Cover Page

Protocol Title: A Phase 1, Dose Escalation, Double Blind, Placebo Controlled Clinical Trial with Controlled Human Malaria Infections (CHMI) to Evaluate Safety, Tolerability, Pharmacokinetics, and Protective Efficacy of an Anti-Malaria Human Monoclonal Antibody, MAM01, in Healthy, Malaria-Naive Adults

Protocol Number: Gates MRI-MAM01-101

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Sponsor Name: Bill & Melinda Gates Medical Research Institute (Gates MRI)

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Short Title: Safety, Tolerability, Pharmacokinetics and Protective Efficacy of MAM01 in Healthy Adults

Protocol Number: Gates MRI-MAM01-101

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Sponsor Name: Bill & Melinda Gates Medical Research Institute (Gates MRI)

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List of Abbreviations

Abbreviation	Description
% AUC_{ext}	Percent AUC extrapolated
λz	Terminal Elimination Rate Constant
ADA	Anti-Drug Antibodies
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Events Special Interest
ALT	Alanine Aminotransferase
AUC	Area Under the Curve
$AUC_{0-\infty}$	Area Under the Curve Time =0 extrapolated to infinity
AUC_{0-CHMI}	Area Under the Curve Time= 0 to the Controlled Human Malaria Infections Challenge
AUC_{0-168}	Area Under the Curve from Time=0 to Time=168
$AUC_{210-378}$	Area Under the Curve from Time=210 to Time=378
AUC_{0-t}	Area Under the Curve from Time=0 to the Last Measurable Concentration
AST	Aspartate aminotransferase
BMI	Body Mass Index
CBC	Complete Blood Count
C_{CHMI}	Concentration at the time of Controlled Human Malaria Infections
CDC	Center for Disease Control
CFR	Code of Federal Regulations
CHMI	Controlled Human Malaria Infections
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
CL/F	Ratio of Clearance to Bioavailability
CMP	Complete Metabolic Profile
COA	Certificate of Analysis
CONSORT	Consolidated Standards of Reporting Trials
COVID or COVID-19	Coronavirus (SARS-CoV-2) Disease
C_{max}	Maximal observed blood concentration
CRADA	Cooperative Research and Development Agreement
CRF	Case Report Form
CRO	Contract Research Organization
CRS	Cytokine Release Syndrome
CSP	Circumsporozoite Protein
CV	Coefficient of Variance
CVD	Center of Vaccine Development
DAIDS	Division of Acquired Immunodeficiency Syndrome
DoD	Department of Defense
DOT	Directly Observed Therapy
EC	Ethics Committee
EC80	Effective concentration leading to 80% maximal response

Abbreviation	Description
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic Acid
EPI	Expanded Program on Immunization
FAAN	Food Allergy and Anaphylaxis Network
FcRN	Neonatal Fc Receptor
FDA	Food and Drug Administration
FiH	First-in-Human
FOCBP	Female of Childbearing Potential
Gates MRI	Gates Medical Research Institute
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	Hepatitis B Surface Antigen
HCG	Human Chorionic Gonadotropin
[redacted]	[redacted]
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HSPB	Human Subjects Protection Branch
ICF	Informed Consent Form
ICH	International Council for Harmonization
ID	Identification
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IIC	Internal Infectivity Controls
IM	Intramuscular
IND	Investigational New Drug
IP	Investigational Product
IPTi	Intermittent Preventative Treatment of Infants
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LLIN	Long-Lasting Insecticidal Bed Nets
LMIC	Low- and Middle-Income Countries
mAb	Monoclonal Antibody
MAD	Multiple Ascending Dose
NIAID	National Institute of Allergy and Infectious Diseases
NOAEL	No-Observed-Adverse-Effect Level
NIH	National Institutes of Health
OHARO	Office of Human and Animal Research Oversight
OHRP	Office for Human Research Protections
PCR	Polymerase Chain Reaction

Abbreviation	Description
PD	Pharmacodynamic
PEF	Peak Expiratory Flow
Pf	Plasmodium falciparum
Ph Eur	European Pharmacopeia
PI	Principal Investigator
PK	Pharmacokinetic
PMC	Perennial Malaria Chemoprevention
PP	Per Protocol
qRT-PCR	Quantitative Polymerase Chain Reaction Assay
QS	Quantum Satis
RUO	Research-Use Only
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SC	Subcutaneous
SMC	Seasonal Malaria Chemoprevention
SoA	Schedule of Activities
SOP	Standard Operating Procedures
SPAQ	Sulfadoxine-Pyrimethamine-Amodiaquine
SP	Sulfadoxine-Pyrimethamine
SRT	Safety Review Team
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Terminal Half Life
TBD	To Be Determined
ULN	Upper Limit of Normal
UMB	University of Maryland, Baltimore
UMD	University of Maryland
UPIRTSOs	Unanticipated Problems Involving Risk to Subjects or Others
US FWA	United States Federalwide Assurance
USA	United States of America
USAMRDC	United States Army Medical Research and Development Command
USP	United States Pharmacopeia
VAMS	Volumetric Absorptive Microsampling Method
Vz	Apparent Volume of Distribution
WBC	White Blood Cell
WHO	World Health Organization
w/v	Weight Per Volume

Sponsor Signatory Page

See appended electronic signature page

Sponsor Signatory	**Date**
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Principal Investigator Signature Page

I have read the protocol, appendices, and accessory materials related to Gates MRI-MAM01-101 Protocol entitled "A Phase 1, Dose Escalation, Double Blind, Placebo Controlled Clinical Trial with Controlled Human Malaria Infections (CHMI) to Evaluate Safety, Tolerability, Pharmacokinetics, and Protective Efficacy of an Anti-Malaria Human Monoclonal Antibody, MAM01, in Healthy, Malaria-Naive Adults" and agree to the following:

- To conduct this study as described by the protocol and any accessory materials
- To protect the rights, safety, and welfare of the participants under my care
- To provide oversight to all personnel to whom study activities have been delegated
- To control all investigational products provided by the sponsor and maintain records of the disposition of those products
- To conduct the study in accordance with:
  - consensus ethical principles derived from international guidelines including the Belmont Report, Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - current International Council for Harmonization Guideline for Good Clinical Practice (GCP)
  - applicable laws and regulations
- To obtain approval for the protocol and all written materials provided to participants prior to initiating the study at my site
- To obtain informed consent – and updated consent in the event of new information or amendments – from all participants enrolled at my study site prior to initiating any study-specific procedures or administering investigational products to those participants
- To maintain study records of each participant and all data required by the protocol.

_____ _____

Principal Investigator Signatory Date

Name: [redacted], MD

Title: Professor of Medicine, Director, Malaria Vaccine and Challenge Unit

Affiliation: University of Maryland, Baltimore Center for Vaccine Development and Global Health

City and Country: Baltimore, Maryland, USA

Protocol Version History and Summary of Changes

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Protocol Version 7.0	05 Sept 2024
Protocol Version 8.0	03 Oct 2024

1 PROTOCOL SUMMARY

1.1 Synopsis

1.1.1 Title

Protocol Title: A Phase 1, Dose Escalation, Double Blind, Placebo Controlled Clinical Trial with Controlled Human Malaria Infection (CHMI) to Evaluate Safety, Tolerability, Pharmacokinetics, and Protective Efficacy of an Anti-Malaria Human Monoclonal Antibody, MAM01, in Healthy, Malaria-Naive Adults

Short Title: Safety, Tolerability, Pharmacokinetics and Protective Efficacy of MAM01 in Healthy Adults

1.1.2 Rationale

Malaria is a life-threatening, mosquito-borne disease that impacts regions of Central and South America, Africa, South and Southeast Asia, the Caribbean, the Middle East and Oceania with more than 94% of worldwide malaria cases and deaths occurring in the Sub-Saharan Africa (World Health Organization (WHO) Malaria Report 2022). Despite multiple public health interventions, there were an estimated 241 million malaria cases and approximately 627,000 deaths in 2020 (WHO Malaria Report 2022). Further reducing the global malaria burden will require the development and implementation of new prevention strategies, including the use of vaccines such as RTS,S/AS01 (Mosquirix™), expanded monthly chemoprevention and antibody-based prophylaxis currently under development. Recently published results from a clinical trial in Mali sponsored by the National Institutes of Health (NIH) demonstrated that among adults who were cleared of existing parasitemia, administration of the long-acting monoclonal antibody CIS43LS led to protection for at least 4 months (Kayentao 2022). A second, more potent monoclonal antibody, L9LS, prevented parasitemia after malaria challenge with *Plasmodium falciparum* (*Pf*) at concentrations of ~10 μg/mL which appear achievable for at least 4 months in duration in children (Wu 2022). These data provide first proof of concept that a monoclonal antibody-based drug may provide prophylaxis for an entire malaria season (6 months or more) in children after a single injection.

Based on the interim analysis from Part A, the effective MAM01 concentration leading to 80% maximal protective response (EC80) falls between 35 and 100 μg/mL, but lack of challenge data in that range of MAM01 concentrations limits further clarification. This is critical information for further development because these concentration values lie within the range of expected concentrations in infants and children for efficacious 4 to 6 month malaria protection.

1.1.3 Objectives and Endpoints

Table 1 outlines study objectives and endpoints**.**

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of a single dose of MAM01 following intravenous (IV) or subcutaneous (SC) administration • To assess the safety and tolerability of administration of a repeated SC dose of MAM01 • To characterize safety laboratory parameters of MAM01 following SC or IV administration	• Solicited local and systemic adverse events (AEs) in the SC cohorts (ie, for injection site reactions) through 7 days post-dose • Unsolicited AEs through Day 28 (single dose or multiple dose) • All serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) and Adverse Events Special Interest (AESIs) through 168 days post-dose (end of trial) • All SUSARs, SAEs and AESIs through 336 days for participants that are re-dosed (Part A Cohorts 2 and 3). • Safety laboratory assessments by grade (grade 1 and above) through end of trial
Secondary	
• To characterize the pharmacokinetics (PK) of MAM01 following SC or IV administration • To characterize the PK of a repeated SC dose of MAM01	PK parameters including: • Maximal observed concentration (C_{max}) • Total area under the curve (AUC) from Time=0 to the last measurable MAM01 concentration (AUC_{0-t}) • Partial AUC's Time= 0 to the CHMI challenge (AUC_{0-CHMI}) • Concentration at the time of CHMI (C_{CHMI}) • Blood terminal elimination rate constant (λz) • Terminal half-life ($t_{1/2}$) • AUC from Time=0 extrapolated to infinity ($AUC_{0-\infty}$) • % AUC extrapolated (% AUC_{ext}) • Bioavailability of SC formulation • For Part A (Cohorts 2 and 3) (participants that are redosed): accumulation ratio $AUC_{0-168}/AUC_{210-378}$
• To characterize protective efficacy against *Pf* following CHMI challenge	• Presence or absence of *Pf* infection (as determined by quantitative polymerase chain reaction assay (qRT-PCR)) after CHMI (through Day 27 post CHMI) • Time to parasitemia after CHMI in each cohort
• To assess the formation of anti-drug antibodies (ADAs) following MAM01 SC and/or IV administration	• Titers of ADAs to MAM01 • For Part A (Cohorts 1, 4 and 5), up to Day 280 • For Part A (Cohorts 2 and 3), up to Day 378 • For Part B (Cohort 6) up to Day 168
Exploratory	
[redacted]	

1.1.4 Disclosure Statement

This is a First-in-Human (FiH) trial of MAM01 monoclonal antibody (mAb) targeting the *Pf CSP*. It is a randomized, double-blind, controlled trial of MAM01 versus placebo to be conducted in healthy adults.

MAM01, also known as mAb-1797, is an engineered version of a human monoclonal antibody generated following vaccination with RTS,S/AS01 vaccine. It binds a unique and conserved epitope at the central region of the NANP repeat regions of the *Pf*CSP and has been shown to protect against malaria infection in multiple *in vivo* studies in animal models. MAM01 was adapted using site-directed mutagenesis in the Fc region, resulting in the inclusion of an LS mutation that has been found to increase product half-life in plasma through antibody recycling through the FcRN receptor (Booth 2018).

1.1.5 Overall Design

This randomized, two-part, dose-escalation design trial will evaluate the safety, tolerability, PK, and protective efficacy of MAM01, as well as safety and PK of repeat SC dosing. Part A will have a double-blind, placebo-controlled design. Part B will randomize participants to one of three open-label MAM01 dose groups; a separate non-randomized group will be enrolled to include participants who will receive no treatment and act as infectivity controls. The primary hypothesis is that MAM01 will be safe and well-tolerated when administered by either IV or SC routes and with repeated SC dosing. The secondary hypotheses are that MAM01 will (1) be detectable in human serum with definable half-life and (2) confer sterilizing protection following a CHMI by mosquito bites. The trial will be conducted at the University of Maryland School of Medicine in the United States of America (USA) and the CHMI mosquito bite challenge will be supported by Sanaria Inc. (Rockville, MD). Study design details are further outlined in Figure 1 and Section 4.2.

1.1.5.1 Trial Participants

Potential participants will be screened to enroll and randomize approximately 61 eligible participants. Alternative participants (n ~ 5) may be recruited to serve as stand-by participants in the event that eligible participants do not show up for Day -1 visit. In Part A, placebo participants will serve as infectivity controls for the CHMI procedure, and the alternative malaria-naïve participants may be also added to the trial to replace any dropouts prior to the CHMI to serve as additional infectivity controls. The additional infectivity control participants will not receive administration of MAM01 or placebo. Assuming that all cohorts are allowed to undergo treatment, approximately 48 participants will be exposed to MAM01 and approximately 7 to placebo.

In Part B, prior to CHMI, a separate non-randomized group of 6 participants will be enrolled, will not receive treatment, and will serve as infectivity controls.

1.1.5.2 Part A

In Part A, the Single Ascending Dose (SAD) component of the trial will have 5 dosing cohorts with approximately 37 participants in total. Participants will be confined at the trial site for at least 6 hours post investigational product (IP) administration. Dose rationale details are outlined in Section 2.4.4. See Table 4 and Figure 1 for the cohort profiles and stepwise dose escalation plan.

Cohort 1 will include 2 sentinel participants: 1 participant will receive 1.5 mg/kg IV MAM01 and 1 participant will receive placebo IV. Following sentinel evaluation for safety, 5 additional participants will receive 1.5 mg/kg IV MAM01 and 1 participant will receive placebo IV.

Thereafter, dose escalation will be staggered by two weeks to allow an adequate safety assessment. Cohort 5 participants will receive the highest dose, 40 mg/kg IV, MAM01 or placebo. CHMI will be initiated for Cohorts 1, 2, 3, 4 and 5 at approximately Day 181 after mAb dosing for the main cohort of participants in Cohort 1.

All participants of Cohorts 2 and 3 will receive a second dose of MAM01 (open label) at least 210 days (± 7 days) post-dose (and after the initial CHMI procedure). These participants will receive a dose of 5 mg/kg SC to help assess for the safety and PK impact of ADA (if any) with repeat dosing. The planned doses may be modified by protocol amendment following completion of the Good Laboratory Practice (GLP) repeat dose toxicology study prior to trial launch and/or accumulation of safety/tolerability/PK data from single-dose ascending cohorts.

1.1.5.3 Part B

In Part B, a single-cohort (Cohort 6) dose expansion phase is planned to evaluate additional concentrations to inform the EC80 based on CHMI. This is desired, as protection was demonstrated in Part A Cohort 5 (> 100 μg/mL at the time of CHMI), but the absence of participants exposed to concentrations between 35-100 μg/mL in the Part A cohorts limits the assessment of the lower concentrations of MAM01.

A total of 18 participants will be randomized into one of 3 dose groups with 6 participants each randomized to receive a single fixed SC dose of open-label MAM01. Trial participants will be confined for at least 2 hours at the trial site for safety monitoring following dosing. Each participant in this cohort will have up to 10 visits over 84 days. A CHMI will be conducted 35 days after receiving the SC dose of MAM01. In addition, a separate non-randomized group will be enrolled prior to CHMI to include 6 participants who will receive no treatment and act as infectivity controls. (See Table 5 and Figure 1).

1.1.5.4 Controlled Human Malaria Infection (CHMI)

Each CHMI procedure will be conducted using *Anopheles stephensi* mosquitoes reared by an experienced insectary at Sanaria Inc., Rockville, Maryland, USA and entomologic staff who travel to University of Maryland to conduct the mosquito bite challenge.

Mosquitoes are infected via membrane feeds of pathogen-free blood containing the cultured *P. falciparum* NF54 strain and reared per standardized procedures until they are infectious (containing mature sporozoites in the salivary glands). During the mosquito feeding step (known as CHMI Bite Challenge) of the CHMI procedure, up to 5 mosquitoes at a time will be allowed to feed on each participant under controlled conditions. Following exposure, the mosquitoes will be immediately dissected to confirm the presence of a blood meal and to determine the infectivity rate and the salivary gland score. If fewer than five mosquitoes have a blood meal, then additional mosquitoes will be allowed to feed until 5 bites showing presence of a blood meal and a minimum 2+ salivary gland score has been achieved for each participant.

Participants randomized to receive placebo (IV or SC) in Cohorts 1-5 will also serve as an infectivity internal reference for the CHMI procedure. Trial participants will have additional visits related to the CHMI procedures. Rescue antimalarial therapy will be initiated after 2 positive qRT-PCR results or a positive thick blood smear. Those who remain negative will be empirically treated on Day 27 (Visit 28).

If any participant in Cohort 1-5 in Part A or Cohort 6 in Part B drops out of the trial before either CHMI procedure starts, the participant may be replaced by an additional malaria-naïve participant to serve as infectivity control to ensure at least 6 volunteers validate the infectivity of the CHMI procedure. The replacement infectivity control participants will not receive administration of MAM01 or placebo.

1.1.6 Post CHMI Follow-Up

Regardless of CHMI outcome and following the parasitemia evaluations, participants who received MAM01 will continue to follow the Schedule of Activities (SoA), as outlined in Appendix 1: Table 8 (for participants in Cohorts 1, 4 and 5), Table 9 (for participants in Cohorts 2 and 3 receiving repeated dosing with IP following the CHMI procedure), and Table 10 (for participants in Cohort 6 - Dose Expansion Cohort). CHMI procedures are outlined in Table 11 for Part A, and in Table 12 for Part B.

1.1.7 Interim Analyses

Two interim analyses are planned: a blinded interim analysis of safety and tolerability after a minimum of 56 days for all of the cohorts of Part A (dose escalation), and an unblinded assessment of efficacy after the first CHMI procedure, and a unblinded analysis of PK from Part A participants prior to the CHMI.

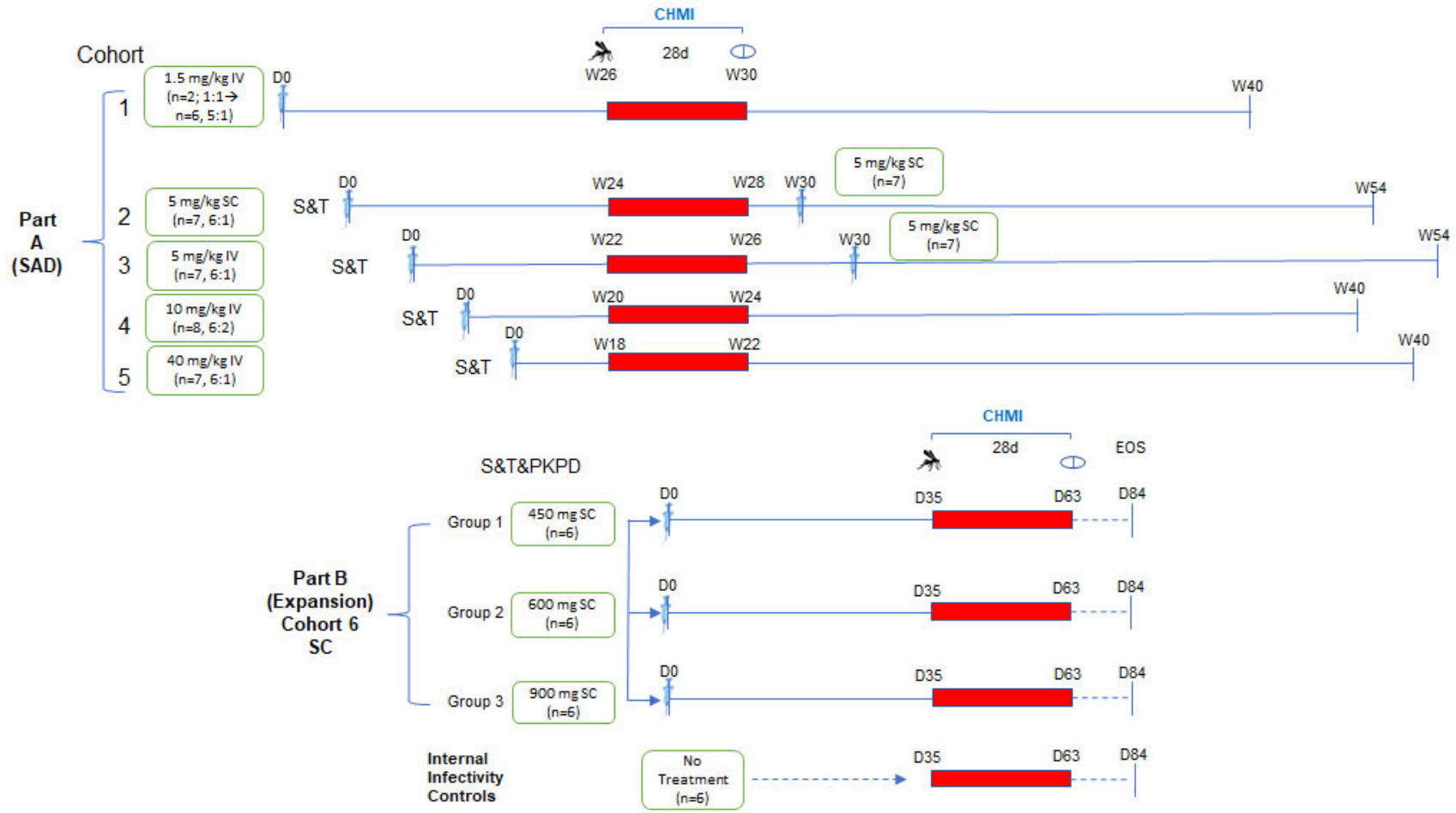
Further details are included in Section 9.

1.1.8 Total Duration of Trial Participation

The maximum Screening duration will be 60 days. The trial duration for participants in:

- Part A single dose cohorts (Cohorts 1, 4, and 5) is approximately 280 days (40 weeks)
- Part A repeat dosing (Cohorts 2 and 3) will remain active for approximately 378 days (48 weeks).
- Part B (expansion phase) is approximately 84 days (12 weeks)

Figure 1: Trial Schematic



CHMI=controlled human malaria infections, D=Day, EOS=End of Study, IV=intravenous, S&T=safety and tolerability, SC=subcutaneous

2 INTRODUCTION

2.1 Disease Burden of Malaria and Focus on *P. falciparum*

Malaria is a life-threatening, mosquito-borne disease caused by the parasite *Plasmodium* that is transmitted through the bites of infected female *Anopheles* mosquitoes (WHO 2022a). Small numbers of *Plasmodium* sporozoites enter thru the saliva of the probing mosquito into the skin and search for a blood vessel to enter the circulation. Once in the bloodstream, they quickly move to the liver where they invade hepatocytes and develop into tissue schizont lifecycle stage, and then multiply asymptomatically within the hepatocytes, producing merozoites. The merozoites then emerge from the liver to infect erythrocytes, replicating in the red cells in large numbers (10^9-10^{13} or more parasites), leading to the symptoms and pathology of malaria (Beeson 2019).

