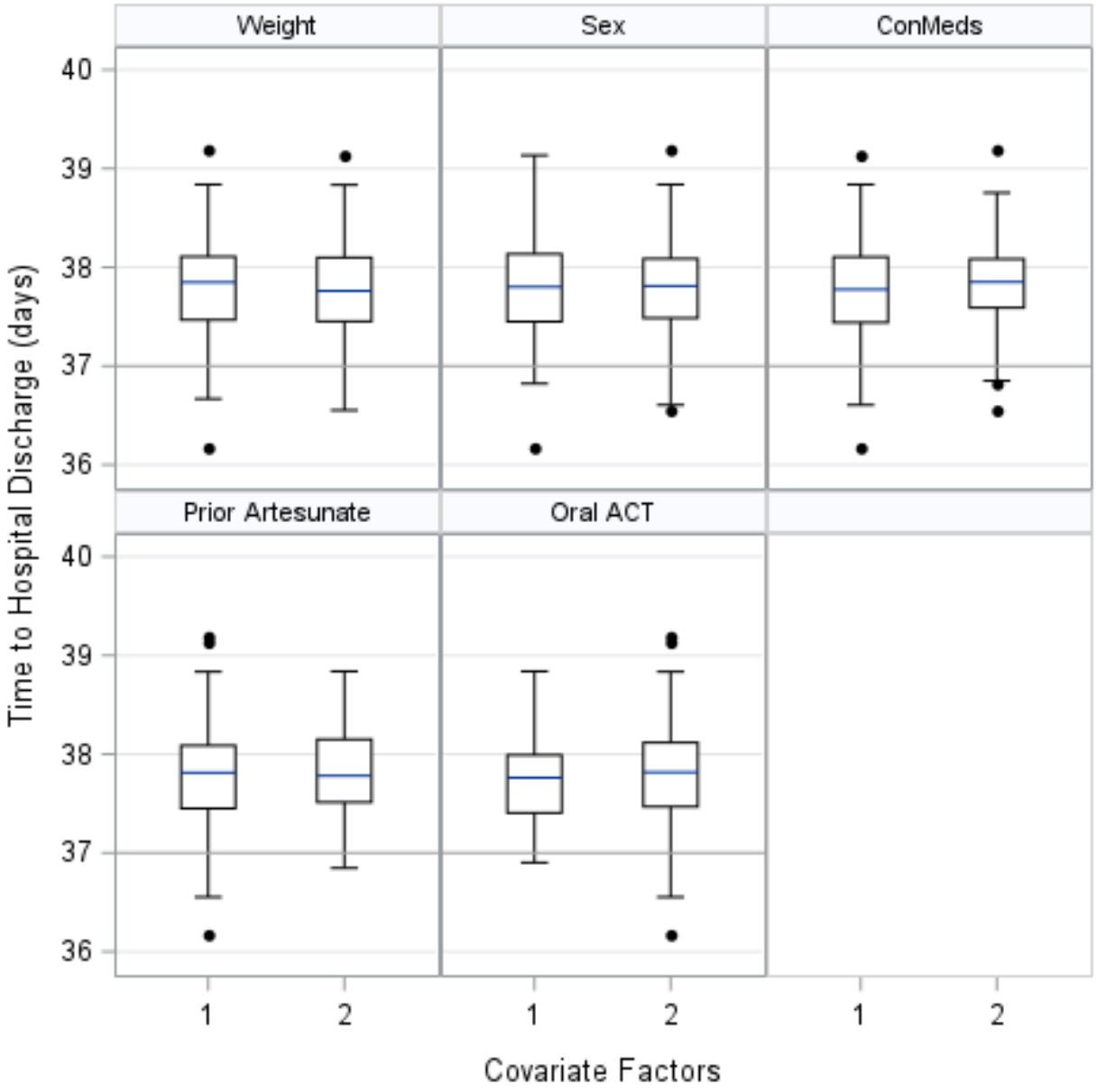
Figure 208: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – BCS vs $t_{1/2}$ at 48 Hours Post-First Dose of IV Artesunate

Figure 209: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – BCS vs $t_{1/2}$ at the End of Planned IV Artesunate Dosing

Figure 210: Markers of Physiological Dysfunction vs Exposure Parameter by Exposure Parameter and Timepoint – BCS vs $t_{1/2}$ at Time of First Hospital Discharge

Figure 211: Boxplots of Time to Hospital Discharge by Covariate – PD Analysis Population

[Implementation Note: This is a sample figure.]



Notes: ConMeds = Receipt of Concomitant Medications.
Covariate Factor levels are as follows. Weight: {1 = <20 kg, 2 = ≥20 kg}. Sex: {1 = Male, 2 = Female}. ConMeds: {1 = Did Not Receive Concomitant Medications, 2 = Received Concomitant Medications}. Prior Artesunate: {1 = No IV Artesunate or Other Artemisinin-Based Therapy Before Enrollment, 2 = Received IV Artesunate or Other Artemisinin-Based Therapy Before Enrollment}. Oral ACT: {1 = Did Not Receive Any Oral ACT, 2 = Received Oral ACT}.

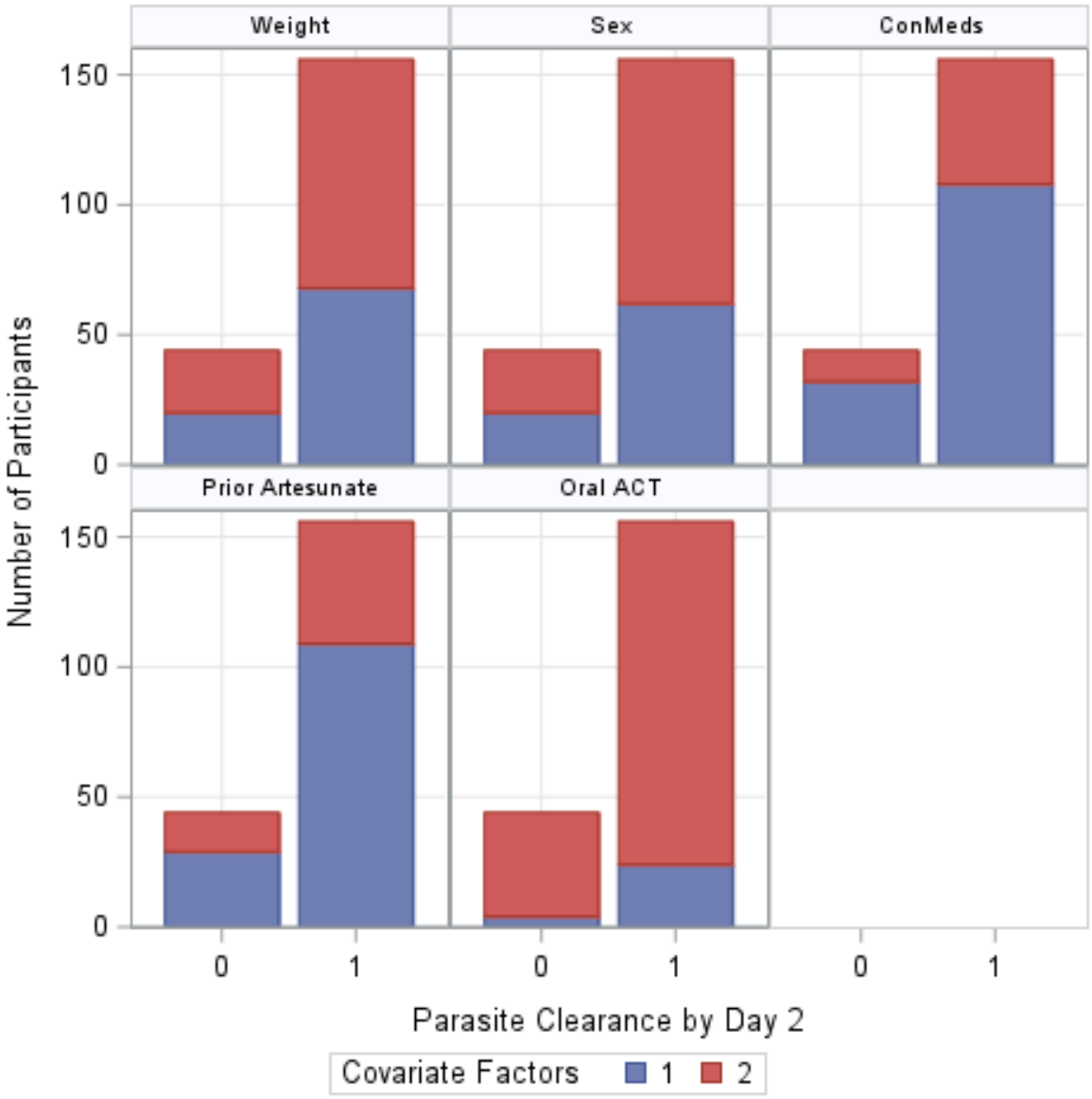
Figures with similar format:

Figure 212: Boxplots of PCT_{50} by Covariate – PD Analysis Population

Figure 213: Boxplots of PCT_{90} by Covariate – PD Analysis Population

Figure 214: Stacked Bar Charts of Total Parasite Clearance by Day 2 – PD Analysis Population

[Implementation Note: This is a sample figure.]

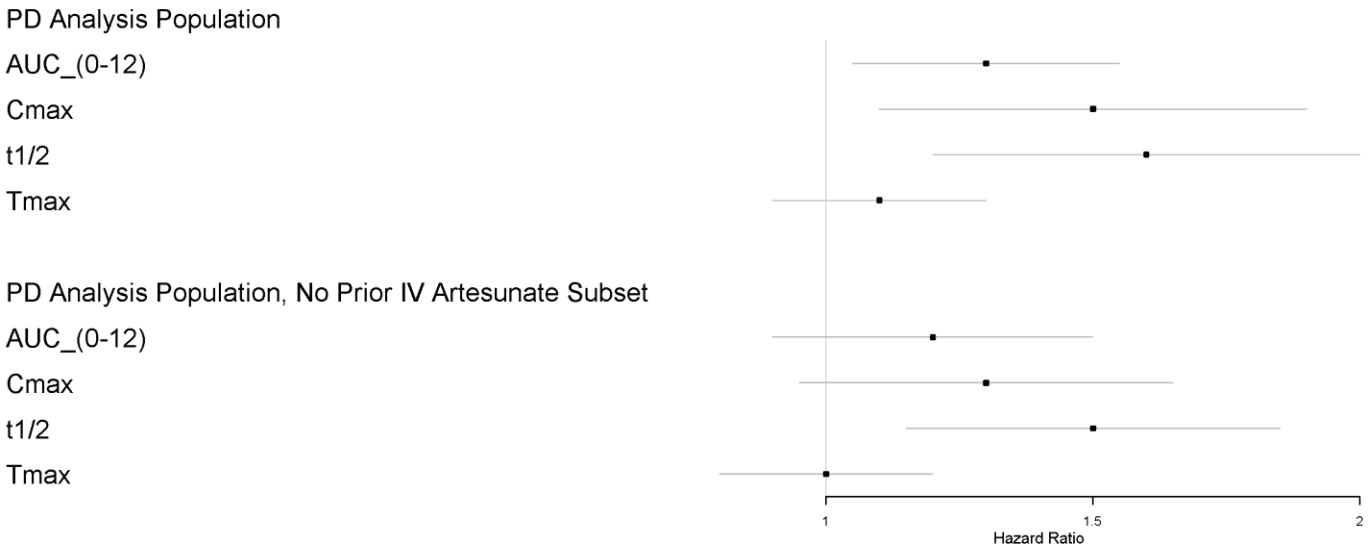


Notes: ConMeds = Receipt of Concomitant Medications.
Covariate Factor levels are as follows. Weight: {1 = <20 kg, 2 = ≥20 kg}. Sex: {1 = Male, 2 = Female}. ConMeds: {1 = Did Not Receive Concomitant Medications, 2 = Received Concomitant Medications}. Prior Artesunate: {1 = No IV Artesunate or Other Artemisinin-Based Therapy Before Enrollment, 2 = Received IV Artesunate or Other Artemisinin-Based Therapy Before Enrollment}. Oral ACT: {1 = Did Not Receive Any Oral ACT, 2 = Received Oral ACT}.
Total parasite clearance by day 2 is determined using blood smears collected within 50 hours post-first dose of IV artesunate.

Figure 215: Forest Plots of Hazard Ratios for Time to Hospital Discharge by PK Exposure Parameter – PD Analysis Population

[Implementation Note: This is a sample figure. Exposure parameters will include AUC_{0-12}, C_{max}, $t_{1/2}$, and T_{max}. Units will also be given in parentheses for each exposure parameter. Bars correspond to the limits of the 95% CIs for the hazard ratios.

"PD Analysis Population, No Prior IV Artesunate Subset" will be updated to "PD Analysis Population, No Prior IV Artesunate or Other Artemisinin-Based Therapy Subset".]