Malaria mainly impacts regions of sub-Saharan Africa, Central and South America, South and Southeast Asia, the Caribbean, the Middle East, and Oceania. There are 5 types of *Plasmodium* parasites that can infect humans. However, the Gates Medical Research Institute (Gates MRI) has chosen to focus on *Pf* prevention given that more than 95% of worldwide malaria cases and 96% of all deaths occur in the African Region (WHO 2022a). People with malaria display high fever, shaking chills, flu-like symptoms, headaches, muscle aches, nausea, and vomiting within 10-15 days after infectious mosquito bite. If left untreated, *Pf* malaria infection can progress to 'severe malaria' and multi-organ failure, which can be fatal within 24 hours (WHO 2022a).

After repeat infections with *Pf* in high transmission regions, older children and adults may acquire partial protective immunity against the blood merozoites, such that they do not develop high blood parasitemias or severe disease. They may not even show symptoms. However, they can still remain infected with merozoites in the bloodstream chronically (up to ~1 year) and contribute to spread of the disease (Center for Disease Control (CDC) 2022). Newborns in high transmission areas are initially protected for the first few months of life, presumably by maternal antibodies (Hviid 2004). However, as the maternal antibodies wane, young children become highly vulnerable to infection, disease and death from falciparum malaria. Thus, WHO considers children from 3 months – 5 years of age to be at the highest risk of malaria complications in endemic settings and targets for additional prevention measures. In lower transmission settings, all populations will be vulnerable to *Pf* infection as parasitemias occur less frequently, and thus, all age groups have no or little protective immunity (CDC 2022).

About 2,000 cases are diagnosed in the USA each year, mostly travelers and immigrants from endemic countries who do not take advantage of travel chemoprophylaxis (CDC 2022). In contrast, despite malaria being a preventable and treatable disease with multiple public health interventions available in endemic regions to minimize morbidity, there were an estimated 241 million clinical malaria cases in endemic areas globally in 2020 (increasing from 227 million cases in 2019). In 2021, globally an estimated 619,000 people died because of malaria infection, almost exclusively from *Pf,* with 96% in Sub-Saharan Africa. Children under the age of five are the most vulnerable and account for ~77% of the global mortality (WHO 2022a).

Further reduction of the global malaria burden will require the development and implementation of new prevention strategies, including expansion of the use of chemoprevention in infants (perennial malaria chemoprevention (PMC; formerly Intermittent Preventative Treatment of Infants (IPTi)) and young children thru either seasonal malaria chemoprevention (SMC) and the use of prevention vaccines, such as the recently WHO-recommended RTS,S/AS01 vaccine (also referred to by its tradename Mosquirix™) (WHO 2021). These tools were developed for disease burden reduction, and all pediatric malaria prevention tools incur significant delivery challenges

in Sub-Saharan Africa. While current tools save millions of lives, the burden of malaria remains high, and new prevention tools, like monoclonal antibodies, are needed (WHO 2022c).

2.2 Available Products for Prevention of Malaria in Children and Development Rationale for Monoclonal Antibodies

As mentioned, falciparum malaria is a preventable infection and treatable disease. Four approaches are currently available to prevent and/or reduce malaria burden in endemic low- and middle-income countries (LMICs):

(1) Foremost is effective case management–prompt diagnosis and effective treatment of malaria infection early in the febrile illness (due to significant blood stage infection) and before organ failure ensues. In moderate to severe transmission settings, this alone has proven insufficient to reduce disease burden significantly.

(2) As a vector-borne illness, community and personal prevention tools have been implemented to reduce mosquito bites and hence transmission risk in order to prevent malaria disease in vulnerable populations. First, mechanical interventions such as the use of bed nets or house screens provide a form of personal protection to reduce mosquito bites in endemic countries. Implementation of long-lasting insecticidal bed nets (LLINs) can provide both personal and community benefit through the reduction of infectious female Anopheline mosquitoes in villages, and these have resulted in the greatest contribution to malaria reduction in the last 20 years (Bhatt 2015). These LLINs are the main form of vector control in sub-Saharan African countries today (WHO Malaria Report 2021).

(3) Chemoprevention drugs have been shown to reduce morbidity and mortality in high-risk populations (pregnant women, infants, and children). This strategy requires full treatment doses of antimalarials designed to eliminate subclinical blood-stage parasitemia and provide a period of post-dose prophylaxis (WHO 2022b). Traditionally, sulfadoxine-pyrimethamine (SP) was recommended in non-seasonal malaria settings with moderate-high transmission for all infants at Expanded Program on Immunization (EPI) visits up to 12 months of age (called IPTi). This has not been widely implemented. WHO has recently re-named this strategy as Perennial Malaria Chemoprevention (PMC-SP) and is considering extending the range to later EPI visits up to 2 years of age. In highly seasonal intense transmission settings, the WHO SMC guidance (WHO 2012) recommends delivery of four to five rounds of monthly dosing of sulfadoxine-pyrimethamine-amodiaquine (SMC-SPAQ) to children 3 months of age to less than 5 years of age to prevent malaria during the peak transmission (rainy) season that typically lasts approximately 3-5 months. Despite SMC-SPAQ's effectiveness of 80-90% when administered fully and correctly to the appropriate populations, approximately 40% of eligible children are not covered by SMC due to issues with maintaining adherence, drug resistance to SPAQ and delivery problems (Cairns 2021).

(4) The RTS,S/AS01 vaccine is the first malaria prevention vaccine currently approved and recommended by WHO for its use in young children aged 6 months to 5 years, living in regions with high to moderate transmission (WHO 2021), and it is available in select African countries. The RTS,S/AS01 vaccine was shown to provide partial protection against malaria in young African children, preventing 39% cases of malaria illness and 29% cases of severe malaria, respectively, in the Phase 3 study. It is being provided on the EPI schedule in implementing countries. However, the RTS,S/AS01 vaccine will provide a limited duration of partial protection and is predicted to be in limited supply until at least 2028 (WHO 2022b).

Finally, another promising future prevention strategy involves the combined use of chemoprevention drugs and the RTS,S/AS01 vaccine in campaign-style administration just before the seasonal rains. In a randomized controlled trial designed to assess seasonal malaria prevention strategies with either the RTS,S/AS01 vaccine or monthly SMC-SPAQ chemoprevention, administration of the RTS,S/AS01 vaccine alone was noninferior to SMC chemoprevention alone in preventing uncomplicated malaria. As a very encouraging finding, the combination of these prevention interventions resulted in a substantially lower incidence of uncomplicated malaria, severe malaria, and death from malaria than either intervention alone (protective efficacy against malaria illness of 63% compared to chemoprevention; 60% compared to vaccine) over the entire transmission season (Chandramohan 2021). Data on the reduction of the incidence of malaria blood-stream infection by PCR is pending at this time. Similarly, an antigenically-similar new *Pf* prevention vaccine, R21/Matrix M, has shown promise in Phase 2 trials in high transmission seasonal settings when combined with SMC with Phase 3 trials underway (Datoo 2021; Datoo 2022).

Thus, while falciparum malaria is a preventable and treatable disease, it remains a significant global health burden due to delivery challenges, non-adherence to complex and only partially protective regimens, drug resistance, inadequate policies, and funding limitations. Novel cost-effective therapies such as prophylactic anti-*Pf*CSP monoclonal antibodies, alone or in combination with other products, provide the potential to achieve higher rates of protection at simplified dosing schedules to meet the great medical need to prevent malaria in high burden settings.

2.3 Study Rationale

2.3.1 Role of Prophylactic Monoclonal Antibodies in Malaria Prevention

The focus of the MAM01 program is to develop a passive immunoprophylactic agent that:

1) Has a long half-life to provide protection from *Pf* infection for at least 4-6 months after a single dose (to cover the transmission season in seasonal settings, ideally including the biphasic rains in East Africa or allow recovery post hospitalization);
2) Is potentially easier to deliver than either monthly drugs or the multi-dose RTS,S/AS01 vaccine or R21 vaccine candidate in development:
   a. as a single annual injection prior to the rainy season, due to its prolonged activity, as a malaria preventive agent in children in regions in which seasonal malaria is endemic; or
   b. as one or two dose regimen in holoendemic regions for yearly protection;
3) Targets a conserved region on the sporozoite, to reduce risk of immune evasion;
4) Demonstrates limited interference from pre-existing malaria immunity or antimalarial drugs;
5) Demonstrates a higher degree of protection to prevent infection than pre-erythrocytic vaccines; and
6) Displays improved tolerability and potentially less resistance risk than drugs or vaccines.

To date, prophylactic malaria antibodies target the highly conserved region of the *Pf*CSP. CSP is the major protein on the surface of sporozoites, and is required for sporozoite motility and invasion of hepatocytes (Oyen 2017). In humans, it is only expressed in the mosquito-inoculated parasitic form called sporozoites, a bottleneck in the parasite's lifecycle during which the fewest parasites are present in the human host. Thus, it is hypothesized that anti-*Pf*CSP antibodies can prevent malaria infection by binding to and neutralizing sporozoites in the skin or bloodstream, before they infect cells in the liver. Hence, they provide sterile protection against infection, and prevent release

of any parasitic stages into blood circulation and hence prevent any malaria disease or subsequent complications (Wells 2022).

2.3.2 Landscape of Malaria Monoclonal Antibodies

A US Food and Drug Administration (FDA) approved monoclonal antibody for the prevention of *Pf* malaria infection is not currently available.

Two mAbs for prevention of *Pf* caused malaria have advanced to clinical trials by the NIH. Both of NIH's anti-*Pf*CSP mAb candidates, CIS43LS and L9LS, contain extended half-life mutations in the Fc region of the antibody. CIS43LS was the first anti-*Pf*CSP monoclonal antibody tested in humans in a Phase 1 study conducted in the US (clinicaltrials.gov No. NCT04206332). CIS43LS binds to the conserved junctional region of CSP. The published results demonstrated that among USA adults who had never had malaria infection or vaccination, the administration of the long-acting mAb CIS43LS prevented parasitemia after controlled infection with *Pf*-infected mosquitoes (Gaudinski 2021; Lyke 2023). These data provide first proof of concept that an antibody-based prophylactic agent may protect humans against malaria infection. Critical to determining the future viability of the use of a mAb for malaria prevention is the assessment of these potential tools in high transmission endemic settings. The safety, tolerability, and efficacy of CIS43LS against naturally occurring *Pf* infection has shown potent prevention of malaria infections assessed by thick blood smear for 3-4 months at doses of 10 and 40 mg/kg SC in adults in Mali, a setting of intense seasonal malaria transmission (Kayentou 2022).

The second mAb, L9LS, is thought to be more potent than CIS43LS based on lower effective concentrations required for protection in IV and mosquito bite sporozoite challenge studies in mice (Wang 2020). L9LS binds to the conserved minor repeat region of CSP, specifically the NPNV repeat located in the central repeat region, which contains 1-5 copies of this sequence. Secondary binding to the NANP repeats suggests some overlap with the epitope binding of MAM01 (unpublished data). A Phase 1 CHMI study for evaluation of the safety and efficacy of the L9LS mAb in healthy adults was recently completed at doses of 1 mg/kg IV, 5 mg/kg IV, 5 mg/kg SC and 20 mg/kg IV. It demonstrated safety and good tolerability at all doses, and protection in a controlled human malaria infection model at an antibody concentration of 10-15 mg/mL (Wu 2022). Lower concentrations at the time of challenge were not assessed in the trial. L9LS is also under assessment in a randomized, double-blind Phase 2 study (clinicaltrials.gov No. NCT05304611) in adults and older children (6–10 years old) in Mali, and an age-escalation and efficacy trial in Kenyan children (clinicaltrials.gov No. NCT05400655).

2.4 MAM01 Monoclonal Antibody Development

2.4.1 Nonclinical Development of MAM01

MAM01, also known as mAb-1797, is an engineered version of a human mAb generated following vaccination with RTS,S/AS01 vaccine. It was isolated and characterized via the biotechnology firm Atreca's discovery platform for potent binding to repeat region of *Pf*CSP. Epitope mapping shows it binds to a unique and conserved epitope at the central region of the NANP repeat regions of the *Pf*CSP. As 100% of known *Pf* isolates contain 38-45 copies of the NANP repeats, it is expected to bind to all field isolates of *P. falciparum*.

MAM01 has been shown to protect against malaria infection in *in vivo* studies in animal models – against mosquito bite and IV inoculation of *Pf*CSP-expressing *P. berghei* sporozites in mice and against *Pf* after mosquito bite in humanized mice. MAM01 was adapted using site-directed mutagenesis in the Fc region, resulting in the inclusion of an LS mutation that enhances neonatal

Fc receptor (FcRN) binding and antibody recirculation, which has been shown to extend product half-life in plasma (Booth 2018).

A GLP tissue cross reactivity study with biotinylated MAM01 found no risk for off-target binding of MAM01 in human tissues. No target organs of toxicity or adverse local reactions were noted in a pivotal 4-week GLP toxicity study in cynomolgus monkeys given MAM01 by IV, SC, or intramuscular (IM); there were also no MAM01-related effects on the respiratory, cardiovascular, or central nervous systems. The no-observed-adverse effect level (NOAEL) was 300 mg/kg/dose via IV administration, supporting the proposed clinical starting and ending dose of 1.5 and 40 mg/kg, IV, respectively. Lack of adverse reactions following SC or IM injections at 152.1 mg/dose supports use of MAM01 formulated at 152.1 mg/mL for these routes of administration in humans. The terminal half-life after single IV or SC injection in monkeys followed by a 6-month postdose period was approximately 26 or 29 days, respectively, confirming that the LS mutation on MAM01 confers prolonged systemic exposures in monkeys supporting its intended use in humans. Bioavailability of MAM01 for SC or IM routes in monkeys reached approximately 42% and 77%, respectively, after multiple dosing. Overall, the nonclinical safety profile of MAM01 supports dosing of humans in the proposed Phase 1 clinical trial.

2.4.2 Previous Human Experience

There is no human experience with MAM01 prior to this ongoing trial.

In Part A of the trial, 24 participants received MAM01 doses ranging from 1.5 mg/kg to 40 mg/kg given IV, and 6 participants received two separate doses of 5 mg/kg SC. An additional 7 participants received placebo. MAM01 was generally well tolerated with mild systemic solicited symptoms reported on the memory aid card, which generally resolved within 48 hours. No fever or allergic reactions have been noted, and no AEs or SAEs related to the study drug were reported. No local reactions were recorded after SC injection up to 300 mg. Further details are available in the updated Investigator's Brochure.

These observations are consistent with the published data on the aforementioned other malaria mAbs targeting different sites on *Pf*CSP, for which the predominant local reactogenicity complaint has been mild pain/tenderness, although reports of mild injection site pruritus, redness and swelling have occurred at modestly higher frequencies with up to 2 mL of mAb administered by SC administration. Malaise, muscle pain, dizziness and headache have been the most frequently reported solicited complaints noted in the 3 days post product administration and these have also been mostly transient and mild in severity; these reactions have been transient, resolved without sequelae within 24 hours of onset, and treated with over-the-counter analgesics and antipyretics. No infusion-related reactions have been reported (Gaudinski 2021, Wu 2022, Lyke 2023).

2.4.3 Rationale for Study Design

This randomized, two-part, dose-escalation design trial will evaluate the safety, tolerability, PK, and protective efficacy of MAM01, as well as safety and PK of repeat SC dosing. Part A will have a double-blind, placebo-controlled design. Part B will randomize participants to one of three open-label MAM01 dose groups; a separate non-randomized group will be enrolled to include participants who will receive no treatment and act as infectivity controls.

Part A of this Phase 1 trial will evaluate MAM01 safety and PK at ascending doses of 1.5 mg/kg IV, 5 mg/kg given SC split at two injections sites, 5 mg/kg IV, 10 mg/kg IV and 40 mg/kg IV. It is expected that this trial design will support estimation of a protective titer of MAM01 in humans following a CHMI. Two cohorts will evaluate repeat dosing of 5 mg/kg SC for safety and assessment for the development and impact of ADA.

Part B of the trial will evaluate three additional fixed doses to explore antibody concentrations around the preliminary estimate of protective titer from Part A of the protocol and will support future trials assessing the SC administration route in malaria-endemic countries. Doses will be administered open label. Dose selection is described in Section 4.2.1.1.

2.4.4 Justification for Dose

The safety and potential therapeutic range of MAM01 are unknown.

The selection of doses to be tested is based on available clinical data from a related mAb, L9LS, (Wu 2022) and the No-Observed-Adverse-Effect Level (NOAEL) from the 4-week GLP toxicology study of MAM01 in cynomolgus monkeys. Preclinical studies showed that L9LS and MAM01 had comparable exposure-response relationships for parasitemia and overlapping epitopes for minor (NVDP) to major (NANP) repeat regions of *Pf*CSP [*Technical report, MAM01P02*], further supporting use of L9LS clinical data to inform dose selection for MAM01. See Investigator's Brochure for further details.

[redacted] are shown in Table 2 below. The NOAEL in monkeys supports a Maximum Recommended Starting Dose (MRSD) of 9.7 mg/kg (FDA 2005) with an applied safety factor of 10, which is greater than the proposed starting dose of 1.5 mg/kg (see below). The ending dose of 40 mg/kg, IV, provides an estimated exposure multiple of 10-fold to the monkey NOAEL, based on maximal plasma concentrations, providing sufficient margins of safety in humans at this dose. Lack of adverse injection site reactions following SC administration of MAM01 at 152.1 mg/dose, supports its planned use in humans at a concentration of approximately 150 mg/mL.

Table 2: Projected Safety Multiples

	NOAEL				Multiples at Proposed Starting and Ending Doses in Humans[a]		
Species and Study	**Dose, route**	**$AUC_{0\text{-}168}$[b] (µg×h/mL)**	**C_{max}[b] (µg/mL)**	**[redacted]**	**Parameter**	**1.5 mg/kg**	**40 mg/kg**
Cynomolgus monkey, 4-Week GLP, IV, including CV, CNS, Respiratory	300 mg/kg, IV	806,000	10,200	97	Dose: AUC: C_{max}	65 17 246	2.4 0.65 9.3

AUC=Area under the curve; C_{max}=Maximum concentration; CNS=Central nervous system; CV=Cardiovascular; GLP=Good Laboratory Practice; HED=Human equivalent dose; NA=Not applicable; NOAEL=No-observed-adverse-effect level; NOEL=No-observed effect level; SAD=Single-ascending dose; SD=Single dose

[a]Based on human starting and ending doses of 1.5 mg/kg, IV and 40 mg, IV, respectively, and projected systemic exposure of 41.5 µg/mL (C_0) and 46,800 µg×h/mL (AUC) at 1.5 mg/kg and 1095.8 µg /mL (C_0) and 1,235,664 µg×h/mL (AUC) at 40 mg/kg.
[b]Data represents mean steady-state sex-combined C_{max} and $AUC_{0\text{-}168}$ values
[redacted] according to FDA guidance (FDA 2005)

The results from the L9LS clinical trial in healthy adults in the USA (Wu 2022) provide valuable information in determining the starting dose for MAM01. A population PK simulation approach was used to predict the exposures of MAM01 at the time of CHMI and for determining the starting dose for MAM01. This approach is based on the assumption that MAM01 has similar population PK characteristics and half-life of 56 days as observed for the L9LS data. These results indicate that maintaining trough plasma concentrations of approximately 10 µg/mL is likely required to achieve prolonged protection against infection of *Pf* sporozoites.

The lowest dose (1.5 mg/kg) was selected to achieve concentrations below the targeted protective titer (estimated at an EC80 of 10 µg/mL) at the time of CHMI to evaluate the dose response.

Intermediary doses were chosen to assess the absolute bioavailability (5 mg/kg SC and IV) and explore the ranges of exposures near the target EC80 at 6 months after the infection. The dose justification for the highest antibody exposure is outlined in Appendix 2.

The projected drug levels (based on a virtual participant population with weight at baseline between 45 and 90 kg) at the time of the revised CHMI schedule are outlined in

Table 3.

Table 3: Phase 1 Part A Drug Concentration Estimations at Time of CHMI*

Cohort #	Dose mg/kg	Route of Adminis-tration	Planned Interval Between Dose and CHMI	Estimated MAM01 Concentration at Time of CHMI Median* µg/mL [5 -95% CI]	Actual MAM01 Concentration pre_ CHMI Median* µg/mL [5 – 95% CI]
1	1.5	IV	26 weeks	3.07 [0.92 – 6.8]	3.07 [2.56 –3.51]
2	5	SC	24 weeks	8.15 [2.69 – 18.02]	6.94 [4.34 – 10.37]
3	5	IV	22 weeks	14.08 [4.72 – 28.23]	14.90 [8.64 – 18.42]
4	10	IV	20 weeks	32.97 [12.55 – 61.15]	33.00 [21.44 – 35.86]
5	40	IV	18 weeks	151.77[59.84 – 282.25]	121.00 [90.94 – 156.10]

Assumption: Based on similar PK to L9LS mAb given IV and SC
*Based on the adjusted CHMI date, whereby Cohort 1 will be 6 months after IP dosing.

Furthermore, the doses for Part B of the trial were selected based on the clinical PK profile of MAM01 in Part A of the trial. The maximum dose for Part B of the trial will not exceed the dose(s) of MAM01 determined to be safe in Part A.

A population model was developed to characterize the PK profiles from Part A participants (second interim analysis). This model was then applied in a simulation mode to predict the doses necessary to achieve the target exposures at the time of the CHMI for Part B.

2.5 Benefit/Risk Assessment

2.5.1 Potential Benefits

No direct benefits are anticipated for healthy adults in this Phase 1 study. Others may benefit from the knowledge gained in this study that may aid in improvements in malaria prevention.

2.5.2 Potential Risks

Risks of MAM01: The risks of MAM01 in humans is unknown, as this is the first in human study.

Risks of mAb Administration in general: Administration of mAbs may cause immune reactions such as acute anaphylaxis, serum sickness and the generation of antibodies. However, these reactions are rare and more often associated with mAbs targeted to human proteins or with the use of mouse mAbs that would have a risk of human anti-mouse antibodies (Hansel 2010). In this regard, because MAM01 is a human antibody and it is targeted to a malaria parasite antigen with no intended binding to human tissues, it is expected to have a low risk of such side effects.

Typically, the side effects of mAbs are mild to moderate and may include local reactions at the injection site (including pain, redness, bruising, swelling) and systemic reactions such as fever, chills, rigors, nausea, vomiting, pain, headache, dizziness, shortness of breath, bronchospasm, hypotension, hypertension, pruritus, rash, urticaria, angioedema, diarrhea, tachycardia or chest pain. Clinical use of mAbs that are targeted to cytokines or antigens associated with human cells may be associated with an increased risk of infections (Hansel 2010); however, this is not expected to be a risk for a mAb targeted to a parasite antigen. Severe reactions, such as anaphylaxis,

angioedema, bronchospasm, hypotension and hypoxia, are infrequent and more often associated with mAbs targeted to human proteins or with non-human mAb, such as a mouse mAb (Hansel 2010). Most infusion-related events occur within the first 24 hours after initiation of mAb administration.