Figures with Similar Format:

Figure 216: Forest Plots of Hazard Ratios for PCT_{50} by PK Exposure Parameter – PD Analysis Population

Figure 217: Forest Plots of Hazard Ratios for PCT_{90} by PK Exposure Parameter – PD Analysis Population

Figure 218: Forest Plots of Odds Ratios for Total Parasite Clearance by Day 2 by PK Exposure Parameter – PD Analysis Population

[Implementation Note: The x-axis label for this figure will be "Odds Ratio".]

14.3.1.1 Solicited Adverse Events

No solicited adverse events are collected for this study.

14.3.1.2 Unsolicited Adverse Events

Figure 219: Frequency of Related Adverse Events by MedDRA System Organ Class and Severity

[Implementation Note: This figure includes serious and non-serious unsolicited adverse events deemed related to study product or study procedure.

This figure will have 3 panels: "Related to IV Artesunate (N=X)", "Related to Oral ACT (N=X)", and "Related to Study Procedures (N=X)".

The SOCs should be sorted in descending frequency; e.g., for this figure, "Infections and infestations" should be listed first.]

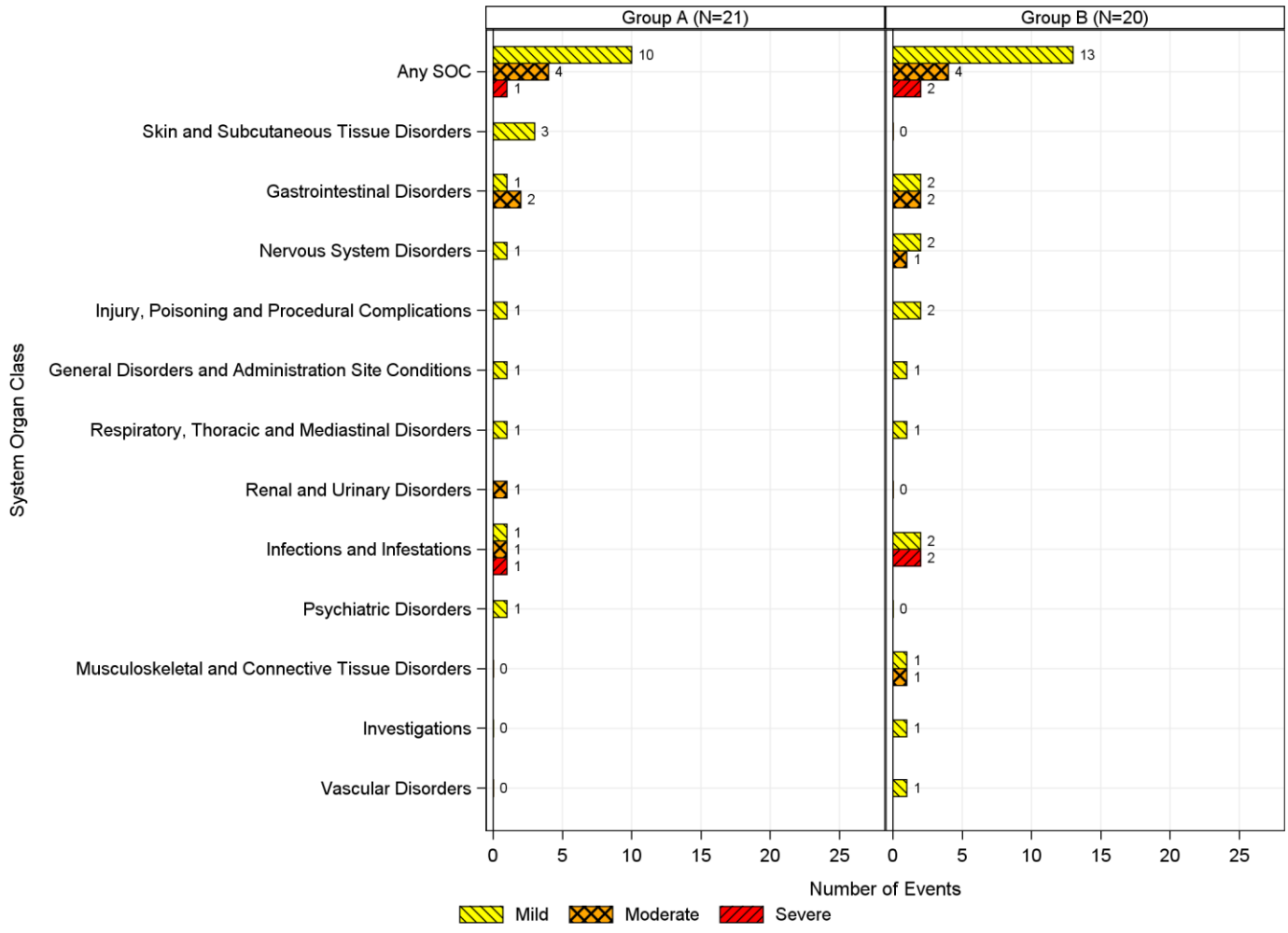
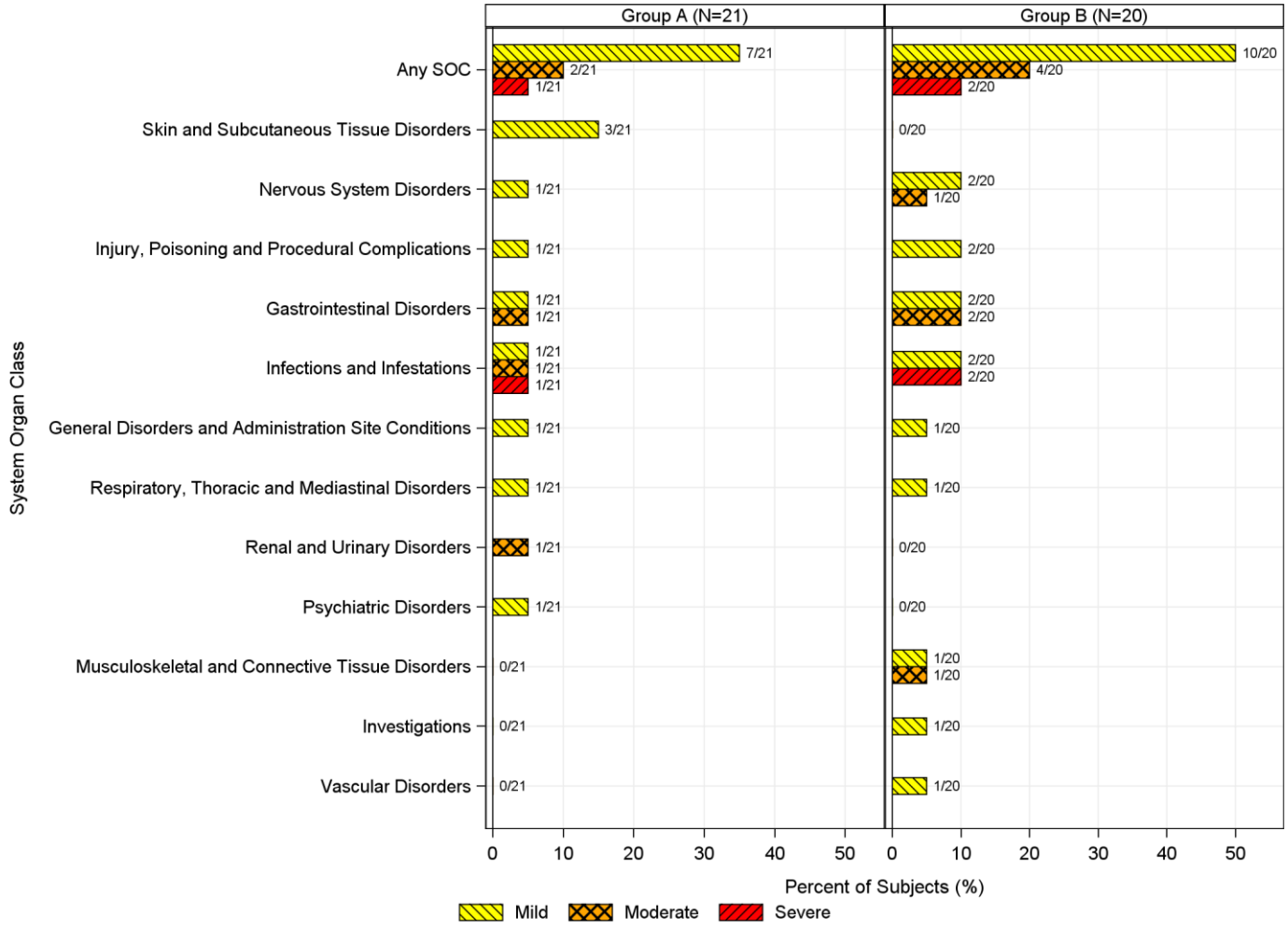


Figure 220: Incidence of Related Adverse Events by MedDRA® System Organ Class and Maximum Severity

[Implementation Note: This figure includes serious and non-serious unsolicited adverse events deemed related to study product or study procedure.

This figure will have 3 panels: "Related to IV Artesunate (N=X)", "Related to Oral ACT (N=X)", and "Related to Study Procedures (N=X)".

The SOCs should be sorted in descending frequency; e.g., for this figure, "Infections and infestations" should be listed first.]

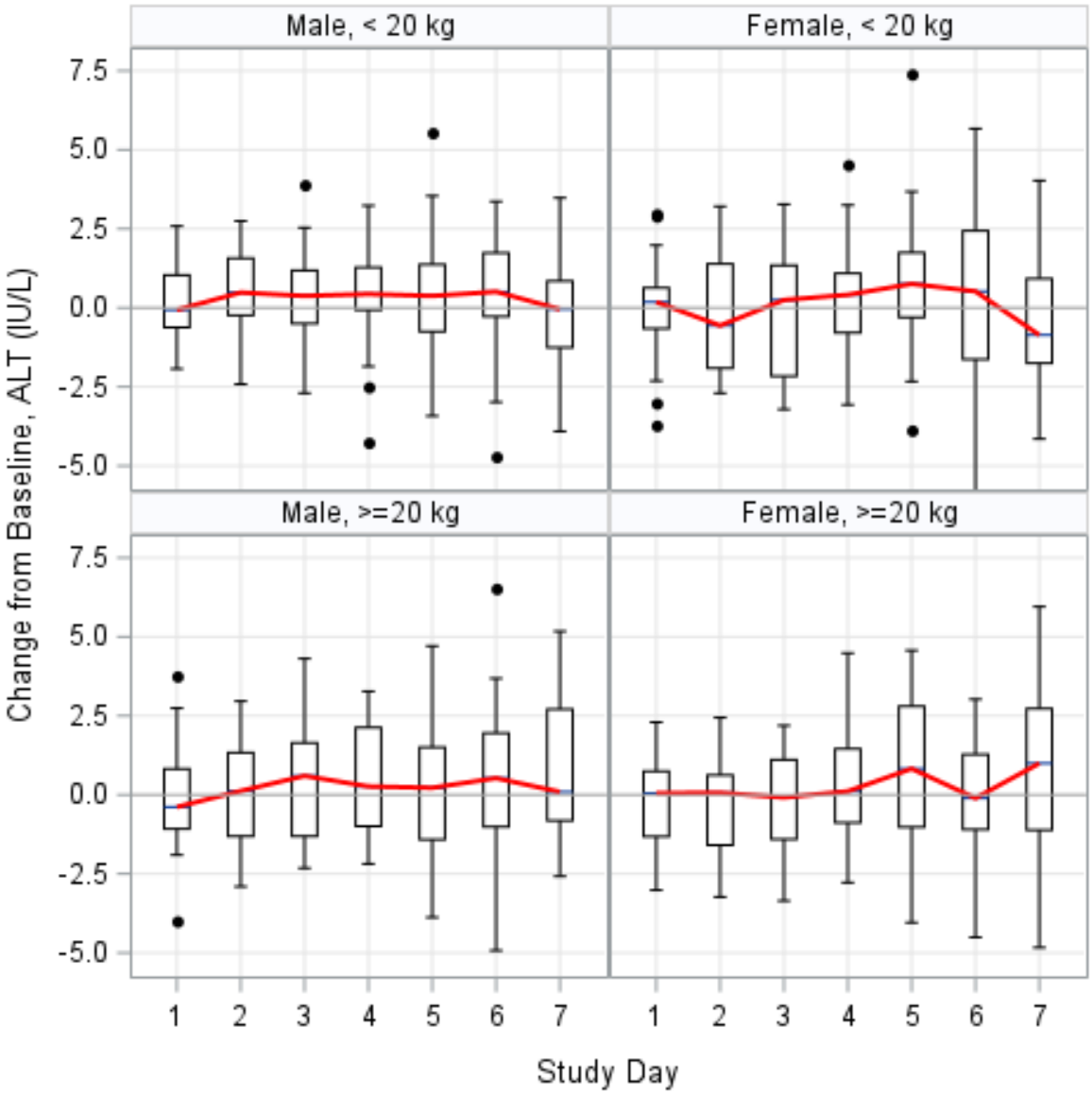


14.3.5 Displays of Laboratory Results

14.3.5.1 Chemistry Results

Figure 221: Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter, Sex, and Weight Group – ALT (IU/L)

[Implementation Note: This is just a sample figure.]