Published experience with human mAbs directed against cell surface targets on lymphocytes shows that infusion of a mAb may be associated with cytokine release, causing a reaction known as cytokine release syndrome (CRS) (Bugelski 2009). CRS reactions commonly occur within the first few hours of infusion start and with the first mAb infusion received. This is because the cytokine release is associated with lysis of the cells targeted by the mAb and the burden of target cells is greatest at the time of the first mAb treatment. With licensed therapeutic mAbs, CRS is managed by temporarily stopping the infusion, administering histamine blockers and restarting the infusion at a slower rate. Supportive treatment may also be indicated for some signs and symptoms.

Delayed allergic reactions that include a serum sickness type of reaction characterized by urticaria, fever, lymph node enlargement, and joint pains, typically occur several days after mAb exposure and are more commonly associated with chimeric types of mAbs (Hansel 2010). In general, and with due consideration of the needs dictated by individual participant symptoms and treating clinician discretion, immediate and delayed reactions to study product would be managed according to the principles of the American Academy of Allergy, Asthma, and Immunology guidelines established in the Drug Allergy: 2022 Practice Parameters Update (Khan 2022). Participation in this study may limit a participant's eligibility for future mAb studies.

Risks of Blood Drawing: Blood drawing may cause pain, bruising, and a feeling of lightheadedness or fainting. Rarely, it may cause infection at the site where blood is taken. In this study, microsampling of capillary blood will be used to reduce patient burden by eliminating the need for venipuncture when only PK and ADA draws are needed. Problems from use of an IV for blood drawing are generally mild and may include pain, bruising, minor swelling or bleeding at the IV site and rarely, infection, vein irritation (phlebitis), or blood clot.

Risks of Mosquito Bites for CHMI: Risks associated with CHMI include local inflammatory reactions, lymphadenitis, persistent local pruritus and larger local reactions involving the whole forearm, allergic reactions to mosquito bites. Another remotely possible risk includes a systemic allergic reaction to the mosquito saliva.

Risks of Acquiring Malaria Infection: There is also the possibility of complications of malaria, which are seen during naturally acquired malaria *when diagnosis and treatment are delayed* and high levels of parasitemia develop. Under the carefully controlled conditions of this study that supports early diagnosis and treatment, the chance of such complications is unlikely and the risk of death from malaria infection is very small. Transient abnormalities, e.g. fever, headache, myalgia, shaking chills, abdominal discomfort, nausea, vomiting, mild anemia, leukopenia, thrombocytopenia, hepatosplenomegaly, hepatic tenderness and fatigue, are expected consequences of malaria. In uncontrolled circumstances, malaria infections can lead to kidney, liver or brain injury (seizures, coma) and death.

Risks of Antimalarial Medication: Additional risks include possible side effects of the antimalarial medication. For atovaquone/proguanil (Malarone®) can include nausea, vomiting, abdominal pain, anorexia, diarrhea, headache, cough and rarely, anemia, oral ulcerations, insomnia, fever, edema, rash and alopecia. For chloroquine (alternate), these can include nausea, vomiting, diarrhea, abdominal pain, dizziness, headaches, sleep disturbances, blurred vision, pruritus, skin rash, exacerbation of psoriasis or porphyria, tinnitus, and photosensitivity. Rarely, there may be

changes in electrocardiograms and hypotension. Another remotely possible risk includes a systemic allergic reaction to chloroquine (or Malarone®). The study team will discuss these medications and their possible side effects in detail both as part of the informed consent process, prior to CHMI, and prior to initiation of treatment for diagnosed malaria infections.

Risks of Screening Procedures: Typical for any diagnostic testing and will be described in the consent form.

3 OBJECTIVES AND ENDPOINTS

Table 1 outlines study objectives and endpoints.

4 STUDY DESIGN

4.1 Trial Population

Malaria naïve adult participants between 18 and 50 years of age (inclusive) of both sexes who are capable of and willing to provide Informed Consent and who are deemed healthy based on clinical judgment following medical evaluation may be eligible for the trial. Potential participants with history of any autoimmune disease or immune deficiency or other impairment to the immune system (e.g. human immunodeficiency virus (HIV)), or any current uncontrolled medical, psychiatric condition or substance abuse problems that, in the opinion of the Investigator, will make it unlikely that the participant will comply with the protocol will not be eligible for the trial. Females of reproductive potential, who consent to participate in the trial, must agree to use an effective contraceptive method defined as one that results in a failure rate of less than 1% per year when it is used consistently and correctly. Adequate contraceptive precautions include intrauterine contraceptive device, oral contraceptives, diaphragm, or condom in combination with contraceptive jelly, cream, or foam; Norplant® or Depo-Provera®, through completion of the trial visits to minimize any potential risk.

The complete list of eligibility criteria (including details regarding effective contraception methods), as well as medical conditions, prior/concomitant therapy, and results from diagnostic assessments serving as a basis for exclusion from trial participation are outlined in Section 5.

4.2 Design Overview

This clinical trial is a Phase 1, interventional, 5-cohort SAD and repeated dose (Part A) study with a one-cohort dose expansion (Part B) in healthy male and female adults between 18 and 50 years of age (inclusive) at the time of signing the Informed Consent. Written Informed Consent must be given before any Screening procedure is started. Each of the two Screening windows (for Part A and Part B) can last up to 60 days, and Screening for infectivity controls can occur at the discretion of the Investigator.

Potential participants will be screened to enroll and randomize approximately 61 eligible participants. Placebo participants will serve as infectivity controls in Part A. Additional malaria-naïve participants may be added to the trial to replace any dropouts prior to CHMI to ensure at least 6 infectivity controls undergo each CHMI procedure. The additional infectivity control participants will not receive administration of MAM01 or placebo. Assuming that all cohorts are allowed to undergo treatment, approximately 48 participants will be exposed to MAM01 and approximately 7 to placebo.

The Trial Schema is shown in Figure 1. SoA for Part A (dose escalation) SC and IV cohorts are shown in Appendix 1.

4.2.1 Part A

Part A is the SAD component of the trial and will have 5 dosing cohorts with approximately 37 participants in total. Cohort 1 will include 2 sentinel participants: 1 participant will receive 1.5 mg/kg IV MAM01 and 1 participant will receive placebo. Following at least a 24-hour observation period for safety assessment, 5 additional participants will receive 1.5 mg/kg IV MAM01, and 1 participant will receive placebo. Assuming there are no safety concerns at administration, all participants in subsequent cohorts will be dosed on the same day (+/- 1 day; see Appendix 1).

Thereafter, dose escalation (Cohort 2: 5 mg/kg SC; Cohort 3: 5 mg/kg IV; Cohort 4: 10 mg/kg IV) will be staggered by two weeks to allow an adequate safety assessment per cohort as shown in Figure 1. Cohort 5 participants will receive the highest dose, 40 mg/kg IV, MAM01 or placebo.

4.2.1.1 Part A Dose Escalation

Part A will evaluate doses and routes for MAM01 administration. Dose escalation will occur sequentially in 6 steps (Table 4).

Table 4: Part A - Dose Escalation

Gates MRI-MAM01-101: Part A – Dose Escalation											
		MAM01 Administration									
Cohort	Participant	Day 0		Week 30 (Day 210) (± 7 days)		CHMI					
		Dose (mg/ kg)	Route	Dose (mg/ kg)	Route	Week 26 (Day 181) (± 7 days)	Week 24 (Day 168) (± 7 days)	Week 22 (Day 154) (± 7 days)	Week 20 (Day 140) (± 7 days)	Week 18 (Day 127) (+ 7 days)	Enrolled only to CHMI
1	N=8 (6:2)	1.5	IV			X					
2	N=7 (6:1)	5	SC	5	SC		X				
3	N=7 (6:1)	5	IV	5	SC			X			
4	N=8 (6:2)	10	IV						X		
5	N=7 (6:1)	40	IV							X	
IIC	As needed	Not dosed									X
Total	37 (30:7)										

CHMI=Controlled Human Malaria Infection; IIC= Internal Infectivity Controls; IV=intravenous; SC=subcutaneous

Step 1 will begin with Cohort 1 (1.5 mg/kg IV). Step 2 will enroll Cohort 2 (5 mg/kg SC). Step 3 will enroll Cohort 3 (5 mg/kg IV). Step 4 will enroll Cohort 4 (10 mg/kg IV). Step 5 will enroll Cohort 5 (40 mg/kg IV). Dose escalation from one cohort to the next will be determined by the Safety Review Team (SRT) based on review of the current cohort's blinded safety data (AE profile and safety laboratory assessment results) at least through Day 7 (See Section 4.3.2.1). In Step 6, participants from Cohort 2 and Cohort 3 (including initial placebo recipients) will receive an unblinded second dose of MAM01, 5 mg/kg SC, approximately 210 days (30 weeks) post the first dose and well after the Part A CHMI procedure.

Step 1

- Cohort 1: 8 participants, 2 sentinel participants will be randomized 1:1 to receive MAM01 1.5 mg/kg IV (n=1) or placebo (n=1). Following at least a 24-hour safety review period, the 6 remaining participants of Cohort 1 will be randomized 5:1 to receive MAM01 1.5 mg/kg IV (n=5) or placebo (n=1).

Step 2

- Cohort 2: 7 participants, will be randomly assigned 6:1 to receive MAM01 5 mg/kg SC (n=6) or placebo (n=1).

Step 3

- Cohort 3: 7 participants, will be randomly assigned 6:1 to receive MAM01 5 mg/kg IV (n=6) or placebo (n=1).
- Comparison of the PK of Cohorts 2 and 3 will enable estimation of the bioavailability of MAM01.

Step 4

- Cohort 4: 8 participants, will be randomly assigned 6:2 to receive MAM01 10 mg/kg IV (n=6) or placebo (n=2).

Step 5

- Cohort 5: 7 participants, will be randomly assigned 6:1 to receive MAM01 40 mg/kg IV (n=6) or placebo (n=1).

The 7 placebo participants in Cohorts 1-5 will serve as the infectivity controls for the CHMI procedure.

Prior to the Part A CHMI procedure (Cohorts 1-5), all participants will have a blood sample drawn for MAM01 concentration determination on the day prior to the CHMI mosquito-bite procedure; the time of the blood sampling and of the mosquito-bite procedure will be captured for analysis purposes. Variation in MAM01 blood concentrations across participants at the time of CHMI are expected based on dose and time elapsed since product administration and will provide important information on blood MAM01 concentration levels required for protection from malaria *Pf* infection at the time of pathogen exposure.

Step 6 Repeat Dosing: This component of Part A (from participants in Cohort 2 & 3) will provide additional evaluation of PK and ADA formation. At least 210 days (± 7 days) post-dose (and after the initial CHMI procedure), these participants will receive a second MAM01 dose of 5 mg/kg SC regardless of the initial assignment and administration route and assignment used for the initial dose. The planned doses may be modified following the audited interim analysis of the Investigational New Drug (IND)-enabling GLP toxicology studies prior to trial launch and/or accumulation of safety/tolerability/PK data from single-dose ascending cohorts through a protocol amendment.

- Part A Repeated Dose (Multiple Ascending Dose [MAD]): This component of Part A (from Cohorts 2 and 3) will provide additional evaluation of PK and ADAs formation. Approximately 210 days following administration, participants from Cohort 2 and from Cohort 3 will return to the clinic to receive 5 mg/kg MAM01 SC. All participants will receive SC administration regardless of the administration route received on Day 1.

4.2.2 Part B

Part A safety, tolerability, efficacy, any available PK, and immunogenicity data will be used to assess the need for further dose refinement and to inform Part B dose selection. Part B (optional expansion cohort; Cohort 6) will further assess safety and tolerability of SC administration of the targeted dose of MAM01 selected from the interim analysis of Part A results. The expansion cohort dose will be defined following review of the unblinded interim analysis and codified with a protocol amendment.

Part B (Cohort 6) will evaluate three fixed doses of MAM01 delivered by SC injection to achieve desired MAM01 concentrations at CHMI. The doses for Part B (Cohort 6) were selected by applying a PKPD model from the Part A data to estimate a (data-driven) protection threshold at CHMI. The maximum dose for Part B of the trial will not exceed the dose(s) of MAM01 determined to be safe in Part A.

As a result, participants in the three Cohort 6 dosing groups will take part in the CHMI procedure at the same time (Table 5). No participants will receive placebo in Part B of the trial.

Table 5: Part B – Dose Expansion

Gates MRI-MAM01-101: Part B – Dose Expansion					
Group Within Cohort 6	**Participants**	**MAM01 Administration**		**CHMI**	
		Dose (mg)	**Route**	**Estimated Drug Concentration at CHMI**	**CHMI Week 5 Day 35 (± 7 days)**
1	N=6	450 mg	SC	40 μg /mL	X
2	N=6	600 mg	SC	50-55 μg /mL	X
3	N=6	900 mg	SC	90-100 μg /mL	X
Total	N=18				
Internal Infectivity Controls	N=6	Not Dosed			

CHMI=controlled human malaria infection, SC=subcutaneous

In addition to the 18 participants receiving MAM01, 6 infectivity controls for CHMI will be recruited (see Section 4.2.3.2.1).

CHMI procedures for Part B are captured in Table 12. For further details please refer to Section 4.2.3.1.

Participants in Part B, Groups 1-3 are expected to complete the trial by approximately 12 weeks post IP administration.:

4.2.3 Controlled Human Malaria Infection (CHMI) Management and Procedures

4.2.3.1 Overview of Parasitemia Management

The intent of the CHMI is to evaluate if MAM01 can prevent *Pf* infection among all participants thru a consistent *Pf* sporozoite inoculation delivered via the bites of infectious laboratory-reared *An. stephensi* mosquitoes. Following CHMI procedure, to meet the criterion for confirmed blood stage malaria infection, a case of *Pf* parasitemia will be defined as a second positive real-time qRT-PCR result, > 12 hours and < 60 hours from the first positive, or a single thick blood smear with two confirmed parasites. The time to infection will be defined as the time to the first of the 2 positive qRT-PCR assays or thick blood smear. This criterion reduces risk of false positives from qRT-PCR, but still allows for *Pf* blood stage infection to be identified before symptoms of malaria occur, and at a lower limit of quantification than would be typically detectable by blood smear microscopy (Friedman-Klabanoff 2019).

Pf infections in all participants will be treated promptly when the criterion for a case of *Pf* parasitemia is met, and administered as DOT by a clinician until the specified course of treatment is completed. In exceptional cases, a video meeting can be arranged between participant and study personnel to document antimalarial administration on the 2nd and 3rd day of treatment. Treatment regimens subsequently described are known to be effective against the *Pf* strain being used in the CHMI. Participants may also be provided with treatments like antiemetics, acetaminophen, and ibuprofen, as needed, for management of symptoms.

At the end of the CHMI procedure, all remaining CHMI procedure participants will receive empiric antimalarial treatment at Day 27 post CHMI procedure, if they have not already been treated for confirmed parasitemia by this timepoint.

Refer to the SoA (Appendix 1) for the safety laboratory evaluations that are required to be performed at the onset of antimalarial treatment.

Following treatment for a confirmed case of *Pf* blood stage infection, cure will be documented by a negative qRT-PCR test result at Day 49 after CHMI (±5 days).

4.2.3.2 Controlled Human Malaria Infection (CHMI) Management and Procedures

4.2.3.2.1 Screening for Infectivity Control Participants

- For any infectivity control participant (who does not receive MAM01 or placebo), the timing of the Screening visit is at the discretion of the Investigator except that a Screening visit will be completed at least 1 week before the CHMI procedure to assess eligibility. A Screening visit will be performed to include a full medical history, complete medical exam and vitals signs, Screening laboratory tests, serum pregnancy test for women of child-bearing age, a review of changes in adverse events or medical history, and assessment of concomitant medications (see Table 11).

4.2.3.2.2 Screening for Malaria Challenge for Participants Who Have Received IP (Part A Cohorts 1-5; Part B Cohort 6) and Infectivity Controls

- **Day -1:** Before the malaria challenge: A review of changes in adverse events or medical history, review of concomitant medications and targeted physical exam and vital signs will be performed, and an assessment of eligibility for mosquito bite challenge will be undertaken. Laboratories will include a CBC with differential, ALT and creatinine. Capillary blood will be collected for MAM01 PK, and serum will be stored for evaluation of anti-CSP antibodies (if needed). A qRT-PCR assessment for existing (baseline) *Plasmodium* infection will be obtained. A urine pregnancy test (females of childbearing potential only) will be performed. The pregnancy test must be negative within 24 hours before challenge, and pregnancy prevention counseling will be reviewed for females only.
- **Day 0** (day of mosquito challenge) will require a review of changes in AEs of medical history and review of Screening laboratories and final assessment of the select exclusion criteria performed to confirm eligibility to participate. A urine pregnancy test will be performed if not obtained on Day -1.
- If there are dropouts in the cohorts undergoing CHMI (those who withdraw prior to mosquito challenge), they may be replaced by infectivity controls to ensure that at least 6 persons who do not receive any dose of MAM01 complete a successful mosquito challenge.

4.2.3.2.3 Mosquito Challenge Procedures (CHMI Day 0)

- Participants will be issued study participation cards identifying them as having been exposed to falciparum malaria and listing contact numbers for study physicians.
- The malaria challenge will be administered per University of Maryland Standard Operating Procedures (SOP) to ensure 5 bites of infectious mosquitoes (defined as having a visible blood meal and >2+ salivary gland sporozoite index).
- After challenge, the participants will be observed for a minimum of 30 minutes. Itchy mosquito bites may be treated with 1% hydrocortisone cream.
- Post-challenge vital signs (oral temperature, blood pressure, and pulse) will be recorded.
- Participants will be instructed to contact study personnel immediately should they manifest any signs or symptoms they perceive as serious.
- Participants will be counseled on mosquito avoidance behavior beginning 6 days after CHMI until 27 days after CHMI.

4.2.3.2.4 CHMI Day 6, Outpatient Post-malaria Challenge Surveillance Initiation

- Participants will follow-up in the clinic and a targeted history and targeted physical exam will be completed. A review of all current medications (focusing on antibiotics) will be conducted.

- Vital signs (oral temperature, blood pressure, pulse) will be recorded.
- Parasitemia monitoring by qRT-PCR and microscopy will commence.
- Any solicited or unsolicited AEs, AESIs (Groups 4 and 5), or SAEs that have occurred since the mosquito challenge will be assessed.
- Participants will be counseled on mosquito avoidance behavior.

4.2.3.2.5 CHMI Day 7-17, Daily Post-malaria Challenge Surveillance

- Participants will be checked daily for the presence of falciparum malaria in their blood (qRT-PCR) during the period of time they are most at risk for the development of falciparum malaria. A small quantity of blood (~2 mL) will be obtained daily for malaria diagnostics (qRT-PCR and a thick blood smear). Microscopic analysis of the thick blood smear will commence on the blood sample for which an initial qRT-PCR test is positive, and continue with all samples until a diagnosis of *Pf* parasitemia is confirmed. Febrile or otherwise symptomatic individuals will have malaria diagnostics performed every 8-12 hours at the discretion of the Investigator for the purposes of malaria diagnosis and treatment until they are declared malaria positive.
- A review of changes in AEs or medical history and review of all current medications (focusing on antibiotics) will be conducted.
- A focused physical exam will be performed as indicated. Vital signs (oral temperature, blood pressure, pulse and pulse oximetry) will be recorded.
- Any solicited or unsolicited AEs, AESIs (Groups 4 and 5), SUSARs or SAEs that have occurred since the last visit will be assessed.
- A diagnosis of Pf parasitemia is confirmed by either 2 qRT-PCR positive tests or a thick blood smear positive for malaria. Participants will be promptly contacted to initiate a full course antimalarial rescue therapy given by direct observed therapy. (In exceptional cases, a video meeting can be arranged between a participant and study personnel to document antimalarial administration). Time to positivity is defined as time to first positive PCR. See Section 6.6 for acceptable regimens. qRT-PCR and microscopy testing may cease upon initiation of rescue therapy.
- Venous blood for safety labs and a urine pregnancy test (if applicable) will be collected on the day a participant is considered malaria-positive. Safety labs consist of CBC with differential, ALT, and serum creatinine.
- Study participants who have been diagnosed with malaria may discontinue the scheduled daily follow-up visits after completion of oral antimalarial therapy. Next follow-up visit will be on Day 49 (±5).
- If by Day 20 post CHMI, the study participant has not contracted malaria and is free of signs and symptoms of malaria, they will continue with scheduled intermittent clinical evaluations and malaria diagnostics.

4.2.3.2.6 Days 20, 23 and 27, Outpatient Post-malaria Challenge Surveillance for Participants Who Remain Malaria Free

- Participants who remain aparasitemic will be seen in clinic for continued malaria surveillance and evaluation on Days 20, Day 23 and Day 27.
- A review of changes in adverse events or medical history and all current medications (focusing on antibiotics) will be conducted.
- Vital signs (oral temperature, blood pressure, pulse, pulse oximetry (room air)) will be recorded. A focused medical exam may be performed, if medically indicated.

- Any solicited or unsolicited AEs, AESIs (Groups 4 and 5), SUSARs or SAEs that have occurred since the last visit will be assessed and a targeted physical exam will be performed as indicated.
- A small quantity of blood (2 mL) will be obtained for malaria diagnostics (qRT-PCR and thick blood smear). In the case a test is confirmed positive for Pf parasitemia, safety labs should be obtained prior to initiating rescue therapy.
- On day 27, urine will be collected on all females of childbearing potential to perform a urine β-HCG pregnancy test.
- All participants still negative for malaria at the time of the day 27 visit will be empirically treated with a curative dose of an antimalarial. Regimens are listed in Section 6.5.4.

4.2.3.2.7 Day 49 (+/- 5 days), Outpatient Post-malaria Challenge Surveillance for Participants Who Were Confirmed Positive for Malaria

- Participants who were confirmed for malaria infection after CHMI and treated will have an office confirmation of cure assessment on Day 49.
- A review of changes in adverse events or medical history and all current medications (focusing on antibiotics) will be conducted.
- Vital signs (oral temperature, blood pressure, pulse) will be recorded.
- On Day 49, urine will be collected on all females of childbearing potential to perform a urine β-HCG pregnancy test.
- A small quantity of blood (2 mL) will be obtained for malaria diagnostics (both thick blood smear and qRT-PCR) as a proof of cure, along with a CBC with differential, ALT and serum creatinine (safety labs).

4.2.4 Follow-Up through End of Trial

Trial follow-up will continue via clinic visits through approximately 40 to 54 weeks (depending on Cohort in Part A) after the IP administration or 12 weeks in Part B. The visit schedule is based on intervals of time after IP administration and/or CHMI procedure. SoA are shown in Appendix 1.

Participants who receive IP but later chose to opt out of the CHMI procedure as scheduled are expected to continue follow-up according to the schedule for the IV or SC group the end of the study; however, among these participants, sample collection may be discontinued for pregnant women or others in which it is contraindicated.

4.3 Criteria for Dose Escalation Evaluation

4.3.1 Safety Variables

AEs; vital signs (blood pressure, heart rate, temperature, pulse oximetry (room air); height and weight and calculated body mass index (BMI); physical examination; and safety laboratory assessments, including hematology and biochemistry.

See Section 9 for additional details regarding analysis.

4.3.2 Dose Escalation Decision Process

4.3.2.1 Safety Review Team (SRT)

A SRT will be established as the team responsible for safety review and the dose escalation and dose expansion Go/No Go decisions for the trial. Details on the membership of the SRT will be featured in the charter that will be developed for the SRT's data review and deliberation processes (including the format of data to be reviewed and the cadence of meetings).

The SRT will review the blinded safety and tolerability data accumulated after the last planned participant for a cohort has completed all follow-up 7 days after dosing based on details provided in Section 4. The SRT may request additional meetings as deemed appropriate. The SRT will review all available blinded safety collected at the time of review to determine whether or not any pausing event has occurred (see Section 7.1.1). If a pausing event does not occur, the SRT may recommend that dose escalation or progression to the Dose Expansion Phase occur. The SRT recommendation will be communicated to the Sponsor Chief Medical Officer for approval.

If the SRT observes that a pausing rule is met, dose escalation will be paused and the Sponsor will be informed as soon as possible and within 24 hours of becoming aware of the event. The Independent Data Monitoring Committee (IDMC) (described in Section 10.1.2) will then review all relevant unblinded safety data and recommend the next course of action(s) to the Sponsor.

Pausing rules for the cohort (as further described in the SRT charter) include:
1. At least one participant experiences a ≥ Grade 3 AE assessed as related to study product (except Grade 3 solicited local injection reaction lasting less than 48 hours);
2. At least 2 participants in a cohort experience systemic Grade 2 AE of a similar nature assessed as related to study product by the SRT;
3. A SAE of any grade assessed as related to study product;
4. Any occurrence of infusion reactions requiring discontinuation of study drug, a Grade 3-4 immediate hypersensitivity reaction or immune complex disease associated with study product;

4.3.2.2 Trial Intervention Discontinuation Rules for Individual Participants

For most individuals, there is only a single dose of MAM01 administered. In Part A Cohorts 2 and 3, participants will repeat a 2nd dose of study product unless any of the following apply:
1. Pregnancy;
2. Unresolved malaria infection from prior Part A CHMI;
3. Immediate hypersensitivity reaction associated with study product;
4. Intercurrent illness that is not expected to resolve prior to the next scheduled product administration (if applicable);
5. Diagnosis of a new chronic or clinically significant medical condition that in the opinion of the Investigator would jeopardize the safety or rights of the participant;
6. Repeated failure to comply with protocol requirements;
7. The IND Sponsor or the study Principal Investigator (PI) decide to terminate the study; or
8. The Institutional Review Board (IRB) or the FDA halt the study.

4.3.3 End of Trial Definition

A participant is considered to have completed the trial if they complete the final scheduled visit for their assigned cohort. Infectivity controls (who did not receive test article) are considered to have completed the trial if they complete malaria treatment and their final evaluation post CHMI (see Appendix 1, Table 11). The end of the trial is defined as the date of the last visit of the last participant or last scheduled procedure shown in the SoA for the last participant.

5 TRIAL POPULATION

This trial will enroll approximately 61 males and females between 18 to 50 years old (inclusive) who are capable and willing to provide informed consent. See Section 5.1 and Section 5.2 for inclusion and exclusion criteria, respectively. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Additional recruitment of infectivity controls who will not receive test article but participate in the CHMI to ensure proper infectivity after mosquito challenge are authorized at the discretion of the Investigator. They must meet the same inclusion and exclusion criteria.

5.1 Inclusion Criteria

Participants are eligible to be included in the trial only if all the following criteria apply:

Age

1. Participant must be 18 to 50 years of age (inclusive), at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are healthy as determined by medical evaluation including medical history, physical examination and laboratory tests.

Weight

3. BMI 18 to 30 kg/m^2 (inclusive) to a maximum of 220 pounds.

Sex and Reproductive Potential

4. Both males and females are eligible to participate as per the following:
   a. Female participants physically capable of pregnancy, have at least one negative pregnancy test during Screening, on the day of enrollment, prior to IP administration, prior to CHMI and at the start of antimalarial treatment, and who agree to use effective contraception to avoid pregnancy from 28 days before enrollment through 10 months after last administration of investigational product are eligible to participate. An effective contraceptive method is defined as one that results in a failure rate of less than 1% per year when it is used consistently and correctly. Adequate contraceptive precautions include intrauterine contraceptive device, oral contraceptives, diaphragm, or condom in combination with contraceptive jelly, cream, or foam; Norplant® or Depo-Provera®, through the completion of study visits to minimize any potential risk.
      i. Effective contraception does not apply to participants of child-bearing potential with same sex partners, when this is their preferred and usual lifestyle.
      ii. Adequate contraception does not apply to women with documented surgical sterility (tubal ligation, bilateral oophorectomy, salpingectomy, or hysterectomy), congenital sterility, who have a diagnosis of infertility and are not undergoing treatment, or women who have not had a menstrual period in at least 1 year.

Informed Consent

5. Capable of giving signed Informed Consent which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF) and in this protocol, and completion of a test of understanding if he/she may participate in the CHMI procedure.

Laboratory criteria within range at Screening:

6. White Blood Cell (WBC) 3,500-12,000/mm^3
7. WBC differential either within institutional normal range or accompanied by the PI or designee approval
8. Platelets = 125,000 – 500,000/mm^3
9. Hemoglobin within institutional normal range or accompanied by the PI or designee approval
10. Creatinine ≤ 1.1 x upper limit of normal (ULN)
11. ALT ≤1.25 x ULN
12. Grade 1 subclinical abnormalities in other chemistries will not lead to exclusion if the investigator considers them not clinically significant

Laboratory criteria documented any time prior to enrollment:

13. Non-reactive HIV antibody testing (or confirmatory testing if previously in a documented HIV vaccine trial)
14. No evidence of active hepatitis B and/or hepatitis C infection
15. Negative sickle cell Screening test

Additional requirements:

16. Participants who agree to stay in contact with the trial site for the duration of the trial, provide updated contact information as necessary, and have no current plans to relocate from the trial area for the duration of the trial
17. Reported completion of primary Coronavirus Disease (COVID) vaccine series is documented
18. Adequate venous access for IV administration and phlebotomy.
19. Agrees to participate in a CHMI and to comply with post-CHMI follow-up requirements
20. Agrees to refrain from blood donation to blood banks for 3 years following CHMI
21. Agrees not to travel to a malaria endemic region during the entire course of trial participation

5.2 Exclusion Criteria

Participants are excluded from the trial if any of the following criteria apply:

Medical Conditions

1. Acute illness or fever ≥99.5°F (or ≥37.5ºC) on day of dosing
2. Women who are pregnant or breastfeeding
3. Evidence and/or history of clinically significant medical condition(s) as judged by the Investigator, including malignancies, diabetes mellitus, and unstable or uncontrolled hypertension.
4. A 5-year cardiovascular risk of ≥10% using the Gaziano nomogram (Appendix 3)
5. History of any autoimmune disease or immune deficiency or other impairment to the immune system, including but not limited to HIV, autoimmune conditions or immunosuppressive therapy.
6. Any current medical, psychiatric, occupational, or substance abuse problems that, in the opinion of the Investigator, will make it unlikely that the participant will comply with the protocol.

Prior/Concomitant Therapy

7. Any medications or other therapies that may impact the immune system such as allergy injections, interferon, immunomodulators, cytotoxic drugs or other drugs known to be frequently associated with major organ toxicity within 180 days prior to Day 0
8. Immunosuppressive agents including systemic steroids within 180 days prior to Day 0. Individuals using inhaled or topical corticosteroids are permitted
9. Receipt or donation of blood or blood products within 180 days prior to Day 0 or planned receipt or donation during the trial period
10. Receipt of antibody or biologic therapy within 180 days prior to Day 0 whether licensed or investigational (e.g., immunoglobulin products, mAbs, or antibody fragments)
11. Known intolerance to atovaquone or proguanil, and either artemether/lumefantrine or chloroquine phosphate

Prior/Concurrent Clinical Trial Experience

12. Participation in an interventional clinical trial and/or receipt of any investigational drug within 180 days prior to administration of trial drug on Day 0
13. Concurrent enrollment in another interventional trial

Diagnostic Assessments

14. Female participants: positive serum pregnancy test
15. Safety laboratory values outside of normal range, for age and sex that are suggestive of a disease state. Grade 1 abnormalities (as per Division of Acquired Immunodeficiency Syndrome (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, July 2017; see Appendix 4) will not lead to exclusion if the Investigator considers them not clinically significant
16. Electrocardiogram (ECG) with clinically significant abnormalities (examples may include: pathologic Q waves, significant ST-T wave changes, left ventricular hypertrophy, any non-sinus rhythm excluding isolated premature atrial contractions, right or left bundle branch block, advanced A-V heart block). ECG abnormalities determined by an investigator to be clinically insignificant as related to trial participation do not preclude trial enrollment. Consultation may be sought by a cardiologist at investigator discretion.

Other Exclusions

17. Unable to pass the test of understanding for the CHMI procedure, after informed consent and two attempts
18. History of allergy or hypersensitivity to the trial drug, excipients or related substances.
19. Any history of a severe allergic reaction with generalized urticaria, angioedema or anaphylaxis prior to enrollment that has a reasonable risk of recurrence during the trial
20. Previous receipt of a malaria vaccine or mAb (either experimental or RTS,S) in CHMI trial, and receipt of malaria mAb.
21. History of malaria infection, or history > 6 months spent in a malaria endemic region within 5 years prior to enrollment.
22. History of recent use (within 30 days) and/or use or planned use of any antimalarial drug (hydroxychloroquine, chloroquine, mefloquine, atovaquone or proguanil, artemether or lumefantrine) that would coincide with study product or CHMI.

23. Routine use of antibiotics, or use of antibiotics with known antimalarial effect (azithromycin, trimethoprim/sulfamethoxazole or tetracyclines) within 4 weeks prior to CHMI.
24. History of psoriasis or porphyria, which may be exacerbated after treatment with chloroquine
25. Anticipated use of medications known to cause drug reactions with chloroquine or atovaquone-proguanil (Malarone) such as cimetidine, metoclopramide, antacids, and kaolin.
26. Receipt or anticipated receipt of any vaccine within 14 days of IP administration or CHMI procedure. Details regarding COVID vaccination during trial participation are outlined in Section 7.4.
27. Bleeding disorder diagnosed by a doctor (e.g., factor deficiency, coagulopathy, or platelet disorder requiring special precautions) or significant bruising or blood draws
28. History of a splenectomy, sickle cell disease or sickle cell trait
29. History of skeeter syndrome or anaphylactic response to mosquito-bites
30. Individuals who are acting as trial personnel or immediate family members (brother, sister, child, parent) or the spouse/partner of trial personnel.

5.3 Lifestyle Considerations

No restrictions are required.

At Screening, participants must confirm their intention to continue living within the site's catchment area throughout their participation in the trial.

5.4 Screening

Screening assessments can be done at any time during the initial Screening window (Day -60 to Day-2; see Appendix 1), except for written informed consent, which must be completed prior to any Screening procedure. Screening for participants for Part B of the trial can be initiated during a second Screening window after the initial mosquito bite challenge. Screening for infectivity controls can occur anytime at the discretion of the Investigator.

5.4.1 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to a trial intervention/entered in the trial. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (i.e., why eligibility criteria were not met), and any SAE.

5.4.2 Re-Screening

If a participant fails to meet eligibility criteria upon initial screening, a one-time only re-screening may be performed. Repeat screening procedures may be performed if they can be completed within the original or subsequent screening window. Part A screen failures may be rescreened for Part B, and will not be required to repeat sickle cell testing if performed during their initial screening. Re-screening may proceed after providing new informed consent and a new participant identification (ID) should be assigned with the following exceptions:

- If a participant presents with an acute illness on the day of planned trial intervention (e.g., elevated temperature, acute respiratory illness or urinary tract infection), and meets all other eligibility criteria and can be rescreened after resolution of their illness within the Screening

window (see Appendix 1). If rescreening occurs in the original Screening window, a new informed consent and participant number are not required.

- If there are technical or operational difficulties with collection, processing, or running of Screening laboratory tests (e.g., laboratory reports hemolyzed blood) or conducting a Screening procedure (e.g., ECG machine error), the participant can be rescreened. If rescreening occurs in the original Screening window, a new informed consent and participant number are not required.
- If a participant is undergoing Screening and the trial reaches a pausing rule. The participant may be re-screened if and when the IDMC recommends, and the Sponsor determines, that the trial may continue. In this case, a new participant ID number and obtaining a new informed consent is not required.

6 TRIAL INTERVENTION

Trial intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a trial participant according to the trial protocol.

Four trial interventions will be used in this trial: participants will either receive MAM01 or placebo based on randomization as described in the section on trial design (Section 6.4.1).

Additionally, most study participants will undergo a CHMI challenge (see Appendix 1) whereby he/she will be bitten by 5 mosquitoes infectious with the NF54 strain of *Pf* to initiate malaria infection (see Section 6.5). All those challenged with infected mosquitoes will be later cured with FDA-approved antimalarials at the time of detection of malaria in the bloodstream or empirically on Day 27 (see Section 6.5).

6.1 Trial Drug Administration

Trial schema is shown in Figure 1 and dosing schedule in Table 4. Study design details are further outlined in Section 4.

With the exception of infectivity controls, participants will receive a single IV infusion or SC injection of MAM01 or placebo in the Dose Escalation Phase (Part A) or Expansion Phase (Part B). Additionally, participants from Cohort 2 and 3 will receive a second dose of MAM01 5 mg/kg at least 210 days (+/- 7 days) post the first dose regardless of the administration route or product received initially.

If the participant is assigned to an IV infusion group, the IV access will be placed in an arm vein in an aseptic manner. MAM01 or placebo will be administered with 50-120 mL of normal saline over about 15-30 minutes. Infusions lasting longer than 30 minutes are allowed at the discretion of the clinician Investigator. If the participant experiences side effects during the infusion, the rate of infusion may be slowed or stopped to alleviate symptoms.

If the participant is assigned to SC administration group, the SC administration site(s) to be used must be acceptable to the clinician and the participant. The preferred site of SC administration is the abdomen, but upper arm or thigh may be used. The injection will be given undiluted. Given the weight criterion of the study, the maximum dose in the 5 mg/kg SC arms is 500 mg or a maximum volume of 3.33 mL. A SC dose will be given by a standard needle maximum volume of 2 mL per injection site. Hence, for Part A, up to two injection sites may be deemed necessary by the clinician. For Part B where the SC dose volumes are greater, up to 3 injections may be given. SC administration sites should be at least 2 inches apart. See the Pharmacy Manual for further details.

6.2 Composition of Trial Drugs

6.2.1 MAM01 Drug Product

The MAM01 Drug Product is a sterile liquid that is colorless to slightly brownish yellow in color, clear to slightly opalescent solution with no preservative. MAM01 Drug Product is composed of 150 mg/mL MAM01 in 10 mM sodium acetate, 9 % (w/v) sucrose, 0.015 % (w/v) polysorbate 80, at pH 5.2. The nominal quantities MAM01 Drug Product per vial is 150 mg, provided in 2 mL glass vials closed with a gray rubber stopper and sealed with an aluminum cap and white flip seal.

6.2.2 MAM01 Placebo Drug Product

The MAM01 Placebo Drug Product is a sterile liquid that is colorless and clear with no preservative. MAM01 Placebo Drug Product is composed of 10 mM sodium acetate, 9 % (w/v) sucrose, 0.015 % (w/v) polysorbate 80, at pH 5.2. The Placebo Drug Product is of the same chemical composition as the MAM01 Drug Product formulation buffer without active pharmaceutical ingredient. The nominal quantities of Placebo Drug Product per vial is 1mL, provided in 2 mL glass vials closed with a gray rubber stopper and sealed with an aluminum cap and white flip seal.

The composition, function and quality of each ingredient in the trial investigational drug and placebo are provided in Table 6 and Table 7, respectively.

Table 6: Composition of the MAM01 Drug Products

Ingredient	Quality Standard	Nominal Amount/Vial	Function
MAM01	In House	150 mg	Active Pharmaceutical Ingredient
Sodium acetate	USP	0.65 mg	Buffer
Glacial acetic acid	USP, Ph. Eur.	0.13 mg	Buffer
Polysorbate 80	USP	0.15 mg	Surfactant
Sucrose	USP, Ph. Eur.	90 mg	Stabilizer/Tonicity Modifier
Water For Injection	USP	QS to 1.0 mL	Solvent

USP, United States Pharmacopeia; Ph. Eur., European Pharmacopeia; QS, quantum satis

Table 7: Composition of the MAM01 Placebo Drug Products

Ingredient	Quality Standard	Nominal Amount/Vial	Function
Sodium acetate	USP	0.65 mg	Buffer
Glacial acetic acid	USP, Ph. Eur.	0.13 mg	Buffer
Polysorbate 80	USP	0.15 mg	Surfactant
Sucrose	USP, Ph. Eur.	90 mg	Stabilizer/Tonicity Modifier
Water For Injection	USP	QS to 1.0 mL	Solvent

USP, United States Pharmacopeia; Ph. Eur., European Pharmacopeia; QS, quantum satis

6.2.3 Dose Modifications

No dose modification of trial interventions is allowed beyond the dose escalations explained in Section 4.

6.3 Preparation/Handling/Storage/Accountability

6.3.1 MAM01 and Placebo

Further guidance and information for preparation, handling, storage, and accountability are provided in the Pharmacy Manual.

6.3.1.1 Preparation and Handling

See Pharmacy Manual.

6.3.1.2 Storage

The study drug and placebo must be stored at 2-8ºC in a secure location with no unauthorized access. For further details refer to the Pharmacy Manual.

6.3.1.3 Accountability

The MAM01 mAb and placebo are to be supplied and administered by the Investigator or appropriately qualified site personnel named on the delegation of authority log. Under no circumstances will the Investigator allow the trial interventions to be used other than as directed by this protocol. Although appropriate personnel may be designated to administer trial interventions and maintain drug accountability records, the Investigator is ultimately responsible for all drug accountability.

The trial pharmacist or qualified designee is responsible for confirming appropriate temperature conditions have been maintained during transit and during site storage for all trial interventions received and that any discrepancies are reported and resolved before use of the trial interventions. The trial pharmacist is also responsible for making an inventory of the trial interventions upon receipt, ensuring adequate accountability of all used and unused trial interventions, and record maintenance (i.e., receipt, reconciliation, and final disposition records). All used and unused vials of MAM01 and placebo must be retained until final reconciliation or as indicated by the Sponsor.

The Investigator or designee must maintain accurate records of the receipt and disposition of all trial interventions. Documentation of trial intervention disposition should identify the participant receiving the trial intervention, the amount and date of dispensation, and any unused trial intervention(s). This documentation is required in addition to drug accountability information recorded on the Case Report Forms (CRFs). A written explanation must be provided for any discrepancies.

Authorization for any unused trial interventions and supplies to be destroyed is the responsibility of the Sponsor. Unused supplies may be destroyed or returned to the Sponsor per sSonsor decision. Sponsor will provide specific instructions to the clinical site on handling of unused supplies. If supplies are to be destroyed, this will be conducted as per the facility's institutional policy or per local regulations. Any disposal of trial interventions conducted at the clinical site must be documented in the trial file.

6.4 Measures to Minimize Bias: Randomization and Masking

6.4.1 Randomization

Randomization will be based on a randomly generated sequence of participant identification (identifier) numbers (randomization schedule) using a validated Interactive Response Technology (IRT). The randomization schedule will be prepared by a statistician who will not be involved in the analysis of the study in order to maintain the blind of the study team. Please see the IRT manual for more details.

Randomization may occur up to 24 hours in advance of trial drug administration in Part A and up to 72 hours in advance in Part B of the trial.

6.4.2 Masking (Blinding)

Part A of the trial has a double-blind design in which participants and all site personnel will be blinded to the randomization, with the exception of the unblinded pharmacist(s) at the trial site. The unblinded pharmacist will prepare doses of MAM01 and placebo and provide them to the

clinic appropriately masked to the authorized nurse/clinician administering the study drugs. Please see Pharmacy Manual for details.

Part B of the trial is open label. Participants will be randomized to receive open-label MAM01 in one of three dose groups. In addition, prior to the CMHI, a separate non-randomized group will be enrolled to include participants who will receive no treatment and serve as infectivity controls.

For the first interim analysis in Part A, the Sponsor will review unblinded aggregate PK analyses and will remain blinded to clinical data. For the second interim analysis in Part A, the Sponsor will be unblinded to PK, safety and efficacy results at the participant level after completion of the CHMI. See Section 9.2.7 for additional details. An unblinding plan will be prepared to describe the purposes for unblinding, the roles and responsibilities of team members who will be involved in the unblinding steps and the preparation and review of unblinded analyses, the specific analyses that will be reviewed, and the level of access each role will have to unblinded interim data.

Any trial staff members who are inadvertently unblinded must not participate in the evaluation of AEs. A delegation of authority log will be maintained by the site and will identify the individual(s) authorized to function in roles with access to study blinding information. The Investigator will be blinded through completion of the safety assessment of redosing in Part A of the trial.

6.4.3 Masking Break

For Part A of the trial, the IRT will be programmed with blind-breaking instructions. In addition, instructions on emergency unblinding in case of system outage will be provided in the IRT manual. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant's treatment assignment is unblinded at any time during the trial, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF, as applicable.

For Part B of the trial, MAM01 will be given open label.

6.4.4 Trial Intervention Compliance

All trial interventions will be administered at the clinical site and participant compliance will be recorded in the source documentation and CRF.

6.5 Malaria Challenge Product

The malaria challenge procedure involves introduction of *Pf* sporozoites by mosquito inoculation to mimic natural infection in endemic regions.

6.5.1 CHMI Agreements and Regulatory Considerations

The trial site and Sanaria are required to complete an agreement to allow Sanaria personnel to conduct the CHMI procedures and mosquito infectivity assessments within the trial site location. Each CHMI procedure will be conducted using *An. stephensi* mosquitoes reared by an experienced insectary at Sanaria under their Master File. The Sanaria entomologic staff will transport the infectious mosquitoes, travel to University of Maryland for the mosquito bite challenge and prepare cups of infected mosquitoes for challenge, and then dissect the mosquitoes to determine

their sporozoite burden. The actual mosquito bite challenge will be conducted by University of Maryland staff.

6.5.2 Description of Parasite Strain

Mosquitoes are infected via membrane feeds of pathogen-free blood containing the cultured *Pf* NF54 strain and reared per standardized procedures until they are infectious (containing mature sporozoites in the salivary glands). The NF54 strain of *Pf* is drug sensitive to atovaquone/proguanil, chloroquine, and artemether/lumefantrine.

A total of 5 bites from infectious mosquitoes showing presence of a blood meal and a minimum 2+ salivary gland score is considered a suitable inoculum.