Figures with Similar Format:

Figure 222: Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter, Sex, and Weight Group – AST (IU/L)

[Implementation Note: This figure will include Study Days 1, 2, 3, 4, 5, 6, and 7 on the x-axis.]

Figure 223: Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter, Sex, and Weight Group – Blood Urea Nitrogen (mmol/L)

[Implementation Note: This figure will include Study Days 1, 2, 3, 4, 5, 6, and 7 on the x-axis.]

Figure 224: Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter, Sex, and Weight Group – Calcium (mmol/L)

[Implementation Note: This figure will include Study Days 1, 2, 3, 4, 5, 6, and 7 on the x-axis.]

Figure 225: Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter, Sex, and Weight Group – Creatinine (µmol/L)

[Implementation Note: This figure will include Study Days 1, 2, 3, 4, 5, 6, and 7 on the x-axis.]

Figure 226: Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter, Sex, and Weight Group – Direct Bilirubin (µmol/L)

[Implementation Note: This figure will include Study Days 1, 2, 3, 4, 5, 6, and 7 on the x-axis.]

Figure 227: Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter, Sex, and Weight Group – Glucose (mmol/L)

[Implementation Note: This figure will include Study Days 1, 2, 3, 4, 5, 6, and 7 on the x-axis.]

Figure 228: Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter, Sex, and Weight Group – Potassium (mmol/L)

[Implementation Note: This figure will include Study Days 1, 2, 3, 4, 5, 6, and 7 on the x-axis.]

Figure 229: Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter, Sex, and Weight Group – Serum Bicarbonate (mmol/L)

[Implementation Note: This figure will include Study Days 1, 2, 3, 4, 5, 6 7, and 14 on the x-axis.]

Figure 230: Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter, Sex, and Weight Group – Serum Lactate (mmol/L)

[Implementation Note: This figure will include Study Days 1, 2, 3, 4, 5, 6, and 7 on the x-axis.]

Figure 231: Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter, Sex, and Weight Group – Sodium (mmol/L)

[Implementation Note: This figure will include Study Days 1, 2, 3, 4, 5, 6, and 7 on the x-axis.]

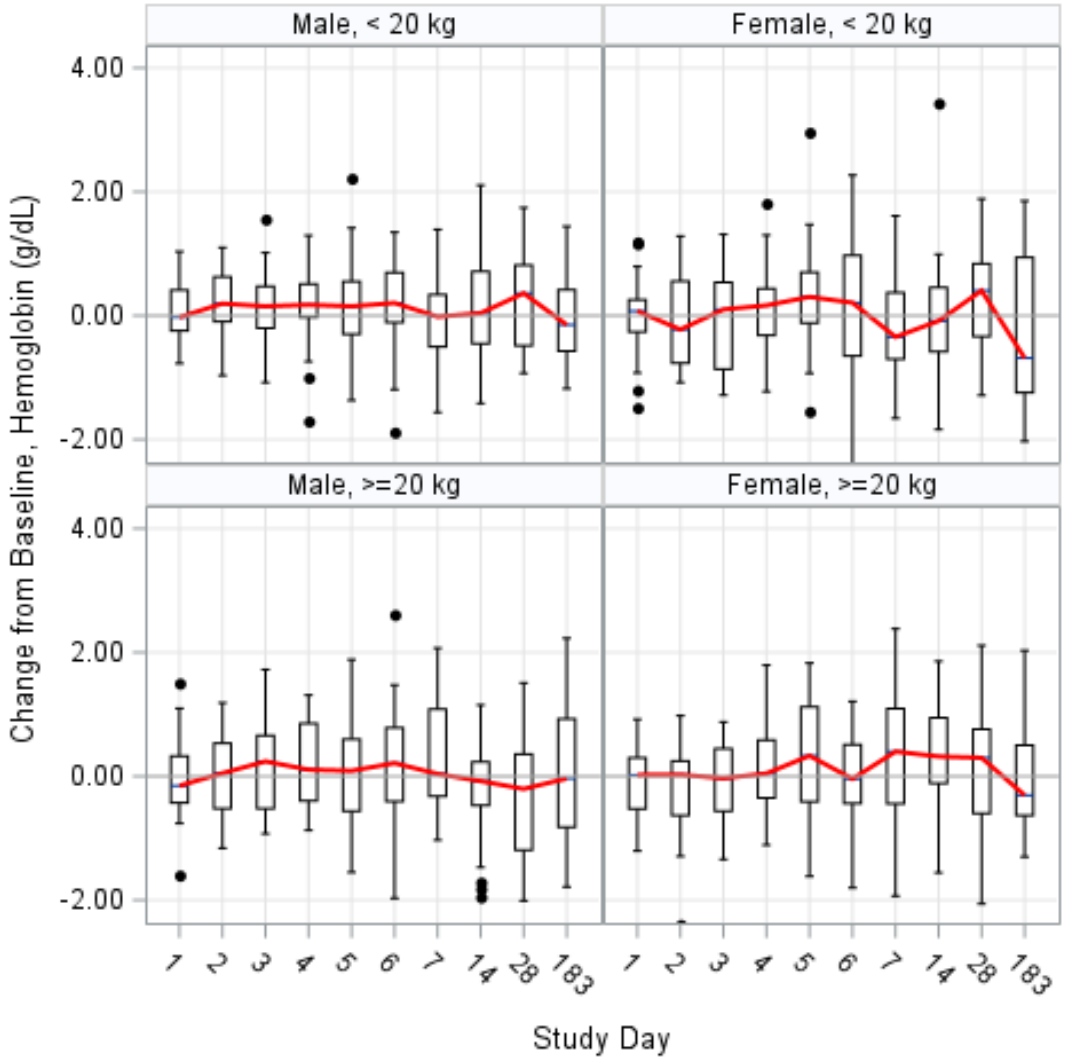
Figure 232: Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter, Sex, and Weight Group – Total Bilirubin (µmol/L)

[Implementation Note: This figure will include Study Days 1, 2, 3, 4, 5, 6, and 7 on the x-axis.]

14.3.5.2 Hematology Results

Figure 233: Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter, Sex, and Weight Group – Hemoglobin (g/dL)

[Implementation Note: This is just a sample figure.]