6.5.3 *P. falciparum*-infected Mosquitoes (*Anopheles stephensi*)

6.5.3.1 Preparation and Handling

The preparation of infected mosquitoes will be performed according to a Type II Master Files, MF #14118 (Pf NF54) Malaria Challenge Model, SOPs for the *Pf* model used. The mothers of CHMI mosquitoes (*An. stephensi*) must be fed on FDA-regulated human blood products (Certificate of Analysis (COA) provided by the blood bank). The same blood source will be used for the in vitro cultivation of *P. falciparum* parasites. Mosquitoes will be constantly monitored for lifecycle progression. Emerged females (~ 4 days old) will be fed with mature gametocyte cultures of *Pf* (NF54), via artificial membrane feeding system. Mosquito infectivity will be monitored until the development of malaria sporozoites in the salivary glands. A batch record will be generated based on (1) the prevalence of infected mosquito per carton and (2) sporozoite load of the infected mosquitoes. The top ranked cartons will be used in CHMI procedures.

6.5.3.2 Transport and Storage

The Sanaria entomology team will ship the infectious mosquitoes to the trial site at University of Maryland. The containers of infected mosquitoes will be maintained at optimum conditions (temperature 26°C and humidity 80%) in a secure reach-in incubator in the University of Maryland until use in the challenge procedure.

6.5.3.3 Accountability

Any mosquitoes not used for malaria challenge are the responsibility of the Sanaria entomology team, who may repurpose, dispose of, or destroy the mosquitos in accordance with Sanaria SOPs. Sanaria personnel will provide reports of each mosquito-bite CHMI in support of the University of Maryland, Baltimore (UMB) IND for CHMI.

6.5.4 Antimalarials for Rescue Therapy

All participants who receive bites of infectious mosquitoes will be treated with a full curative dose of an FDA-approved antimalarial either when confirmed positive for malaria parasites or nucleic acids in the bloodstream, or at the end of the monitoring period (Day 27 post CHMI). Drugs are administered for 3 days by direct-observed therapy or video observation. The study site is responsible for procurement and documentation of antimalarial drugs, and proper storage and disposition. Administration will be documented on the appropriate CRFs.

- First line of treatment is an atovaquone/proguanil treatment (Malarone® or generics) regimen: Four adult strength (250 mg atovaquone/100 mg proguanil hydrochloride) tablets as a single daily dose for 3 days.
- Alternative regimens include artemether-lumefantrine or chloroquine.

- standard artemether-lumefantrine (CoArtem® or generic) treatment: four 20 mg/120 mg tablets taken twice daily for 3 days (6 doses) with food.
- standard chloroquine (Aralen® or generics) regimen: Total of 1500 mg chloroquine base (2500 mg salt) given orally in divided doses: 600 mg base (1000 mg salt) initially, followed by 300 mg base (500 mg salt) given 6, 24, and 48 hours later.

Additional alternate antimalarial treatment medications for *Pf* as by the CDC Malaria Treatment Guideline for Clinicians (Malaria_Treatment_Table.pdf (cdc.gov)) may be used in the case of allergies or intolerances to atovaquone/proguanil, artemether/lumefantrine or chloroquine.

6.6 Concomitant and Prohibited Medications

Participants receiving any medications or other therapies that may impact the immune system such as allergy injections, interferon, immunomodulators, cytotoxic drugs or other drugs known to be frequently associated with major organ toxicity within 180 days prior to Day 0 are not eligible for the trial (see Section 5.2). Receipt of any vaccine within 14 days of IP administration or CHMI procedure is also not permitted.

Documentation of concomitant medications is found in Section 8.3.The Medical Monitor should be contacted if there are any questions regarding a concomitant or prior therapy.

6.7 Intervention after the End of the Study

There is no intervention planned after the end of the trial.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION

7.1 Discontinuation of Study Intervention

A participant withdrawn from the study intervention (e.g., any participant who does not receive the study intervention(s)) will be withdrawn from the study.

7.1.1 Pausing Rules

Pausing rules (reasons for pausing the study) are in effect during the active enrollment and dosing period. Section 4.3.2.2 outlines pausing rules.

If any of the pausing criteria are met as determined by the SRT, enrollment/participant accrual as well as additional dosing of enrolled participants will be suspended pending IDMC's review of all available safety data and the Sponsor will be notified in an expedited manner.

Refer to Section 4.3.2.1 for the role of SRT and Section 10.1.2 for the role of the IDMC.

If the Investigator and/or the SRT observe that a pausing rule is met, the Investigator will inform the Sponsor and/or the SRT as soon as possible and within 24 hours of the observation. The SRT and/or Sponsor will notify the Investigator and the IDMC members of any pause in enrollment and participant dosing as soon as possible and within 24 hours of receiving notification of the pausing rule being met.

When a pausing rule is met, the IDMC members will convene an urgent ad hoc review meeting, review all relevant unblinded safety data, and make a recommendation to the Sponsor. The FDA will be advised of the IDMC actions and recommendations.

The IDMC may recommend continuation of the study pause or resumption of enrollment and dosing with or without changes to the protocol. The final decision to pause or resume study activities will always be the responsibility of the Sponsor. All IDMC recommendations will be stored according to the IDMC Charter.

All Sponsor decisions will be documented in a memorandum to the study file. The Sponsor or delegate is responsible for prompt communication to the study site of decisions related to pausing or resuming the study activities, including notification to the Investigator, relevant IRBs/ Independent Ethics Committees (IECs) and regulatory authorities.

The clinical site will be allowed to resume activities only upon receipt of written notification from the Sponsor.

7.2 Participant Discontinuation or Withdrawal from the Study

A participant may request withdrawal from the study at any time. Participants will be followed for safety unless they withdraw consent if they choose to withdraw and/or will be dosed with curative antimalarial medication should the withdrawal occur post-CHMI. Participants who have received CHMI cannot be withdrawn until they receive a curative dose of an antimalarial. A participant may also be withdrawn from the study at any time for the following reasons:

- at the request of the primary care provider if being in the study is no longer in the best interest of the participant

- participant is judged by the Investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results
- at the discretion of the IRB/IEC or government agencies as part of their duties, Investigator, or Sponsor.

If possible, a discontinuation visit should be scheduled for any participant who wishes to discontinue or withdraw from the study. At this visit, topics around participant safety including the need for ongoing contraception for women of child-bearing potential (see Section 10.5), as well as the use of already collected biospecimens, will be discussed. The procedures and specimen collection indicated in the SoAs will be performed if possible and as needed.

The time and reason for withdrawal should be noted in the space provided for this purpose in the CRF. If a participant withdraws consent, the reason, if specified, will be documented in the CRF.

Participants who are withdrawn because of occurrence of AE should be clearly distinguished from participants who are withdrawn for other reasons. Participants who are withdrawn because of an AE will be followed until the event resolves or stabilizes.

Refer to Section 10.1.5 regarding the informed consent process.

All data collected until the date of withdrawal/last contact of the participant will be used for the analysis, unless the participant requests destruction of any samples taken and not tested. The Investigator must document this in the site study records and the CRF. If the participant withdraws consent for disclosure of future information the Sponsor may retain and continue to use any data collected before such withdrawal of consent.

If the participant leaves the study, the participant's medical information will still be used or shared to the extent allowed by law. Any leftover samples will be destroyed after testing is completed unless the participant withdraws consent to sample use, in which case the samples will be destroyed at that time. Any test results from the samples collected before withdrawal can still be included in the analyses.

A participant who becomes pregnant during the study period will be asked to complete all visits and procedures (except any involvement in the CHMI) through end of study, as described in the SoAs. After she completes the scheduled end of study visit or in the event that she voluntarily withdraws from the study, and if she agrees to provide additional information regarding the pregnancy, the Investigator will utilize the 'Pregnancy Outcome Form' during the remaining gestation period to collect information on the health of the participant, the outcome of the pregnancy, and the health of the neonate. Neonate follow-up will occur for 6 weeks beyond the delivery date (refer to Section 10.5).

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits (3 failed visits) and is unable to be contacted by the study site (3 failed attempts per failed visit). The exception is any participant who is in the midst of a CHMI procedure in which case contact attempts must continue until the participant completes a curative antimalarial regimen. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, telephone calls and, if necessary, a home visit by a member of the study team). These contact attempts should be documented in the participant's medical record and the CRF. Site specific SOPs will be followed.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up from the study.

7.4 COVID-19 Contingency Plans

Participants are asked not to schedule COVID booster vaccinations within 14 days before or after IP administration or CHMI procedure. In the event that Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) coronavirus disease (COVID-19) pandemic affects the conduct of this trial, the sponsor will evaluate if in-person visits are necessary to fully ensure the safety of trial participants and whether alternative methods for safety assessments (e.g., phone contact, virtual visit, alternative location for assessment such as local laboratories or home visits) could be implemented when necessary and feasible, and would be sufficient to ensure data integrity and safety of participants (FDA 2020).

Any contingency plans must be sufficient to ensure the safety of trial participants. COVID testing prior to site visits including CHMI is authorized as needed at the discretion of the Investigator, but should be captured in the CRF. Changes in study visit schedules, missed visits, or withdrawal of the study intervention or participant discontinuations may lead to missing information (e.g., for protocol-specified procedures) must be captured in the CRF that explains the basis of the missing data (i.e., COVID-19). Approaches to be used to protect trial participants and manage study conduct during possible disruption of the study as a result of COVID-19 control measures at the study site must be documented. Depending upon the nature of the changes described above, a protocol amendment may be required under the applicable regulations. Deviations because of COVID-19 will be described in the clinical study report or in a separate study-specific document) including but not limited to the following:

- Contingency measures implemented to manage study conduct during disruption of the study as a result of COVID-19 control measures.
- A listing of all participants affected by the COVID-19 related study disruption by unique participant number identifier and by investigational site, and a description of how the individual's participation was altered.
- Analyses and corresponding discussions that address the impact of implemented contingency measures (e.g., trial participant discontinuation from investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data on the results reported for the study.

8 TRIAL ASSESSMENTS AND PROCEDURES

Trial assessments and procedures are described in this section and summarized in the SoAs in Appendix 1. Protocol waivers or exemptions are not allowed. No trial assessments or procedures may be conducted before the participant provides written informed consent.

All protocol-required laboratory assessments must be conducted in accordance with the Trial's Laboratory Manual and the SoAs. All protocol-required safety laboratory tests will be performed by a designated laboratory. Information about the laboratory(ies), including any instructions for performing and interpreting specific tests, will be maintained in the Trial Laboratory Manual.

8.1 Screening Assessments for Eligibility

Prior to any trial procedure, all eligible participants will be assigned a unique participant identifier. This participant identifier will be used throughout the trial for participant identification.

Screening procedures will be conducted during the 60-day Screening Period until 2 days before the planned Day 0 visit. Screening assessments can be done at any time during this period, Eligibility for randomization will be based on the inclusion and exclusion criteria described in Sections 5.1 and Section 5.2.

Eligibility criteria will be checked during the Screening Period and prior to trial drug administration to ensure that each randomized participant meets all the inclusion criteria and none of the exclusion criteria. The Investigator will also maintain a Screening log to record details of all participants screened to confirm eligibility or record reasons for Screening failure, as applicable.

To evaluate eligibility criteria, the following assessments and procedures will be conducted:

- Demography and medical and treatment history
- Prior and concomitant medication review
- Physical examination, including vital signs (blood pressure, heart rate, pulse oximetry on room air, and temperature), weight and height
- Serum pregnancy test (females only)
- HIV testing, Hepatitis B and C testing
- Hemoglobin electrophoresis for sickle cell Screening
- 12-lead ECG
- Laboratory safety tests (CBC with differential, complete metabolic profile (CMP))

Assessments and procedures unique to the Screening period are provided in this section.

8.2 Demography and Medical and Treatment History

Information on demographic characteristics (e.g., age, sex assigned at birth, gender, place of birth, occupation,) will be obtained and a medical and treatment history will be conducted during the Screening period to assess eligibility. Identifying and location information will be kept at the trial site and will not be entered into the trial database. All conditions that exist prior to Screening will be recorded in the medical history section of the CRF. Any clinically relevant new condition or fluctuation of an existing condition observed for 28 days after either IP administration or the CHMI procedure will be recorded as an AE (see Section 10.4.7).

8.3 Prior and Concomitant Medication Review

Prior and concomitant prescription or over-the-counter medications, vitamin or dietary supplements, herbal products, or vaccines (including COVID-19 vaccination) will be assessed starting 60 days before Screening and prior to IP administration and CHMI. Concomitant medications will be assessed at study visits for 28 days after IP administration or the CHMI procedure. See Section 5.2 for prior medication requirements listed for eligibility.

Any prescription or over-the-counter medication, vitamin or dietary supplement, herbal product, or vaccine that a participant receives must be recorded along with:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose, route, and frequency.

Additionally, in the case of a SAE, AESI or Suspected Unexpected Serious Adverse Reaction (SUSAR) at any time through the end of the study, all medications and therapies will be recorded on an electronic CRF (eCRF).

The Medical Monitor should be contacted if there are any questions regarding a concomitant or prior therapy.

8.4 Physical Examination and Vital Sign Assessments

8.4.1 Full Physical Examination and Vital Signs

A full physical examination and medical history will be conducted during Screening to assess enrollment eligibility. Physical examination at Screening will include, at a minimum, assessment of height and weight, body temperature, percent oxygen saturation by pulse oximetry, pulse and resting blood pressure, in addition to assessments needed to determine eligibility. Physical examination assessments will include general appearance and specific organ systems (head, ears, eyes, nose, throat/mouth, neck, lungs, cardiovascular, gastrointestinal, neurologic systems, skin and lymphatics).

8.4.2 Focused Physical Examination

A review of changes in adverse events or medical history to check for changes since Screening and previous visit(s) as applicable and a focused physical exam may be performed if medically indicated to check eligibility again on Day -1 and all subsequent visits to check for changes in health throughout the trial, as indicated in the SoA (See Appendix 1).

Focused physical exams will be performed if indicated by the participant's medical complaint and will be symptom directed. At a minimum it will include an assessment of organ systems involved in the complaint.

8.4.3 Vital Signs

Vital signs (body temperature, percent oxygen saturation on room air by pulse oximetry, pulse and resting blood pressure) and weight (Part A only) should be repeated at the Day-1 visit.

For all visits through Day 28 after IP administration and during the CHMI procedure (as outlined in Appendix 1), vital signs will consist of body temperature, percent oxygen saturation on room air by pulse oximetry, pulse and resting blood pressure.

8.4.4 Pregnancy Status Assessment

A blood sample will be collected from female participants at Screening for serum β-HCG testing. A negative β-HCG pregnancy test (serum) result for females of child-bearing potential must be confirmed during Screening.

Prior to IP administration on Day -1 or Day 0, a urine pregnancy test will be documented in female participants (unless surgically sterilized) within 24 hours of study product administration.

A pregnancy test (urine or serum) should also be performed before CHMI, at the end of the CHMI procedure (see Appendix 1) and at the study discontinuation visit. Serum β-HCG pregnancy test should be performed anytime during the study if pregnancy is suspected.

During the study, participants will be asked about pregnancy during each visit. If a pregnancy is reported, the Investigator should inform the Medical Monitor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.5.

A participant who becomes pregnant during the study period will be asked to complete all visits and procedures through Week 12, 24 or 48 as described in the SoAs, except any involvement in the CHMI. After she completes the scheduled end of study visit, or in the event that she voluntarily withdraws from the study, and if she agrees to provide additional information regarding the pregnancy, the Investigator will utilize the 'Pregnancy Outcome Form' during the remaining gestation period to collect information on the health of the participant, the outcome of the pregnancy, and the health of the neonate. Neonate follow-up will occur for 6 weeks beyond the delivery date (refer to Section 10.5). If a participant becomes pregnant after their final study visit, but within 10 months of receiving MAM01 or placebo, they should inform the site and the Investigator will utilize the 'Pregnancy Outcome Form,' to report the necessary details to the sponsor and collect information on the health of the participant, the outcome of the pregnancy, and the health of the neonate (refer to Section 10.5)

8.4.5 HIV and Chronic Hepatitis

Participants must not have a reactive HIV antibody at Screening. Likewise, participants with active hepatitis B (as assessed by a positive Hepatitis B surface antigen (HBsAg)) or active hepatitis C (as measured by Hepatitis C virus antibodies and evidence of active liver inflammation) should be excluded.

8.4.6 Sickle Cell Disease Screening

A hemoglobinopathy evaluation will be performed at screen by hemoglobin electrophoresis. Those with sickle cell trait or sickle cell disease should be excluded.

8.4.7 Electrocardiogram

A 12-lead ECG will be performed at Screening using a machine that automatically calculates heart rate and determines intervals for PR, QRS, QT and QTc. A single (unmarked) 12-lead ECG will be obtained.

For participants in the Dose Escalation Phase, an additional ECG will be taken at the 24 hours post-dose visit on Day 1 after the first dose.

8.4.8 Clinical Safety Laboratory Assessments

Screening: At Screening, these will include a CBC and differential and CMP. Abnormal results and findings that make the participant ineligible for study participation will be discussed with the

participant and the participant will be referred for follow-up care with their health care provider if necessary.

Blood samples for subsequent clinical safety laboratory assessments will be performed on Day -1 (Pre-V1), and throughout the study at timepoints specified in the SoA (Appendix 1). Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Clinical safety laboratory parameters for subsequent visits will be limited to:

a. Hematology: CBC (including hemoglobin, platelet count and white blood cell count) and differential to include the absolute counts for neutrophils, lymphocytes, eosinophils, and monocytes;

b. Serum chemistry: ALT and creatinine or CMP. (see Appendix 1)

For participants in Cohort 2 and 3 who will receive a 2nd dose of MAM01, CMP and CBC with differential will be repeated at the visit prior to second drug administration as per the SoA (Appendix 1). For repeat evaluation of CMP, subclinical abnormalities for sodium, potassium, total CO2, chloride, blood urea nitrogen and glucose not deemed clinically significant by the investigator will not be considered an AE unless grade 2 or higher.

All protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual and the SoA.

If laboratory values from non-protocol-specified laboratory assessments require a change in participant management or are considered clinically significant by the Investigator (e.g., AE or SAE), then the results must be recorded in the CRF.

Refer to Appendix 5 for toxicity table for grading for each clinical laboratory test. Laboratory values from the most recent blood sample collected prior to randomization that are outside the normal range and that are suggestive of a disease state (i.e., clinically significant Grade 1 abnormalities or values greater than Grade 1 [refer to Appendix 4]) will lead to exclusion from study enrollment.

8.4.9 Memory Aid Card

A Memory Aid card will be utilized by participants to collect solicited and unsolicited AEs beginning at discharge from the clinic after infusion/injection, through Day 7 (or end of study participation for an individual) for first or subsequent mAb infusion.

Before leaving the clinic after dosing and completion of the post-dosing on-site observation, participants will be given a Memory Aid card and receive guidance on how to fill in the card. All participants will receive a digital thermometer to record temperature. Participants who receive an SC dose will also receive a ruler to measure diameter of redness and/or swelling at the injection site, if present.

The Memory Aid card will be used by the study participants to record the duration, and intensity (refer to Section 8.4.13) of solicited injection site AEs (for participants who receive an SC dose) and solicited systemic AEs up to Day 7 following injection or infusion for all participants. This information should be recorded in the participant Memory Aid card at approximately the same time each evening (refer to Section 8.2 for more information).

No changes to the Memory Aid card will be permitted; however, any verbally recalled information provided by the participant during review of the Memory Aid card will be documented in the source document and reported as an AE, as applicable.

8.4.10 Participant Follow-Up and Unscheduled Visits

Participants will be instructed to contact a study team member to report new or worsening AEs, as well as new diagnoses, and to come to the study clinic if medical attention is needed during the 60 days after test article administration.

For emergencies and other unscheduled visits to a medical facility other than the study clinic, medical records will, to the extent possible, be obtained by the Investigator.

Participants will be asked about the occurrence of SAEs, AESIs, receipt concomitant prescription medications/vaccinations, and change in general health status and any other change in status that may affect the participant's participation, as indicated in the SoA.

Any deviation from protocol procedures, evaluations, and/or visits will be documented.

8.4.11 Collection of Adverse Events and Serious Adverse Events

Details of adverse event definitions, grading, reporting, and resolution are found in Section 10.4.

8.4.12 Timing of Collection of Adverse Events

Solicited AEs (reactogenicity parameters outlined in Section 8.4.13) will be recorded for 7 days after each product administration. The participant may record solicited AEs on the Memory Aid card and these will be reviewed by study investigators for recording in the study database.

Unsolicited AEs will be recorded in the study database with attribution assessments during the following time periods:

1) from product administration to the Day 28 (Week 4) visit; and
2) from CHMI Day 0 through the Day 27 post-CHMI visit or Day 49 post-CHMI visit, depending on the diagnosis of malaria infection (see Appendix 1, Table 11).

AESIs, SUSARs and other SAEs will be collected from Screening through end of the study for each participant.

8.4.13 Solicited Adverse Events

Local injection site solicited AEs, including pain, itching, redness, bruising and swelling will be assessed after dosing and will also be recorded for 7 days from SC recipients only. If more than 1 injection is given, reactions will be assessed separately at each injection site. Site staff will review the memory aid card at visits thru Day 7 and conduct a focused physical exam to complete the AE assessment, as warranted.

Systemic solicited AEs will be assessed for all participants after dosing at Visit 1 and recorded for
7 days. These will include fever, chills, headache, fatigue, muscle aches, nausea and joint pain.

Solicited AEs that continue beyond Day 7 will be captured and marked as continuation of solicited AE(s).

8.4.14 Unsolicited Adverse Events

Unsolicited adverse events will be captured after product administration and the CHMI procedure, as outlined in Section 8.4.12. These will be captured into the study database at all study visits during these time windows.

8.5 Blood Sampling and Sample Storage

In addition to venous samples collected by phlebotomy, PK and ADA samples will be collected by a volumetric absorptive microsampling method (VAMS) from capillary blood collected after fingerprick for Part A. The CE-IVD certified devices used will be Mitra VAMS (Neoteryx), which are designated as a Research-Use Only (RUO) product in the United States. Details on its specifications and use are described in the Laboratory Manual.

In Part B, VAMS devices will be used for the ADA sample collection, but capillary PK samples will be collected using a fingerstick sample into a serum-separator microtainer tube in addition to the venous samples.

The volumes of blood collected will vary among the cohorts and will be listed in the Informed Consent document.

Specific details on sample storage will be provided in the Laboratory Manual.

8.6 Pharmacokinetic Assessments

In Part A, serum from venous blood samples will be collected for measurement of MAM01 PK per the SoA (Appendix 1). Blood concentrations of MAM01 will be measured using a validated immunoassay. In Part B, serum from venous and capillary blood samples (via microtainer) will be collected (Appendix 1).

Additionally, selected venous and capillary (matched) samples in Part B will be used to provide bridging data to support use of data from both sample types in modeling efforts in this and future studies.

For all samples, the actual date and time (24-hour clock) of each sample will be recorded to calculate the actual time elapsed since dose administration.

Remaining samples collected for analyses of MAM01 may also be used to evaluate immunogenicity and/or safety aspects related to any concerns arising during or after the study. Details on processes for collection and shipment of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the end of the study are specified in the ICF.

8.7 Anti-drug Antibody Assessments

Capillary blood samples will be collected on VAMS microsampling devices per the SoA (Appendix 1). Samples on Day 1 and redosing (Week 24) will be collected prior to MAM01 administration. Additional blood samples and selected serum samples for ADA will be collected starting on day 7 as per Appendix 1.

The detection of ADA to MAM01 antibodies will be performed using a validated tiered immunoassay. Samples that screen and then confirm positive will be titered and may be further characterized with qualified or validated assays.

Remaining samples collected for analysis of anti-MAM01 antibodies may also be used to evaluate MAM01 concentration or exploratory biomarkers during or after the study. Details on processes

for collection and shipment of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the end of the study are specified in the ICF.

8.8 Pharmacodynamic Assessments

Venous whole blood samples for [redacted] will be collected in Cohorts 2 and 3 of Part A per the SoA (Appendix 1) and processed to serum. [redacted] will be measured with a validated cell-based assay and/or a validated immunoassay. This measurement would include any pre-existing [redacted] from natural infection. While this background signal is anticipated to be minimized by running studies in non-endemic areas and excluding participants with known history of malaria infection, the baseline sample is essential to characterize increases in [redacted] relative to baseline.

As CSP is not expressed in *Pf* blood merozoites, the emergence of breakthrough blood stage parasitemia will not be affected by prior MAM01 administration.

8.9 Biomarker Assessments

8.9.1 Blood Stage Parasites

After CHMI, a parasite infection that escapes the MAM01 antibody targeting sporozoites will progress to blood stage (merozoite) infection, which causes illness at higher parasite concentrations. Venous whole blood samples for blood stage parasitemia will be collected per the SoA in the CHMI portions of the study (Appendix 1). The presence of pathogens will be detected with a validated quantitative ultrasensitive RT-PCR assay and microscopic assessment of thick blood films.

8.9.2 PCR Analysis for *P. falciparum*

A sensitive qRT-PCR will be used for the detection of *Pf* parasites. The qRT-PCR will be run off venous blood collected in ethylenediaminetetraacetic acid (EDTA) tubes. Optimization experiments have established a high degree of sensitivity. Polymerase Chain Reaction (PCR) primers will be based on the published sequence of the highly conserved (32), stage specific (33) *Pf* 18S ribosomal RNA gene. Primer sequences are identical to the corresponding sequence of the NF54 and 3D7 strains. Samples will be blinded to treatment group, participant ID, and visit number, and assays run daily. Each sample will be run in duplicate along with a water control. The data will be analyzed using the Applied Biosystem 7300 Absolute Quantification Software.

A confirmed parasite detection consists of two sequential positive qRT-PCR tests at > 12 hours but < 60 hours, and the time to infection is recorded as the time of the first positive qRT-PCR. The above PCR algorithm has generally proven highly effective and resulted in parasite detection approximately 3.5 days before detection by microscopy (Friedman-Klabanoff 2019).

8.9.3 Microscopic Visualization of Parasites by Blood Smear

A small aliquot of blood (10 µL) from the same EDTA tube will be placed upon microscope slides for the creation of thick malaria smears. The thick smear will be allowed to dry, lysed with distilled water and stained with Giemsa for analysis of intra-erythrocytic ring forms consistent with malaria.

The thick blood smears will be examined for parasites if either the participant is symptomatic or a qRT-PCR signal is identified (see section 4.2.3.2). Trained Investigators blinded to randomization results will examine 5 separate passes along the 1 cm axis of a blood smear using the 100x oil immersion lens of calibrated microscopes. This will be doubled to ten passes for symptomatic

individuals. Ten passes performed by microscopists examines a total of 0.9-1.1 µL of blood (refer to site SOPs).

The peripheral blood smear provides comprehensive information on the parasite stages, and the density of parasitemia with a sensitivity of 5 to 20 parasites/µL of blood for an experienced laboratory professional although this level can be much higher taking into account reader variability. These assays will be performed on-site in the Malaria Laboratory and Insectary of the University of Maryland Center of Vaccine Development (CVD) and Global Health and the collective experience of the CVD staff is a sensitivity of 2 parasites/µL. The minimum acceptance criteria are NO false positive reads on thick smears and a positive smear will be defined as two unquestionable parasites present on smear. The above technique has proven to be highly effective and accurate with ~45% of individuals being diagnosed before malaria symptoms (personal experience, University of Maryland (UMD)). The slides will be stored until study closure for future review as necessary.

8.9.4 Serum for anti-CSP Antibodies

For participants undergoing CHMI, a serum sample will be collected prior to challenge for research use. These sera will be frozen in case participants fail to become parasitemic after CHMI. An anti-CSP and anti-MSP antibody assay may be performed to look for naturally pre-existing antibodies in this contingency.

8.9.5 Residual Samples

All participants who consent to participate will be asked to agree to future research consent for malaria research only. Remaining sera samples from PK, ADA, and [redacted] antibodies or [redacted] assays from the CHMI portions of the trial will be retained for future research on malaria biomarkers.

9 STATISTICAL ANALYSIS PLAN SUMMARY

This section contains a brief description of the statistical analyses for this trial. Details will be further specified in the full statistical analysis plan (SAP).

9.1 Populations for Analysis

For purposes of analysis, the following populations are defined:

Population	Description
Safety population	All participants who were randomly assigned to trial intervention and received the trial intervention. Participants will be analyzed according to the intervention they received.
Efficacy population	All participants who were randomly assigned to trial intervention, received the trial intervention, and underwent CHMI. Participants will be analyzed according to the intervention they received.
Per protocol (PP) population	All participants randomly assigned to trial intervention and who received the trial intervention and did not significantly deviate from trial procedures. Participants will be analyzed according to the intervention they received.
PK population	All participants who were randomly assigned to trial intervention, received the trial intervention, and have baseline and on-study concentration-time data available. Participants will be analyzed according to the intervention they received.
Immunogenicity population	All participants who were randomly assigned to trial intervention, received the trial intervention, and have at least one valid ADA result. Participants will be analyzed according to the intervention they received.

9.2 Methods

9.2.1 General

Data from Part A and Part B of the trial will be analyzed and presented separately. Placebo and infectivity controls may be combined. The SAP will provide a detailed description of all planned analyses.

9.2.1.1 Power and Sample Size Considerations

Because this is an exploratory trial aimed at characterizing the safety, tolerability, efficacy, and PK of single dose and repeat doses of MAM01, it is designed to be descriptive and is not based on formal hypotheses. Therefore, this trial is not powered to detect any pre-specified differences in potential safety, efficacy, or PK data between treatment groups. The sample size is based on previous experience to adequately assess safety, efficacy, and tolerability. A group of 6 participants to serve as the infectivity controls for each CHMI procedure are included, as historical data suggest that the rate of infection in the reference group may occasionally be <100% (Epstein 2007). The infectivity controls are comprised of the placebo recipients in the cohorts.

In total approximately 61 participants will be included in the trial, 37 participants in the SAD/ MAD phase (Part A) and 24 participants in the expansion phase (Part B). There will in total be 48 participants exposed to MAM01 and 7 participants receiving placebo.

The SAD phase will include 37 participants (Part A), allocated over 5 cohorts as.

- Cohort 1 - 8 randomized, with 2 sentinel participants randomized 1:1 and the remaining 6 participants randomized 5:1 to MAM01 1.5 mg/kg IV or placebo;
- Cohort 2 - 7 randomized 6:1 to MAM01 5 mg/kg SC or placebo;
- Cohort 3 - 7 randomized 6:1 to MAM01 5 mg/kg IV or placebo;
- Cohort 4 - 8 randomized 6:2 to MAM01 10 mg/kg IV or placebo;
- Cohort 5 - 7 randomized 6:1 to MAM01 40 mg/kg IV or placebo.

In Cohorts 2 and 3, at least 210 days (± 7 days) post-initial dose, participants will receive a second dose of MAM01 dose of 5 mg/kg SC. Cohort 4 includes 2 placebo participants to ensure that the minimum number of infectivity controls in Part A is 6, as noted above.

For Part B (Cohort 6), a total of 24 participants will be included: 18 participants randomized to one of 3 open-label doses of MAM01 and a separate non-randomized group of 6 participants who with not receive treatment and will serve as infectivity controls.

9.2.2 Safety Analyses

For Part A, the primary analysis of safety will occur when all participants reach at least Day 168 (Week 24) and will include all available data at the time of analysis. For Part A, Cohort 2 and Cohort 3 participants who receive repeat dosing, the analysis of safety after the second dose will occur when all participants reach at least Day 336 and will include all available data at the time of analysis. For Part B, the primary analysis of safety will occur when all participants reach Day 84 (Week 12). The incidence of solicited local and unsolicited AEs will be summarized by treatment group and combined across all MAM01 dose levels and routes of administration. Summaries will be produced by grade based on data from Screening through Day 7 (for solicited local AEs in the SC cohorts) and through Day 28 (Week 4) or CHMI (CHMI Day 0 through Day 49).

Safety will be summarized in the safety population.

For Part A, an additional supplemental analysis will be done when all participants completed Day 168, where the safety summaries described above will be provided using all available data through Day 361.

9.2.3 Pharmacokinetics Analyses

All available PK data will be summarized at the time of the primary analysis, when all participants reach last PK sample. MAM01 blood and serum concentrations and the following PK parameters, $AUC_{0-\infty}$, C_{min}, C_{max}, C_{D168}, C_{CHMI}, AUC_{0-CHMI}, T_{max}, λz, $t_{1/2}$, clearance (CL), SC Bioavailability, and apparent volume of distribution (Vz), will be summarized by treatment group.

For Part A (Cohorts 2 and 3) participants that are redosed additional PK parameters will be calculated: AUC_{0-168}, $AUC_{210-378}$, accumulation ratio $AUC_{0-168}/AUC_{210-378}$, and C_{min}, C_{max}, T_{max}, $t_{1/2}$, ratio of clearance to bioavailability (CL/F) following the second dose and will be summarized (i) by cohort and (ii) combined.

For Part B, the following PK parameters will be summarized by dose group: AUC_{0-last}, C_{min}, C_{max}, C_{D84}, C_{CHMI}, AUC_{0-CHMI}, and T_{max}.

Each of the PK parameters will be summarized using descriptive statistics, and the number of participants, arithmetic mean, standard deviation, arithmetic percent coefficient of variance (CV), median, minimum, maximum, geometric mean, and geometric percent CV and will be provided by treatment group and country, as appropriate.

PK will be summarized in the PK population.

The MAM01 blood and serum concentration data obtained in this trial will be used to develop individual and population PK models that will aid in the prediction of dose levels in trial participants and assess potential covariates. These analyses will be described in an independent analysis plan and reported separately.

[redacted]

9.2.4 Immunogenicity Analyses

All available ADA titers will be summarized at the time of the primary and supplemental analyses.

- For participants in Part A (Cohorts 1, 4 and 5) through Day 280.
- For participants in Part A (Cohorts 2 and 3), through Day 378.
- For participants in Part B through Day 84.

Among participants in the immunogenicity population, the proportion of participants with titers confirmed above the assay cut point will be summarized calculated by treatment group as appropriate.

9.2.5 Efficacy Analyses

The efficacy of MAM01 based on actual antibody concentration at the time of CHMI is described in Section 9.2.6.

Among participants in the efficacy population, the proportion of participants with *Pf* infection after CHMI (through Day 27 post-CHMI) will be summarized for each dose group. In addition, the time to *Pf* parasitemia will be summarized by dose group.

9.2.6 Pharmacodynamic Analyses

MAM01 levels at the time of CHMI among all participants in Cohorts 1-5 will be used to estimate the EC80 of the antibody.

The [redacted] pharmacodynamic data will be summarized at the time of the primary and supplemental analyses.

- For participants in Part A (Cohorts 2 and 3), through Day 378.

9.2.7 Interim Analyses

9.2.7.1 Part A

Two interim analyses are planned in Part A.

The first interim analysis will focus on safety for all cohorts up to a point triggered when cohort 1 is 16 weeks post dose (time of the initial planned CHMI procedure). This will ensure a minimum of 56 days of safety data for all cohorts in Part A. The Sponsor and SRT will review blinded safety data (from Cohorts 1-5) to inform whether to proceed to Part B of this trial. The IDMC will review unblinded individual and aggregate safety data in a closed meeting.

The second interim analysis will focus on safety and efficacy following the CHMI procedures and PK modelling. This will occur after completion of the CHMI (Day 27). There will be two outputs from this analysis:

- PK at the time of CHMI will be paired with the parasitologic outcome (Day 27) at CHMI by the Sponsor's unblinded pharmacometrics team. A detailed description will be provided in the

PK SAP. The Sponsor will be unblinded at the participant level; the Investigators will remain fully blinded. The purpose of this output is to inform dose selection for Part B and the broader development program.

- This interim analysis output will include all PK samples drawn up to the time of the CHMI (including the pre-CHMI sample). It will explore the MAM01 pharmacokinetic profile and explore MAM01 concentrations at or around the time that any additional safety events (relevant SAEs or AESIs) occurred. The Sponsor will be unblinded at the participant level; the Investigators will remain fully blinded. The purpose of this unblinded interim analysis will be to develop the individual and population PK and PK/PD models and aid in dose selection for future clinical trials.

MAM01 (open label; without placebo comparator) will be given for the re-dosing of all participants in Cohorts 2 & 3. Though access to unblinded results from the second interim analyses will be limited within the Sponsor team, such reviews of data could lead to unblinding of the treatment received by individual participants. An unblinding plan will be prepared and finalized prior to the interim analyses. The plan will describe the purposes for unblinding, the roles and responsibilities of team members who will be involved in the unblinding steps and the preparation and review of unblinded analyses, the specific analyses that will be reviewed, and the level of access each role will have to unblinded interim data.

9.2.7.2 Part B

An interim analysis may be performed for Part B of the study. In this event, details will be provided in the Statistical Analysis Plan.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Trial Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Belmont Report, Declaration of Helsinki and CIOMS International Ethical Guidelines.
- Applicable International Council for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human Use GCP Guidelines.
- 45 CFR 50 and 56, and other applicable laws and regulations.
- The protocol, protocol amendments, ICF, and other relevant documents (e.g., assessment of understanding, Memory Aid cards, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the trial is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial participants.

10.1.2 Trial Oversight

The Sponsor, the IRB/IEC, the institution through which the research is performed, all members of the PI's clinical team, and the national regulatory authority share responsibility for ensuring the safety of participants in this trial.

The Principal Investigator will be responsible for the following:

- Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently, in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the trial at the site and adherence to requirements of ICH and GCP guidelines, USA FDA Regulations, the IRB/IEC, and all other applicable country and local regulations.
- Closely monitoring trial participants and taking whatever measures necessary to ensure their safety. The Principal Investigator may delay an individual's trial drug administration or pause trial drug administration altogether if the Investigator is concerned that the trial drug might place a participant or participants at significant risk. Where specified, the responsibilities of the Principal Investigator may be delegated to a medically qualified team member (designee). The Investigator determines severity and causality with respect to the trial drug for each AE.

The Sponsor has an institutional responsibility to ensure participant safety and is ultimately accountable for safety oversight. The Medical Monitor and the SRT play an important role in this regard and support the Sponsor. The role of the SRT is described in Section 4.3.2.1.

The Medical Monitor is a physician or surgeon contracted by the Sponsor who:

- reviews the safety of the product for protocols in a specific region and, in conjunction with the Sponsor, determines expectedness of AEs.

- Is responsible for safety oversight in-country and plays an important role in the reporting of SUSARs and other SAEs, adverse drug reactions (ADRs) and pregnancies, as described in the protocol.
- in consultation with the Sponsor, may assess the severity and causality for AEs and may upgrade the degree of severity and causality determined by the PI or designee.

The Independent Data Monitoring Committee (IDMC): The IDMC will operate according to a charter approved by the sponsor and all IDMC members. The IDMC structure, participants and other details will be provided in the charter. The charter will be approved prior to enrollment of the first study participant.

The role of the IDMC will be to:

(a) review unblinded safety data if a pausing rule is met; and
(b) make recommendations to the sponsor on further conduct of the study if a pausing rule is met.
(c) review the unblinded safety data from Interim Analysis #1 to recommend expansion of the clinical development program.

The recommendations of the IDMC, along with the sponsor's decision, will be communicated to the Investigator, to the responsible IRBs/IECs and to the USA FDA. The recommendations of the IDMC when evoked, along with the Sponsor's decision, will be communicated to the Investigator, to the responsible IRBs/IECs, and to the USA FDA.

Institutional Review Board (IRB): The UMB Human Research Protections Office, henceforth termed IRB, or Ethics Committee (EC) has institutional responsibility for the safety of research participants. The UMB IRB currently holds and will maintain a United States Federalwide Assurance (US FWA) issued by OHRP for the entirety of the study. Sanaria staff are not engaged in human subjects research, but are supplying infected mosquitoes under their contract with Gates MRI.

The IRB or EC has the authority to terminate, suspend or require changes to the clinical trial.

The protocol, ICF, other written subject information including the test of understanding, the memory card, any proposed advertising or amendments to these documents will be submitted to the IRB for review and written approval before use.

The Investigator will be responsible for getting IRB approval of the annual Continuing Review by the IRB throughout the duration of the study and submission of a final report to the IRB.

The UMB IRB contact information is as follows:

University of Maryland Human Research Protections Office
620 W. Lexington Street, 2nd Floor
Baltimore, Maryland 21201
Telephone: 410-706-5037 / Fax: 410-706-4189
Email: HRPO@umaryland.edu

The national regulatory authority, USA FDA, has the authority to terminate, suspend or require changes to the clinical trial.

10.1.3 Sanaria Reporting Requirements for Use of the *Pf* NF54 Master File

The following reporting requirements related only to the CHMI apply (in addition to the requirements to report to UMD Human Research Protections Office):

Unanticipated Problems Involving Risks to Subjects or Others

Unanticipated problems involving risk to participants or others related to the use of the CHMI material should be promptly reported (48 hours) to Sanaria. A complete written report should follow the initial notification within 10 working days.

Pregnancies and Serious Adverse Events

All pregnancies, SAEs and deaths related to the use of the CHMI material should be reported to Sanaria within 24 hours by telephone, email or fax. An initial written report should follow the initial notification within 2 working days.

Sanaria will be notified about all other adverse events incurred during or as a result of the use of the CHMI material as part of the Final Clinical Study Report. Additionally, the following actions should be promptly reported to Sanaria:

- Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the sponsor, or regulatory agencies.
- The knowledge of any pending compliance inspection/visit by the FDA, Office of Human Research Protections (Department of Health and Human Services), or other government agency concerning clinical investigations or research.
- The issuance of Inspection Reports, FDA Form 483, warning letters, or actions taken by any regulatory agency including legal or medical actions and any instances of serious or continuing noncompliance with regulations or requirements

The contact information for expedited reporting SAEs/SUSARs or any Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSOs) related to the CHMI are listed in the following table:

Sanaria Contact Information

[redacted] M.S.
Managing Director, Regulatory Affairs
Sanaria Inc.
9800 Medical Center Drive, Suite A209
Rockville, MD 20850
Tel: [redacted]
Fax: [redacted]
Email: [redacted]

10.1.4 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

10.1.5 Informed Consent Process

Written informed consent will be obtained prior to conducting any trial-related procedures.

Participants must be informed that their participation is voluntary. The PI or designee will explain the trial to the participant or their legally authorized representative and answer all questions regarding the trial. The PI or designee will conduct the consent discussions on an individual basis with each participant. Adequate time will be allowed for all questions to be addressed. Potential participants will be interviewed to ensure that they meet all entry criteria relating to history.

A test of understanding for the CHMI procedure is required as part of the consent process. A passing score is 80%. If a participant fails the assessment, the CHMI procedures should again be explained to the participant and he/she may repeat the test of understanding. Failure on the second test of understanding is an exclusion criterion.

10.1.6 Informed Consent Forms

10.1.6.1 Informed Consent for Trial Participation

Participants will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations (CFR) 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center. The informed consent will be obtained by the use of a written consent form approved by the IRB or IEC.

A copy of the signed consent forms shall be given to the participant prior to conducting any trial related procedures.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the trial and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

A separate ICF will be used for participants in Part B of the trial. If there is a change to the ICF during the conduct of the trial, participants will be re-consented to the most current version of the ICF.

Any withdrawal of consent for sample testing will be documented in the CRF.

Assay analysis will be conducted in laboratory(ies) working on behalf of Gates MRI and located, but not limited to the USA. Sample storage for future use will be in line with the consent of the participant.

Samples will be kept for a maximum of 10 years from the end of the trial.

10.1.6.2 Informed Consent for Pregnancy Follow-up

If a positive pregnancy test result is reported during trial participation or if a pregnancy is reported within the necessary contraception window (screening through 10 months post MAM01 or placebo treatment), participants are asked to contact the Principal Investigator. Participants who become pregnant after receiving any dose of MAM01 or placebo will be provided a separate informed consent to review and consider for monitoring outcomes of the pregnancy and health of the neonate through 6 weeks post-delivery.

To follow the participant and neonate the informed consent should be reviewed and signed prior to further data collection. A copy of the informed consent should be provided to the participant to explain the importance of the follow-up with the site and details on the birth of neonate through 6

weeks post-delivery. Please refer to the Manual of Procedures on the necessary steps for pregnancy follow-up, especially if the final scheduled trial visit has already been completed and captured in the CRF or will be completed prior to collection of the pregnancy outcomes.

10.2 Research-related Injury

There are no costs to study participants for the research tests, procedures and study product while taking part in this trial. Participants may be compensated for their participation in this trial in accordance with the local IRBs policies and procedures. These compensatory payments will be outlined in the ICF and are subject to IRB approval.

10.3 Data Management

A detailed data management plan will be written and approved by the Sponsor's data manager. All updates to the data management plan must be approved before study close-out and database lock.

10.3.1 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant record or dataset that is transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.

The participant must be informed that his/her trial-related data will be used by the Sponsor in accordance with local data protection law. The level of data disclosure must also be explained to the participant.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.3.2 Dissemination of Clinical Trial Data

Study information and resultant trial data from this protocol will be posted on publicly available clinical trials registers (www.clinicaltrials.gov) before enrolment of participants begins.

The final trial report will include all available safety data, clinical assessments, and concomitant medications through the final study visit. The database will be locked prior to unmasking and preparation of the final study report. All of the above data must have been entered, reviewed, and all queries related to the data addressed. Modifications or additions to the analyses will be included in the relevant SAP. Any decisions to deviate from the planned analyses described in the protocol and in the SAP will be described in detail in the final study report.

The final clinical study report will be reviewed and approved by the Sponsor signatory and the PI.

Summaries of the results of the trial will also be posted as de-identified data on the same websites.

10.3.3 Data Quality Assurance

All participant data relating to the trial will be recorded on printed or electronic CRF using an EDC system, unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation that supports the information entered in the CRF.

The trial will be monitored regularly by the Sponsor or its designee throughout the study period. The Investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this trial including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the Investigator for a minimum of 15 years after trial completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.3.4 Source Documents

Source documentation consists of existing medical records and/or trial records developed and maintained by the Investigator. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.

Data recorded on source documents will be entered onto the CRFs using an EDC system.

Data entered in the CRF that are transcribed from any paper source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial.