Figures with Similar Format:

Figure 234: Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter, Sex, and Weight Group – Neutrophil Count (10^9/L)

[Implementation Note: This figure will include Study Days 1, 2, 3, 4, 5, 6, 7, and 183 on the x-axis.]

Figure 235: Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter, Sex, and Weight Group – Neutrophil Percentage (%)

[Implementation Note: This figure will include Study Days 1, 2, 3, 4, 5, 6, 7, and 183 on the x-axis.]

Figure 236: Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter, Sex, and Weight Group – Platelets (10^9/L)

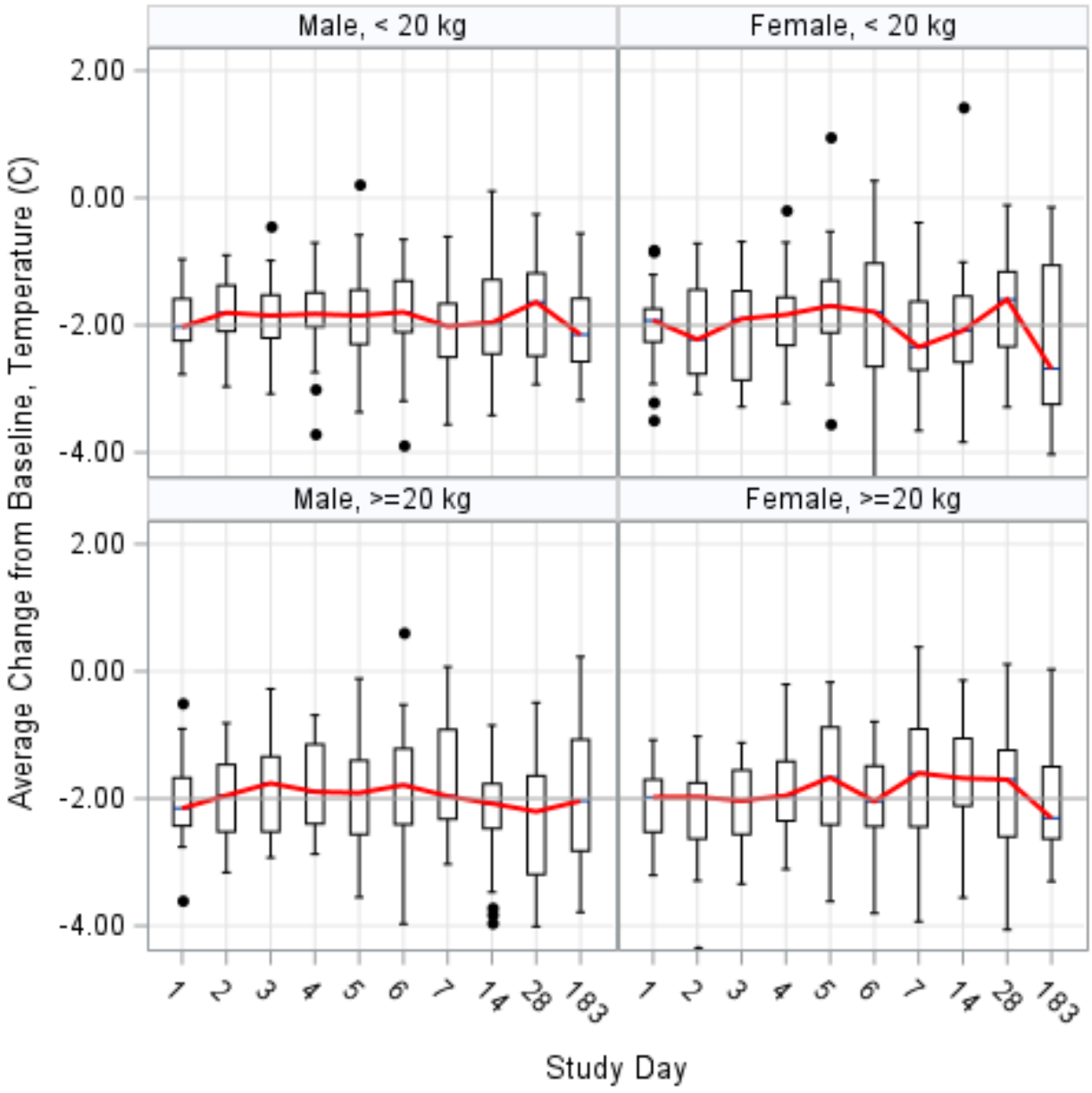
[Implementation Note: This figure will include Study Days 1, 2, 3, 4, 5, 6, 7, and 183 on the x-axis.]

Figure 237: Laboratory Results by Scheduled Visits: Change from Baseline by Laboratory Parameter, Sex, and Weight Group – WBC (10^9/L)

[Implementation Note: This figure will include Study Days 1, 2, 3, 4, 5, 6, 7, and 183 on the x-axis.]

14.3.6 Displays of Vital Signs

Figure 238: Vital Signs by Scheduled Visits: Average Change from Baseline by Vital Sign, Sex, and Weight Group – Temperature (˚C)



Note: Vital signs were collected approximately every 6 hours until 6 hours post parasite clearance. This figure summarizes the average changes from baseline in vital signs for each study day.

Figures with Similar Format:

Figure 239: Vital Signs by Scheduled Visits: Average Change from Baseline by Vital Sign, Sex, and Weight Group – Systolic Blood Pressure (mmHg)

Figure 240: Vital Signs by Scheduled Visits: Average Change from Baseline by Vital Sign, Sex, and Weight Group – Diastolic Blood Pressure (mmHg)

Figure 241: Vital Signs by Scheduled Visits: Average Change from Baseline by Vital Sign, Sex, and Weight Group – Respiratory Rate (breaths/min)

Figure 242: Vital Signs by Scheduled Visits: Average Change from Baseline by Vital Sign, Sex, and Weight Group – Pulse (beats/min)

APPENDIX 3. LISTINGS MOCK-UPS

LISTINGS

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Listing 1: **16.1.6: Listing of Participants Receiving Investigational Product**

(not included in SAP, but this is a placeholder for the interim CSR)

16.2 Database Listings by Participant

16.2.1 Discontinued Participants

Listing 2: 16.2.1: Early Terminations or Discontinued Participants

[Implementation Note: Category will be either "Early Termination" or "Treatment Discontinuation." In the "Reason" column, concatenate any "specify" fields, including AE number and DV number.

Sort order: Participant ID, Category (alphabetically, in the case a participant both terminates early and discontinues treatment).]

Participant ID	Category	Reason for Early Termination or Treatment Discontinuation	Study Day
Note: Discontinuation of treatment only applies to discontinuation of IV artesunate.			

16.2.2 Protocol Deviations

Listing 3: 16.2.2.1: Participant-Specific Protocol Deviations

[Implementation Note: Deviations will be classified as Major or Minor. In the "Deviation" column, concatenate any and all "specify" fields (including visit number, etc.). If "Reason for Deviation" is "Other," concatenate "specify" field, separate by a colon, e.g., "Other: Participant refusal."

Review the site comments carefully. Replace any occurrences of the PATID in the comments with the USUBJID.

Sort order: Participant ID, DV Number.]

Participant ID	DV Number	Deviation	Deviation Category	Study Day	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Participant Termination?	Deviation Affected Product Stability?	Deviation Classification	Deviation Resolution	Comments

Listing 4: 16.2.2.2: Non-Participant-Specific Protocol Deviations

[Implementation Note: Deviations will be classified as Major or Minor. In the "Deviation" column, concatenate any and all "specify" fields (including visit number, etc.). If "Reason for Deviation" is "Other," concatenate "specify" field, separate by a colon, e.g., "Other: Participant refusal."

Sort order: Start Date, Deviation.]

Start Date	Deviation	End Date	Reason for Deviation	Deviation Resulted in Participant Termination?	Deviation Affected Product Stability?	Deviation Category	Deviation Classification	Deviation Resolution	Comments

16.2.3 Participants Excluded from the Efficacy Analysis

Listing 5: 16.2.3: Participants Excluded from Analysis Populations

Participant ID	Analyses in which Participant is Included	Analyses from which Participant is Excluded	Results Available?	Reason Participant Excluded
	[e.g., Safety, Population PK Analysis, PD Analysis]	[e.g., Safety Analysis, Population PK Analysis, PD Analysis]		

Note: "Yes" in the "Results available" column indicates that available data were removed from the analysis. "No" indicates that no data were available for inclusion in the analysis.

16.2.4 Demographic Data

Listing 6: 16.2.4.1: Demographic Data

[Implementation Note: If a participant is multi-racial, in "Race" column, note "Multiple: (list races, separated by a comma)."

Weight-for-age and Height-for-age Z-scores are calculated for participants younger than 60 months. If the participant is older than 60 months, these Z-scores should be displayed as "NA".

Village/Town of Residence will be formatted using SAS PROPCASE (the first letter of each word will be capitalized).

Sort order: Participant ID.]

Participant ID	Sex	Age at Enrollment (years)	Height (cm)	Weight (kg)	Height-for-Age Z-Score	Weight-for-Age Z-Score	Ethnicity	Race	Village/Town of Residence

Listing 7: 16.2.4.2: Pre-Existing and Concurrent Medical Conditions

[Implementation Note: "Condition Start Day" and "Condition End Day" are relative to enrollment (which is Day 1, day before enrollment is Day -1). Rather than use exact study days, categorize as follows:

- > 5 years before enrollment
- 1-5 years before enrollment
- 1-12 months before enrollment
- Within 1 month of enrollment
- During study
- If ongoing, display "Ongoing" in the "Condition End Day" column

Sort order: Participant ID, MH Number.]

Participant ID	MH Number	Medical History Term	Condition Start Day	Condition End Day	MedDRA System Organ Class	MedDRA Preferred Term

16.2.5 Compliance and/or Drug Concentration Data

Listing 8: 16.2.5.1: IV Artesunate Compliance Data

[Implementation Note: Sort order: Participant ID, Timepoint, Administration Date, Infusion Start Time.]

Participant ID	Dose Amount[a]	Infusion Amount[b]	Timepoint[c]	Administered Before Enrollment?	Administration Date	Administration Time
				Yes/No	ddMMMyyyy	hh:mm

Notes:
[a] Dose amount of IV artesunate is calculated as 3.0-mg/kg/dose for participants weighing < 20 kg, or 2.4-mg/kg/dose for children weighing ≥ 20 kg.
[b] Infusion amount of IV artesunate is calculated based on the participant's body weight at screening as: $\{3.0 \text{ mg} \times \text{body weight (kg)}\}/(10 \text{ mg/mL})$ for participants weighing < 20 kg at screening, and as $\{2.4 \text{ mg} \times \text{body weight (kg)}\}/(10 \text{ mg/mL})$ for participants weighing ≥ 20 kg at screening.
[c] Timepoint is given in hours relative to first dose of IV artesunate.

Listing 9: 16.2.5.2: Oral ACT Compliance Data

[Implementation Note: Planned Dose Number will be determined using administration date, whether the treatment was administered, and whether the administration was successful.
Sort order: Participant ID, Administration Date, Administration Time.]

Participant ID	Name of Treatment Administered	Planned Dose Number	Administration Date	Administration Time	Was Treatment Administration Successful?
		X	ddMMMyyyy	hh:mm	Yes/No

Listing 10: 16.2.5.3: Overall Dosing Compliance Data

[Implementation Note: Sort order: Participant ID]

Participant ID	Received IV Artesunate Before Enrollment? (Number of Doses)	Received On-Study IV Artesunate? (Number of Doses)	Received Oral ACT? (Number of Doses)	Transitioned to oral antimalarial therapy per guidelines? (Reason)
	Yes/No (x)	Yes/No (x)	Yes/No (x)	Yes/No (Reason)

16.2.6 Individual Pharmacodynamic and Pharmacokinetic Response Data

Listing 11: 16.2.6.1: Individual BCS Response Data

[Implementation Note: Time from First Dose will be rounded to the nearest tenths place.

Sort Order: Participant ID, Time from First Dose]

Participant ID	Time (hours) from First Dose[a]	Actual Study Day	Actual Time (24 hour clock)	Eye Movement Score (0 or 1)	Best Motor Response Score (0, 1, or 2)	Best Verbal Response Score (0, 1, or 2)	Total BCS
			hh:mm				

Note:
[a] Time (hours) from first dose is relative to first dose of IV artesunate.

Listing 12: 16.2.6.2: Individual DHA Concentrations in Plasma

[Implementation Note: Laboratory Reported Concentration will give verbatim value reported by lab (with minimal formatting, as needed) and will use a character value. Analysis Concentration will report the value actually used in the PK analysis and will use a numeric variable. If no samples are excluded from the PK analysis, then Excluded from PK Analysis and Reason for Exclusion from PK Analysis columns will be removed.

Sort order: Weight Group, Participant ID, and Actual Time.]

Weight Group	Participant ID	Planned Collection Time (h)[a]	Actual Collection Time (h)[a]	Laboratory Reported Concentrations (ng/mL)	Analysis Concentrations (ng/mL)	Excluded from PK Analysis	Reason Excluded from PK Analysis
		0-1 h	0.3 h			Yes/No	
		1-2.5 h	1.8 h				

Note:
[a] Collection times are measured in hours from first on-study dose.