For the purpose of monitoring and auditing the trial, source documentation will consist of existing medical records and/or trial records developed and maintained by the Investigator.

10.3.5 Data Publication Policy The results of this trial may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of trial results.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition. • A new condition or recurrence of an intermittent condition (e.g., headache) not present at baseline, even though it may have been present before the start of the trial. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
Events NOT Meeting the AE Definition
• Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.4.2 Definition of ADR

"Adverse drug reaction" (ADR) or "adverse reaction" means a response to a medicinal product in humans which is noxious and unintended, which occurs at any dose, and which can also result from overdose, misuse or abuse of a medicine. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

10.4.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be a SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
Results in death

Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Is a medically significant / important event or reaction: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.4.4 Definition of Serious Adverse Drug Reaction (Serious ADR)

When an adverse event is judged to be serious and related to an investigational product, it is referred to as Serious ADR and is subject to expedited reporting based on the parameters of this study (see Section 10.4.9).

10.4.5 Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR)

SUSARs are adverse events that occur in a clinical trial participant, which is assessed by the Sponsor and or study investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the study drug.

10.4.6 Definition of AESI

AESIs are adverse events that the Sponsor wants to monitor carefully and which are subject to expedited reporting (within 24 hours of identification; see Section 10.4.9. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

In this trial, the following AEs will be collected and reported as AESIs:

- Infusion reactions requiring permanent discontinuation of the study intervention

- Anaphylaxis (defined in Appendix 4)
- Other severe (Grade 3-4) hypersensitivity reactions
- Immune complex disease

10.4.6.1 Hypersensitivity, Including Anaphylaxis

Administration of polyclonal immunoglobulin preparations and mAbs has been associated with hypersensitivity (including anaphylaxis) that occurs during or after dosing. A hypersensitivity reaction is defined as an acute onset of an illness with involvement of the skin, mucosal tissue, or both during administration of investigational product (but does not meet the definition of anaphylaxis). Anaphylaxis is a rare event, usually occurring after subsequent exposure to antigen, and it is most commonly accompanied by severe systemic, skin and or mucosal reactions. It is potentially a fatal, systemic allergic reaction that is distinct from simple allergic reactions (e.g., rash, pruritus) because of the simultaneous involvement of several organ systems (Sampson 2006). A full definition of anaphylaxis is provided in Appendix 4.

10.4.6.2 Immune Complex Disease

Immune complex disease can manifest in the form of a number of conditions such as vasculitis, endocarditis, neuritis, glomerulonephritis, serum sickness, and arthralgias. Drug-induced immune complex (type III) hypersensitivity reactions can occur when host immune system generates antibodies to drug resulting in soluble circulating antigen-antibody complexes formation and their deposition in blood vessels. Subsequently this initiates tissue damaging inflammatory reactions mediated by complement and/or leukocytes and mast cells. The pathology and clinical manifestations are dependent on the tissues/organs involved, with vascular, skin and renal tissues being common sites of injury. Common examples of immune complex hypersensitivity reactions are serum sickness (systemic) and Arthus reactions (local). The clinical manifestations of serum sickness include skin rash, fever, malaise and polyarthralgias or polyarthritis. Symptoms typically develop 1 to 2 weeks after first exposure to antigen and usually resolve in several weeks after withdrawal of the causative agent. Serum sickness needs to be differentiated from other 'serum-sickness-like' reactions that have a similar clinical presentation (e.g., viral infections, anti-seizure drugs), but are believed to have different pathogenic mechanisms. Both serum sickness and serum sickness-like reactions have been reported with mAbs (e.g., rituximab, infliximab). Clinical presentation and time to onset should be taken into account for the diagnosis and differentiation of these reactions. Diagnosis of these suspected reactions is best confirmed via biopsy of the affected tissues.

10.4.7 Recording and Follow-up of AEs (including SAEs, SUSARs, and AESIs)

Recording
• Care will be taken not to introduce bias when detecting AE and SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences. • During the CHMI assessments, expected symptoms from the malaria infection and/or the antimalarial rescue therapy will be queried by site personnel using a structured list, followed by an open-ended question for other symptoms. Expected symptoms may be attributed to the malaria infection and/or malaria medications. Severity of symptoms and concomitant medications will be recorded. Other (unexpected) symptoms will be recorded as a separate AE as outlined in this section. • When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports)

related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- AE will be reported on the AE CRF using a recognized medical term or diagnosis that accurately reflects the event.
- AE evaluations will be reviewed by the Investigator or a medically qualified delegate. AE CRF pages are to be completed by members of the trial team designated in writing by the Investigator. The onset and resolution dates of an AE and action taken in response to the AE will be documented.
- After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAE and non-serious AESI will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Medical Monitor, the IDMC, or the Sponsor. In this case, all participant identifiers, with the exception of the participant number, must be redacted on the copies of the medical records before submission.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- SAE will be assessed for severity and causal relationship to the study investigational medicinal product.

Follow-up and Resolution

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the trial or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology, if available.
- New or updated information will be recorded in the CRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.
- The onset and resolution dates of the event and medical care taken in response to the event will be documented.
- AEs will be considered resolved when the condition returns to normal or returns to the participant's baseline status as established during Screening, or when the condition has stabilized with the expectation that it will remain chronic
- If the event has not resolved by the final trial visit, it will be documented as "ongoing" on the eCRF, however, follow-up of a SAE must continue until resolved or the condition has stabilized. Information recorded on the CRF must be substantiated in the source documents.
- The resolution date to be recorded on the CRF is the last date on which the participant experienced the AE.

10.4.7.1 Assessment of AE Intensity (Severity)

Assessment of Intensity (Severity)

The Investigator will make an assessment of intensity for each AE reported during the study and assign it to 1 of 5 categories (***with exception to solicited AEs collected in any Memory Aid card completed by the participant***):

Grade 1 Mild symptoms, causing no or minimal interference with usual social and functional activities with intervention not indicated

Grade 2 Moderate symptoms, causing greater than minimal interference with usual social and functional activities with intervention indicated

Grade 3 Severe symptoms, causing inability to perform usual social and functional activities with intervention or hospitalization indicated

Grade 4 Potentially life-threatening symptoms, causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Grade 5 Death related to AE

It is recommended that definitions provided in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 of July 2017 (reported in Appendix 5) be followed. The DAIDS Table provides definitions of intensity grades 1 to 4 for numerous major clinical conditions and laboratory parameters, organized by body system.

It should be noted that the Investigator is not obliged to use the definitions reported in Appendix 4 and medical judgement should prevail.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE (see Section 10.4.3), not when it is rated as severe.

10.4.7.2 Assessment of AE Causality (Relatedness)

Assessment of Causality (Relatedness)
All AEs will be evaluated by the PI or by a medically qualified designee (i.e., Investigator, study physician) to assess the relationship between study intervention and each occurrence of each AE. Causality may be due to a study procedure, the investigational product (MAM01 or placebo), the controlled human malaria infection (CHMI), antimalarial rescue therapy or none of these study activities. The causality assessment will be determined using a two-level scale as follows: ○ **Not related:** There is no reasonable possibility that the event may have been caused by the study intervention. There are other more likely causes for the AE. ○ **Related:** There is a reasonable possibility that the study intervention contributed to the AE. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. For each AE, the Investigator **must** document in the source documents that they have reviewed the AE and provided an assessment of causality.

There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always makes an assessment of causality before the initial transmission of the SAE data. The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The Sponsor or designee will have the opportunity to confirm the seriousness and case causality based on the clinical judgement of the Medical Monitor and Sponsor designee. If a SAE is considered unrelated by the Investigator but the Sponsor believes that there is a reasonable possibility that the event is related, the Sponsor will upgrade the case to a 'related' status. The Sponsor or designee will never downgrade a case from serious to non-serious or related to not related.

10.4.7.3 Assessment of AE Expectedness

AE Expectedness

Expected AEs are AEs consistent with the applicable product information provided by the Sponsor (i.e., Investigator's brochure for MAM01 or package inserts for approved antimalarial drugs).

For the *P. falciparum* NF54 strain of mosquitoes utilized in the CHMI, no serious adverse reactions are considered to be expected by the Sponsor for the purpose of expedited reporting of SUSARs.

10.4.7.4 Assessment of AE Outcome

AE Outcome

The outcome of each AE must be reported to the Sponsor. The outcome of all AEs will be classified as one of the following:

- Resolved
- Resolved with sequelae
- Ongoing
- Death

10.4.8 Treatment of Overdose

The trial intervention will be administered by trained staff. Therefore, overdose is considered unlikely. In case of overdose, appropriate medical treatment will be instituted, guided by a full physical exam and any laboratory investigations. The participant will remain at the Clinical Trial Unit until any symptoms of the overdose have disappeared or, in the Investigator's opinion, it is safe to discharge the participant.

10.4.9 Reporting of SAEs (including SUSARs, AESI and ADR) and Other Immediately Reportable Events to the Sponsor

10.4.9.1 Reporting to Sponsor Via the Electronic Data Capture (EDC) System

Reporting to Sponsor Delegated CRO Safety Team Via the Electronic Data Collection Tool

The primary mechanism for reporting an SAE (including AESI and ADR) and other immediately reportable events (e.g., Pregnancy; see Section 10.4.9.3) by the Investigator to the

Sponsor or delegate will be the EDC system. The Investigator will complete the AE, SAE, and/or Pregnancy CRF, as appropriate with all the current information.

All initial and follow-up SAEs and AESI (regardless of assessment of causal relationship to the study intervention) and pregnancies will be reported to the Sponsor delegate (Pharmacovigilance Contract Research Organization (CRO)) within 24 hours of discovery or notification at the clinical site.

Serious ADRs are reported even after the trial is over if the Sponsor, Medical Monitor, or Investigator become aware of them.

Information not available at the time of the initial report must be documented in a follow-up report or CRF. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested. For hospitalizations, all attempts to obtain the hospital record should be documented in the source documents.

The Investigator is responsible for expedited safety report submission to the Sponsor delegate and the Sponsor delegate reports to the national regulatory authority(ies) within specific time periods of being notified of the event. Therefore, it is important that the Investigator submit additional information requested as soon as it becomes available.

If the electronic system is unavailable, the site may use the paper data collection tool (see Section 10.4.9.2 instead of the EDC, in order to report the event within 24 hours of becoming aware.

If a site receives a report of a new SAE from a trial participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see Section 10.4.9.2).

Contacts for SAE reporting and for all safety personnel are contained in the Team Contact List which will be stored on-site in the Site Regulatory Binder and maintained by the Sponsor.

Refer to Figure 2 for the reporting schema.

10.4.9.2 Reporting via Paper CRF

Reporting via Paper CRF

If the electronic CRF cannot be completed, the paper SAE and/or Pregnancy form provided by the Sponsor should be completed by the Investigator or their designee, and scanned and emailed, or faxed to the Sponsor's Pharmacovigilance CRO within 24 hours of discovery. The Investigator is responsible for ensuring an adequate transmission of the fax and will store the distribution confirmation in the trial file.

At a minimum, the following information should be included in an initial report:

- Protocol number
- Name and contact number of the Investigator
- Site and participant identification number
- Date(s) participant received study intervention
- Event term [with a brief summary of the event(s) and causality assessment]

In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE report form sent by overnight mail or courier service.

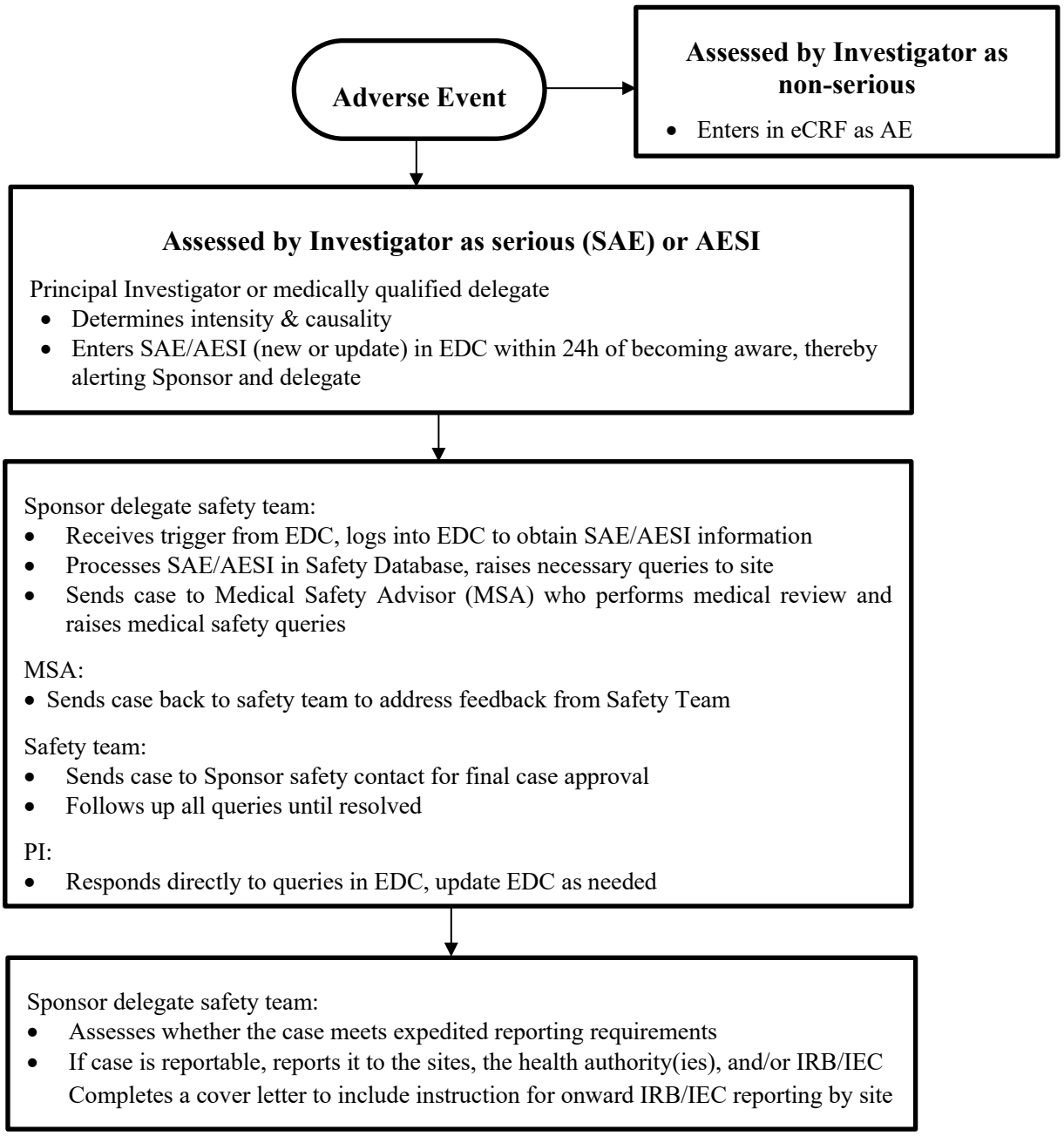
Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE and/or Pregnancy CRF pages within the designated reporting time frames.

Please note: if a pregnancy is reported after the final trial visit of a participant, please refer to the Manual of Operations for additional guidance.

10.4.9.3 Other Events Requiring Immediate Reporting

Other Events Requiring Immediate Reporting
The following events also require immediate reporting to the Sponsor or Sponsor's Pharmacovigilance CRO within 24 hours of learning of the event: • Pregnancy • UPIRTSOs

Figure 2: SAE and AESI Reporting Schemes



10.5 Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Female of Childbearing Potential (FOCBP)

A female is considered fertile following menarche. If fertility is uncertain and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered. If in doubt, the participant should be considered fertile.

Females of non-childbearing potential are defined as:

1. Females who are premenarchal or of post-menopausal status. Post-menopausal status is defined as 12 months with no menses without alternative medical cause.
2. Females who have had surgical sterilization (medically documented hysterectomy, bilateral salpingectomy or bilateral oophorectomy).
3. For females with permanent infertility due to an alternate medical cause other than the above (e.g., Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

Contraception Guidance:

Female participants physically capable of pregnancy or who are lactating, have at least one negative pregnancy test during Screening, on the day of enrollment, prior to IP administration, prior to CHMI and at the start of antimalarial treatment, and who agree to use effective contraception to avoid pregnancy from 28 days before enrollment through 10 months after the administration of investigational product are eligible to participate. At the completion of 10 months after last IP dosing, no scheduled visit for follow-up or pregnancy testing is required. However, the site may contact the participant to assess the effectiveness of contraception to prevent pregnancy.

An effective contraceptive method is defined as one that results in a failure rate of less than 1% per year when it is used consistently and correctly. Adequate contraceptive precautions include intrauterine contraceptive device, oral contraceptives, diaphragm, or condom in combination with contraceptive jelly, cream, or foam; Norplant® or Depo-Provera®, through completion of the trial to minimize any potential risk.

1. Effective contraception does not apply to participants of child-bearing potential with same sex partners, when this is their preferred and usual lifestyle.
2. Adequate contraception does not apply to women with documented surgical sterility (tubal ligation, bilateral oophorectomy, salpingectomy, or hysterectomy), congenital sterility, who have a diagnosis of infertility and are not undergoing treatment, or women who have not had a menstrual period in at least 1 year.

Collection and Reporting Pregnancy Information

In the event of a confirmed or self-reported pregnancy by a female participant, the processes outlined below must be followed:

- If the Investigator is notified of a pregnancy either during the trial or after the last scheduled study visit, the Investigator should remind the participant that the risks of MAM01 to the

fetus/child are currently unknown, and request consent to collect pregnancy outcome data as outlined below.

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study (including end of contraception window, 10 months post treatment). Information will be recorded on the appropriate form/EDC section and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy through specific EDC page or emailed/faxed Pregnancy Form if EDC is not available.
- Investigators must make an effort to collect outcomes of pregnancies discovered during the trial and communicate them to the Sponsor and/or CRO. The health status of the mother and child, the date of delivery, and the child's sex, birth weight and multiparity should be recorded and be reported to the Medical Monitor after delivery. If delivery occurs before the last scheduled study visit, the participant should continue to be followed to determine the outcome of the pregnancy and for SAEs through the final trial visit unless withdrawal of consent has occurred. If delivery occurs after the final trial visit, the Investigator should attempt to maintain contact with the participant to obtain information after delivery.
- The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 weeks beyond the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and should be processes as such.
- Any post-study pregnancy-related SAE considered related to the study intervention by the Investigator will be reported to the Sponsor. While the Investigator is not obligated to actively seek this information in former trial participants, he or she may learn of an SAE through spontaneous reporting.

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APPENDIX 1 SCHEDULE OF ACTIVITIES

Table 8: Schedule of Activities for SAD Cohorts (Part A)

Trial Period	Screen	Trial Drug Administration[1]								Follow-up													ED [2]
#Weeks [3] in Trial		W 0								W 1	W 2	W 4	W 6	W 8	W 10	W 12	W 14	W 16	W 20	W 24 [7]	W 32 [7]	W 40 [7]	
# of Days in Trial	D-60 to D-2	D-7 -1[4] Pre-dose	D0 Pre-dose [5]	D0 EOI [6]	D0 H 1	D0 H 3	D0 H 6	D1 H 24	D2 H 48	D 7	D 14	D 28	D 42	D 56	D 70	D 84	D 98	D 112	D 140	D 168	D 224	D 280	
Window			+7D	+10 min	+10 min	+10 min	+/- 2H	+/- 2H	+/- 2H	+/- 2D	+/- 2D	+/- 2D	+/- 2D	+/- 2D	+/- 2D	+/- 2D	+/- 2D	+/- 2D	+/- 7D	+/- 7D	+/- 7D	+/- 7D	
Informed Consent	X																						
Demography	X																						
Full Medical History	X																						
Physical Exam, Vital Signs, Height and Weight[11]	X																						
HIV Antibody, Hep B & C test	X																						
Sickle Cell Test	X																						
Pregnancy Test and Counseling	X [8]	X [9]																				X [9]	X [9]
CMP[12], CBC with diff	X											X											
Single 12-Lead ECG	X							X															
Prior/Con Meds [13]	X	X	X					X	X	X	X	X											
Safety Labs [10]		X								X				X								X	X
Record AEs	X[23]			X	X	X	X	X	X	X	X	X											
Randomization / Drug Administration [18]			X																				
Memory Aid Card[19]							X	X	X	X													
Vital Signs and Weight [11]		X[11]	X	X	X	X	X	X	X	X	X	X											X
Focused Physical Exam [20]		X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SUSARs[22], AESIs, and SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Capillary Blood [14]		X		X[15]	X[15]	X[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Serum [16]		X										X				X			X		X		
ADA Capillary Blood		X								X		X		X		X		X	X	X	X	X	X
[redacted]																							
CHMI Initiation[21]																			X				

[1] Participant will be observed at the trial site for at least 6 hours post IP administration.
[2] ED is an early discontinuation visit will be scheduled for participants who discontinue or withdraw, whenever possible.
[3] A week is defined as seven calendar days inclusive of weekends and holidays.
[4] Visit 1/Day -1 is the day of randomization and may be done on the same day as Visit 1/Day 0. V1/Day 0 is day of product administration may be scheduled up to 7 days after Visit

V1/Day -1.
[5] Prior to Infusion (IV – Cohorts 1, 3, 4,5) or administration (SC—Cohort 2).
[6] End of Infusion (IV only –Cohorts 1, 3,4,5).
[7] Weeks 24, 32, and 40 assessments are only applicable for participants in Cohorts 1, 4, and 5. Assessments for Cohorts 2 and 3 after CHMI are detailed in Table 9.
[8] Serum pregnancy test result during Screening must be negative for women of reproductive potential before product administration. Complete Pregnancy Prevention Counseling form when pregnancy tests are performed.
[9] Urine pregnancy test performed after Screening, prior to dosing collected between Day -7 to Day-1 must be negative prior to dosing. Complete Pregnancy Prevention Counseling form when pregnancy tests are performed.
[10] Safety labs include (CBC with differential) and Serum Chemistry (ALT, creatinine ONLY)
[11] Vitals signs include blood pressure (BP), temperature, pulse, and pulse oximetry (room air). Weight collected only at day -1 visit. Weight must be obtained a minimum of 1 day, but up to 7 days, prior to planned randomization and study drug administration [Day -7 to -1] to ensure appropriate dose volume.
[12] CMP consists of sodium, potassium, total CO_2, chloride, blood urea nitrogen, creatinine, glucose (random), ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin
[13] Concomitant medications will be collected at Screening, baseline, before dosing and during AE monitoring. They will also be collected at the time of evaluation of any SUSARs, or AESI, or other SAEs. Documentation of COVID vaccination and boosters will be recorded.
[14] For Cohort 2, PK blood draws are defined by time after an injection. For cohorts 1, 3, 4, and 5, PK blood draws are defined by time after end of infusion. Record the exact times of product administration and of blood draw to ensure accurate PK analysis. On the date of CHMI, the PK samples should be collected prior to CHMI. After Week 32 of Cohort 1 and corresponding visits for other cohorts, PK capillary blood (via VAMS collection) in Part A was discontinued.
[15] No PK samples for cohort 2 on D0 EOI, hr 1, and hr 3
[16] PK Serum samples will be collected for all participants in Part A.
[17] [redacted] samples only taken for Cohorts 2 and 3
[18] Randomization may occur up to 24 hrs in advance of or on the same day as trial product administration. Cohorts 1, 3, 4, and 5 will receive an intravenous infusion. Cohort 2 will receive SC dosing
[19] The Memory Aid card will be provided to participants after product administration on D0 and will be reviewed at each visit following administration of the product until day 7.
[20] A full physical exam will be performed during Screening. A focused physical exam including vital signs may be performed, if medically indicated at subsequent visits
[21] Cohorts 1,2,3,4 and 5 will undergo the CHMI procedures, See Table 11 for the CHMI procedure SoA. One CHMI procedure will be performed per participant. The window for CHMI is +2 weeks starting on the time post dose listed in Table 4.
[22] SUSARs are recorded only after administration of Investigational Product.
[23] Adverse events related to Screening procedures should be captured and reported.