Listing 13: 16.2.6.3: Individual PK Exposure Parameter Estimates

[Implementation Note: Parameters that are not estimable for a participant will be listed as "NE".

Sort order: Weight Group and Participant ID.]

Weight Group	Participant ID	AUC_{0-12} (ng*h/mL)	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)
Notes: NE = Not Estimable.					

Listing 14: 16.2.6.4: Individual Parasitemia Results from Thick and Thin Blood Smears

[Implementation Note:

Planned Collection Times may include 0-2 h, 4-8 h, 10-14 h, 22-26 h, 34-38 h, and 46-50 h, etc. For unplanned parasitemia tests, Planned Collection Time will be presented as "-".

Species Identified will only be populated if thin blood smear is performed and can include any of the following: P. falciparum, P. ovale, P. vivax, or P. malariae. If thin blood smear is not performed, Species Identified will be "NA".

Sort order: Weight Group, Participant ID, Actual Collection Time.]

Weight Group	Participant ID	Planned Collection Time (h)[a]	Actual Collection Time (h)[a]	Thick Smear Performed?	Parasite Density (# Parasites per 200 WBC)	Thin Smear Performed?	Species Identified
		0-2 h	0.3 h	Yes/No		Yes/No	
		4-8 h	4.8 h				

Listing 15: 16.2.6.5: Individual Log-Parasite Density v. Time Curve Parameter Estimates

[Implementation Note:

Sort order: Weight Group and Participant ID.]

Weight Group	Participant ID	K (1/h)	t_{lag} (h)

Notes: K = the clearance rate constant estimated from the log-linear phase of the log-parasite density v. time curve. t_{lag} = the estimated duration (h) of the lag time of the log-parasite density v. time curve.

16.2.7 Adverse Events

Listing 16: 16.2.7.3: Unsolicited Adverse Events

[Implementation Note: This listing includes all unsolicited adverse events.

If the event is ongoing (no stop date), indicate "ongoing" for the "Duration."

If related to study treatment, then in the "Relationship to Study Treatment" column indicate whether the SAE was related to IV Artesunate or Oral ACT (e.g., "Related: IV Artesunate" or "Related: Oral ACT").

In the "If Not Related, Alternate Etiology" column, merge the 2 data fields for collecting alternate etiology, separate by a colon.

Sort order: Participant ID, No. of Days Post Enrollment, AE Number.

If the table will be multi-page, move the footnote/explanation to the footer so that it repeats for each page of the table]

Adverse Event	No. of Days Post Enrollment (Duration)	No. of Days Post Enrollment the Event Became Serious	Severity	SAE?	Relationship to Study Treatment	Relationship to Study Procedures	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Participant Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Participant ID: , AE Number:												
Comments:												
Participant ID: , AE Number:												
Comments:												
Note: For additional details about SAEs, see Table 31.												

16.2.8 Individual Laboratory Measurements

Listing 17: 16.2.8.1: Clinical Laboratory Results – Chemistry

[Implementation Note: These listings (for hematology, chemistry, and urinalysis) include all laboratory results, scheduled and unscheduled. These listings are not color-coded, but for abnormal laboratory results recorded as AEs, the AE number and severity should be included in parentheses in the Recorded as an AE? column, e.g., "Yes (001: Mild)".

Sort order: Participant ID, Planned Timepoint, Actual Study Day, Laboratory Parameter.]

Participant ID	Planned Timepoint	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result	Recorded as an AE? (AE Number: Severity Grade)

Listing 18: 16.2.8.2: Clinical Laboratory Results – Hematology

[Implementation Note: These listings (for hematology, chemistry, and urinalysis) include all laboratory results, scheduled and unscheduled. These listings are not color-coded, but for abnormal laboratory results recorded as AEs, the AE number and severity should be included in parentheses in the Recorded as an AE? column, e.g., "Yes (001: Mild)".

Sort order: Participant ID, Planned Timepoint, Actual Study Day, Laboratory Parameter.]

Participant ID	Planned Timepoint	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result	Recorded as an AE? (AE Number: Severity Grade)

Listing 19: 16.2.8.3: Clinical Laboratory Results – Urinalysis

[Implementation Note: These listings (for hematology, chemistry, and urinalysis) include all laboratory results, scheduled and unscheduled. These listings are not color-coded, but for abnormal laboratory results recorded as AEs, the AE number and severity should be included in parentheses in the Recorded as an AE? column, e.g., "Yes (001: Mild)".

Sort order: Participant ID, Planned Timepoint, Actual Study Day, Laboratory Parameter.]

Participant ID	Planned Timepoint	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result

16.2.9 Vital Signs and Physical Exam Findings

Listing 20: 16.2.9.1: Vital Signs

[Implementation Note: This listing includes all vital sign assessments, scheduled and unscheduled.

Sort order: Participant ID, Planned Study Day, Actual Study Day, Actual Time.]

Participant ID	Planned Study Day	Actual Study Day	Actual Time (24 hour clock)	Temperature (°C)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Respiratory Rate (breaths/min)	Pulse (beats/min)

Listing 21: 16.2.9.2: Abnormal Physical Exam Findings

[Implementation Note: This listing includes all abnormal physical exam findings, scheduled and unscheduled. If a participant does not have any findings upon examination, they will not be included in this listing. If reported as an AE, display "Yes" with the AE Description and AE Number in parentheses, e.g., "Yes (Headache; 007)". If there are no abnormal physical exam findings reported as an AE, this column will be removed.

Sort order: Participant ID, Planned Timepoint, Body System, Abnormal Finding.]

Participant ID	Planned Timepoint	Actual Study Day	Body System	Abnormal Finding	Reported as an AE? (AE Description; Number)

16.2.10 Concomitant Medications

Listing 22: 16.2.10: Concomitant Medications

[Implementation Note: "Medication Start Day" and "Medication End Day" are relative to enrollment (which is Day 1, day before enrollment is Day -1).

If ongoing, display "Ongoing" in the "Medication End Day" column. If taken for an AE or MH, display "Yes" with the AE or MH Term and Number in parentheses, e.g., "Yes (Headache; 007)".

Sort order: Participant ID, and CM Number.]

Participant ID	CM Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for an Adverse Event? (AE Description; Number)	Taken for a condition on Medical History? (MH Description; Number)	ATC Level 1 (ATC Level 2)

16.2.11 Pregnancy Reports

No pregnancy information was collected for this study.