Table 9: Schedule of Activities for Repeat Dosing Cohorts 2 and 3 (Part A)

Trial Period	Repeat Baseline	Trial Drug Administration [1]			Follow-Up								ED [2]
# of Weeks [3] in Trial	W30 Pre-dose [4]	W30 D0	W30 D1 H24	W30 D2 H48	W31D7	W 32	W 34	W 38	W 42	W 46	W 50	W 54	
# of Days in Trial	D 203 - 209	D 210	D 211	D 212	D 217	D 224	D 238	D 266	D 292	D 322	D 350	D 378	
Window	-7 to -1 days	+2 days	±2 H	±2 H	±2 days			±7 days					
Vital Signs and Weight [6]	X[6]		X	X	X	X	X						X
Pregnancy Test and Counseling [5]	X											X	X
CMP [12], CBC with diff	X						X						
Focused Physical Exam [11]	X	X	X	X	X	X	X	X	X	X	X	X	X
Product Administration		X											
Prior/Concomitant Meds	X		X	X	X	X	X						
Record AEs			X	X	X	X	X						
Memory Aid Card [10]		X	X	X	X								
Record SUSARs, AESIs, and SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Lab Assessments [7]					X			X				X	X
PK Capillary Blood [9]	X		X	X	X	X	X	X	X	X	X	X	X
PK Serum	X			X			X		X	X		X	
ADA Capillary Blood	X				X	X	X	X	X	X	X	X	X

[redacted]

[1] Participant will be observed at the trial site for at least 6 hours post IP administration (SC).
[2] ED is an early discontinuation visit will be scheduled for participants who discontinue or withdraw, whenever possible.
[3] A week is defined as seven calendar days inclusive of weekends and holidays.
[4] Prior to SC administration of IP.
[5] Urine pregnancy test performed prior to dosing must be negative prior to dosing. Complete Pregnancy Prevention Counseling form when pregnancy tests are performed. Participant may be contacted at the end of the contraception window.
[6] Vitals signs include blood pressure (BP), temperature, pulse, and pulse oximetry (room air). Weight will be collected during the Pre-dose visit only.
[7] Safety labs include Hematology (CBC with differential), Serum Chemistry (ALT, creatinine).
[8] Randomization may occur up to 24 hrs in advance of or on the same day as trial product administration.
[9] PK blood draws are defined by time after an injection. Record the exact times of product administration and of blood draw to ensure accurate PK analysis. After Week 32 of Cohort 1 and corresponding visits for other cohorts, PK capillary blood (via VAMS collection) in Part A was discontinued.
[10] Memory Aid card will be provided to participants after product administration (WK 30 D0 post-dose and-will be reviewed at each visit following administration of the product until day 7 (Wk 31visit)
[11] A focused physical exam may be performed if medically indicated at subsequent visits.
[12] CMP consists of sodium, potassium, total CO_2, chloride, blood urea nitrogen, creatinine, glucose (random), ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin

Table 10: Schedule of Activities for Dose Expansion Cohort (Part B; Cohort 6)

Trial Period	Screen	Trial Drug Administration[1]			Follow-Up							ED[2]
# of Days or Weeks in Trial [3]	D-60 to D-2	D -7 to -1 [4] (Pre-dose)	D0	D0 H 2	D3	W 1 D7	W1 D10	W 4 D28	W 4 [5] D34	W 9 D63	W12 D84	
Window				+1 H	±1 D	±2 days	+4 days	±7 days		±7 days		
Informed Consent	X											
Demography	X											
Full Medical History	X											
Physical Exam, Vital Signs, Height and Weight [6]	X											
HIV Antibody, Hepatitis B & C tests	X											
Sickle Cell Test [7]	X											
CMP [8], CBC with diff	X							X				
Single 12-Lead ECG	X											
Pregnancy Test and Counseling	X [9]	X [10]									X [9]	X [9]
Randomization [11]		X										
Product Administration			X									
Prior/Concomitant Meds[12]	X	X	X[13]		X	X	X	X	X		X	X
Record AEs [14]	X			X	X	X	X					
Vital Signs		X	X[13]	X	X	X	X	X	X	X	X	X
Focused Physical Exam[15]		X		X	X	X	X	X	X	X	X	X
Safety Lab Assessments[16]		X				X					X	X
Memory Aid Card [17]				X	X	X						
Record SUSARs[18], AESIs and SAEs	X	X	X	X	X	X	X	X	X	X	X	X
PK Capillary Serum		X			X	X		X		X	X	X
PK Venous Serum [19]		X			X	X	X	X	X[19,20]	X	X	X
ADA VAMS Capillary Blood		X				X		X	X	X	X	X
CHMI [21]									X			

[1] Participant will be observed at the trial site for at least 2 hours post IP administration.
[2] ED is an early discontinuation visit will be scheduled for participants who discontinue or withdraw, whenever possible.
[3] A week is defined as seven calendar days inclusive of weekends and holidays.
[4] Day -1 is the day of randomization and may be done on the same day as Day 0. Day 0 is day of product administration.
[5] Week 4 (Day 34) is Day -1 of the CHMI
[6] Vital signs include blood pressure (BP), temperature, pulse, and pulse oximetry (room air).
[7] Sickle cell testing is not required for participants who completed this testing while undergoing screening for Part A.
[8] CMP consists of sodium, potassium, total CO_2, chloride, blood urea nitrogen, creatinine, glucose (random), ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin

[9] Serum pregnancy test result during Screening must be negative for women of reproductive potential before product administration. Complete Pregnancy Prevention Counseling form when pregnancy tests are performed. Participant may be contacted at the end of the contraception window.

[10] Urine pregnancy test performed after Screening, prior to dosing collected between Day -7 to Day -1 must be negative prior to dosing. Complete Pregnancy Prevention Counseling form when pregnancy tests are performed.
[11] Randomization to open-label dose group may occur up to 7 days in advance of, or on the same day as trial product administration.
[12] Concomitant medications will be collected at Screening, baseline, before dosing and during AE monitoring. They will also be collected at the time of evaluation of any SUSARs, or AESI, or other SAEs. Documentation of COVID vaccination and boosters will be recorded.
[13] Prior to SC administration.
[14] Adverse events related to Screening procedures should be captured and reported.,
[15] A full physical exam will be performed during Screening. A focused physical exam may be performed if medically indicated at subsequent visits.
[16] Safety labs include Hematology (CBC with differential), and Serum Chemistry (ALT, creatinine)
[17] The Memory Aid card will be provided to participants after product administration on D0 post-dose and will be reviewed at each visit following administration of the product through Day 7 (Week 1).
[18] SUSARs are recorded only after administration of Investigational Product.
[19] PK blood draws are defined by time after an injection. Record the exact times of product administration and of blood draw to ensure accurate PK analysis.
[20] Serum for research [redacted]) should be collected from all participants. See Section 8.9.4.
[21] Groups 1, 2, and 3 will undergo CHMI procedures on Week 5. See Table 11 for the CHMI procedure SoA.

Table 11: Schedule of Activities for CHMI (Part A)

Trial Procedure	Screen Replacements as Infectivity Controls Only[1]	CHMI (all participants)		CHMI Observation					
Week after CHMI		WO		W1	W2-3	W3	W4		W7
Days after CHMI		D-1	D0	D6	D7-17	D20 [11]	D23 [11]	D27 [11]	D49 [12]
Window	-30 to -2 days	-1 day	+2 days	-1 day	+1 day	±1 day	±1 day	±1 day	±5 days
Informed Consent	X								
Full Medical History	X	X[3]	X[3]						
Physical Exam, Vital Signs, Weight	X								
HIV Antibody, Hepatitis B & C test	X								
Sickle Cell Test	X								
Baseline Parasitemia Evaluation (qRT-PCR)		X							
Serum for research[4]		X							
Pregnancy Test & Counseling	X[5]	X[6]		X[10]				X[6]	
CMP[13], CBC with diff	X								
Single 12-Lead ECG	X								
Mosquito bite CHMI			X						
Prior/Concomitant Meds	X	X		X	X	X	X	X	X
Vital signs [2]		X	X	X	X	X	X	X	X
Focused Physical Exam [2]		X	X	X	X	X	X	X	X
Safety Lab Assessments [10]		X		X[10]					X
Record AEs and SAEs				X	X	X	X	X	X
PK Capillary Blood [7]		X							
Parasitemia Monitoring (qRT-PCR and Thick Blood Smear)[8]		X		X	X	X	X	X	X
Phone Contact									[X][12]
Mosquito Avoidance Counseling			X	X					
Anti-Malarial Treatment[9]				(X)	(X)	(X)	(X)	X[14]	

[X] indicates optional procedure.

[1] Screening period is for any participants recruited as replacements to serve as infectivity controls only, if needed All subsequent visits are applicable to infectivity controls and previously randomized participants.

[2] Perform a focused physical exam if medically indicated, otherwise only vital signs (BP, temperature, pulse, pulse oximetry (room air)) are required.

[3] Interim medical history since Screening or last study visit

[4] Serum sample should be stored for future assessment, if necessary, of failed infection in infectivity controls

[5] Serum pregnancy test result during Screening for infectivity controls must be negative for women of reproductive potential before CHMI. Complete Pregnancy Prevention Counseling form when pregnancy tests are performed.
[6] Urine pregnancy test performed on Day -1 must be negative prior to CHMI. Urine pregnancy test at end of CHMI can be either on day 27 or Day 49, depending if the volunteer is confirmed positive for malaria. Complete Pregnancy Prevention Counseling form when pregnancy tests are performed.
[7] Capillary blood PK samples will continue to be collected during this CHMI observation phase as per Table 8 and Table 10.
[8] Parasitemia evaluations with qRT-PCR coupled with preparation of a thick blood smear should continue daily until a participant has a confirmed initial positive qRT-PCR. A first positive qRT-PCR should trigger analysis of the blood smear from that sample and both a PCR and a microscopic analysis of the blood smear at each visit until either subsequent test is positive. A confirmed positive malaria infection is defined as either two positive qRT-PCR or one positive blood smear results prior to or on Day 27. Further parasitemia checks are not needed after confirmed diagnosis and initiation of rescue therapy until test of cure visit (Day 49).
[9] Participant will be treated for malaria at any visit where infection is confirmed.
[10] Safety labs and a urine pregnancy test should be collected once in this time window for volunteers when their malaria test is confirmed positive and prior to treatment. Safety labs include Hematology (CBC with differential), and Serum Chemistry (ALT, creatinine,). Extra serum will be stored per lab manual
[11] Visit only required for those not yet diagnosed with malaria and given rescue therapy
[12] Visit only for those diagnosed with malaria infection and treated. Optional phone contact for those treated empirically
[13] CMP consists of sodium, potassium, total CO_2, chloride, blood urea nitrogen, creatinine, glucose (random), ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin
[14] Empiric antimalarial treatment will be given on day 27 for those CHMI participants not previously diagnosed with malaria infection.

Table 12: Schedule of Activities for CHMI for Part B (Cohort 6)

Trial Procedure	Infectivity Controls Only[1]	CHMI (all participants)		CHMI Observation					
Week after CHMI		WO		W1	W2-3	W3	W4		W7
Days after CHMI		D-1	D0	D6	D7-17	D20	D23	D27	D49[2]
Window	-30 to -2 days	-1 day	CHMI	-1 day	+1 day	±1 day	±1 day	±1 day	±5 days
Informed Consent	X								
Demography	X								
Full Medical History	X	X[3]	X[3]						
Physical Exam, Vital Signs, Weight	X								
HIV Antibody, Hepatitis B & C test	X								
Sickle Cell Test	X								
Pregnancy Test & Counseling	X[4]	X[5]		X[6]					
CMP[7], CBC with diff, serum for research[8]	X								
Single 12-Lead ECG	X								
Mosquito bite CHMI			X						
Prior/Concomitant Meds	X			X	X	X	X	X	
Vital signs[9]			X	X	X	X	X	X	
Focused Physical Exam[9]			X	X	X	X	X	X	
Safety Lab Assessments [6]		X[10]		X[6]					
Record AEs and SAEs				X	X	X	X	X	
Parasitemia Monitoring (qRT-PCR and Thick Blood Smear)[11]		X		X	X	X	X	X	X
Mosquito Avoidance Counseling			X	X					
Anti-Malarial Treatment[12]				(X)	(X)	(X)	(X)	X[13]	

[1] Screening period is for any participants recruited as infectivity controls only. All subsequent visits are applicable to infectivity controls and previously randomized participants.
[2] This is the end of study visit (outlined in Table 10).
[3] Interim medical history since Screening or last study visit
[4] Serum pregnancy test result during Screening for infectivity controls must be negative for women of reproductive potential before CHMI. Complete Pregnancy Prevention Counseling form when pregnancy tests are performed.
[5] Urine pregnancy test performed on Day -1 must be negative prior to CHMI. Complete Pregnancy Prevention Counseling form when pregnancy tests are performed.
[6] Safety labs and a urine pregnancy test should be collected once in this time window for volunteers when their malaria test is confirmed positive and prior to treatment. Safety labs include Hematology (CBC with differential), and Serum Chemistry (ALT, creatinine). Extra serum will be stored per lab manual.
[7] CMP consists of sodium, potassium, total CO_2, chloride, blood urea nitrogen, creatinine, glucose (random), ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin
[8] Serum for research ([redacted]) should be collected from all participants. See Section 8.9.4.

[9] Perform a focused physical exam if medically indicated, otherwise only vital signs (BP, temperature, pulse, pulse oximetry (room air)) are required. For CHMI Day 0, vital signs will be taken before and after malaria challenge.
[10] CHMI Day-1 safety labs only required for participants who have not had labs within the prior 7 days.
[11] Parasitemia evaluations with qRT-PCR coupled with preparation of a thick blood smear should continue daily until a participant has a confirmed initial positive qRT-PCR. A first positive qRT-PCR should trigger analysis of the blood smear from that sample and both a PCR and a microscopic analysis of the blood smear at each visit until either subsequent test is positive. A confirmed positive malaria infection is defined as either two positive qRT-PCR or one positive blood smear results prior to or on Day 27. Further parasitemia checks are not needed after confirmed diagnosis and initiation of rescue therapy until test of cure visit (Day 49). Sample on Day 49 only for those diagnosed with malaria infection and treated.
[12] Participant will be treated for malaria at any visit where infection is confirmed.
[13] Empiric antimalarial treatment will be given on Day 27 for those CHMI participants not previously diagnosed with malaria infection.

APPENDIX 2 DOSE JUSTIFICATION FOR THE HIGHEST ANTIBODY EXPOSURE

The highest dose selected (Cohort 5; 40 mg/kg IV) targets exposures in excess of the highest projected exposure in 3-month old African children.

Per WHO Guidelines (accessed July 2022) for weight-based dosing, the maximum volume for an injection in an infant is 1.0 mL (the equivalent of 150 mg of MAM01). Assuming we initiate dosing for a girl of 3 months of age, we estimate a minimum weight of the infant of 4.3 kg. This is based on the WHO Child Growth Standards weight nomogram for 3-month-old girls, namely 4.5 kg (-2 SD) and 4.0 kg (-3 SD, defined as malnourished) and the Areppim 10th percentile weight for Nigerian girls of 4.3 kg (Areppim Weight Nomograms). This equates to an initial MAM01 dose of approximately 35 mg/kg.

Further, the projected monoclonal antibody half-life in infants was estimated at 37 days given an enhanced infant clearance predicted based on BSA and a 56-day half-life estimate in adults from the L9LS Phase 1 trial (Wu 2022).

Note: there is no published data yet on PK with monoclonal antibodies containing the LS mutations in infants or young children. Hence, the projected MAM01 concentration in that 3-month-old girl at 6 months is 10.43 μg/mL (using 0.5 mL or 75 mg dose) or 20.54 μg/mL (using 1 mL or 150 mg dose).

The higher maximum exposure is a reasonable target in the smallest children and may allow antibody doses administered less frequently than every 6 months in malaria-endemic regions. A 1.0 mL dose (150 mg) in such a child yields an estimated concentration of 35.61 mg/mL at week 1 and an AUC of 30,726 mg*h/mL by month 6, which are below the comparative exposures of 40 mg/kg administered IV given to a 67.85 kg adult. Weight-based dosing estimations are outlined in the table below.

Population	**Pediatric: 3 –6 months old**		**Adult**	
Bodyweight at baseline [kg]	between 4.2 and 7.7 kg		between 45 and 90 kg	
Dose	75 mg (0.5 mL) (max 17.5 mg/kg)	150 mg (1.0 mL) (max 35 mg/kg)	20 mg/kg	40 mg/kg
Route of administration	IM	IM	IV	IV
Projected concentration at Day 1 [μg/mL]	32.5 [28.44-36.9]	65.2 [57-72.5]	551.8 [369.3-776.1]	1093.8 [760.54-1542]
Projected concentration at Day 7 [μg/mL]	26.9 [18.4-41.9]	53.7 [35.6-81.6]	326.2 [234.9-458.2]	653 [472.6-911.2]
Projected concentration at Day 180 [μg/mL]	15.2 [10.43-22.1]	31.1 [20.5-43.8]	40.1 [10.8-93.5]	80.8 [22.2-184.6]

APPENDIX 3 CRITERIA FOR ASSESSING RISK OF CARDIOVASCULAR DISEASE FOR CHMI SCREENING

Assessment for risk of cardiovascular disease

Due to the rare occurrence of cardiovascular events following CHMI, Screening for cardiovascular disease risk and sub-clinical cardiovascular disease will be performed, similar to those instituted in challenge centers worldwide. A 12-lead ECG will be performed in each participant, and 5-year risk for cardiovascular event will be estimated according to the non-invasive criteria for assessing cardiac risk provided by Gaziano in 2008[1]. Study ECGs will be reviewed by a study Investigator, and a study cardiologist (if required). Participants with abnormal cardiovascular symptoms or findings will be referred to a cardiologist for further evaluation. Participants are eligible for inclusion in a CHMI study if they have ≤ 10% risk for fatal or non-fatal cardiovascular event within 5 years as estimated by the Gaziano criteria. During the study, participants will be closely examined and questioned at all follow-up visits for presence of cardiovascular-related signs or symptoms (chest pain or discomfort, shortness of breath, change in exercise tolerance, and palpitations, felt to be cardiac in nature without alternate etiology). Signs or symptoms of an event suggestive of a cardiac etiology will prompt a cardiology work-up.

12-lead electrocardiogram

An abnormal ECG may be defined as showing pathologic Q waves and significant ST-T wave changes; left ventricular hypertrophy; any non-sinus rhythm excluding isolated premature atrial contractions; right or left bundle branch block; or advanced (secondary or tertiary) A-V heart block.

[1] Gaziano TA et al, 2008. Laboratory-based versus non-laboratory based method for assessment of cardiovascular disease risk: the NHANES I follow-up study cohort. Lancet 371 (9616): 923-931

Gaziano criteria (Gaziano et al, 2008)

Criteria used for assessment of cardiovascular risk are age, sex, systolic blood pressure (mm Hg), BMI, presence of diabetes, and smoking status.

Participants are eligible for inclusion **if their 5-year cardiovascular risk is ≤10%** (blue and green on nomogram).

APPENDIX 4 NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID) AND FOOD AND ALLERGY ANAPHYLAXIS NETWORK (FAAN) GUIDANCE FOR ANAPHYLAXIS DIAGNOSIS

National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories) (Sampson 2006).

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:
   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure. Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years.

APPENDIX 5 DIVISION OF AIDS (DAIDS) TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS, VERSION 2.1 OF JULY 2017

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Corrected Version 2.1
July 2017

Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health
US Department of Health and Human Services

Table of Contents

Glossary and Acronyms

AE	Adverse event; Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure.
ALT (SGPT)	Alanine aminotransferase (*serum glutamic pyruvic transaminase)*
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate aminotransferase (*serum glutamic-oxaloacetic transaminase)*
AV	Atrioventricular
Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer or movement, continence, and feeding. Young Children Activities that are age and culturally appropriate, such as feeding one's self with culturally appropriate eating implements.
BMI z-score	Body mass index z- score; A body reference norm. Specifically, the number of standard deviations a participant's BMI differs from the average BMI for their age, sex, and ethnicity.
BMD t-score	Bone mineral density t-score; The number of standard deviations above or below the mean bone mineral density of a healthy 30 year old adult of the same sex and ethnicity as the participant.
BMD z-score	Bone mineral density z-score; The number of standard deviations a participant's BMD differs from the average BMD for their age, sex, and ethnicity.
BPAP	Bilevel positive airway pressure; A mode used during noninvasive positive pressure ventilation.
Chemical Pregnancy	A pregnancy in which a positive pregnancy test is followed by a negative pregnancy test without evidence of a clinical pregnancy loss.
CNS	Central nervous system
CPAP	Continuous positive airway pressure
DAERS	DAIDS Adverse Experience Reporting System; An internet-based system developed for clinical research sites to report Expedited Adverse Events (EAEs) to DAIDS. It facilitates timely EAE report submission and serves as a centralized location for accessing and processing EAE information for reporting purposes.
Disability	A substantial disruption of a person's ability to conduct normal life functions.
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
Hospitalization	Does not include the following hospital admissions: under 24 hours, unrelated to an adverse event (e.g., for labor and delivery, cosmetic surgery, social or administrative for temporary placement [for lack of a place to sleep]), protocol-specified, and for diagnosis or therapy of a condition that existed before the receipt of a study agent and which has not increased in severity or frequency.
INR	International normalized ratio

DAIDS AE Grading Table Corrected Version 2.1-July 2017
Page 1

Glossary and Acronyms

Intervention	Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an adverse event.
IV	Intravenous
IVIG	Intravenous immune globulin
LDL	Low density lipoprotein
LLN	Lower limit of normal
Life-threatening AE	Any adverse event that places the participant, in the view of the investigator, at immediate risk of death from the reaction when it occurred (i.e., it does not include a reaction that would have caused death if it had occurred in a more severe form).
NA	Not applicable
Participant ID	The identification number assigned to a study participant which is used to track study-related documentation, including any reported AEs.
PR Interval	The interval between the beginning of the P wave and the beginning of the QRS complex of an electrocardiogram that represents the time between the beginning of the contraction of the atria and the beginning of the contraction of the ventricles.
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc Interval	The measure of time between the onset of ventricular depolarization and completion of ventricular repolarization corrected for ventricular rate.
RBC	Red blood cell
SI	Standard international unit
ULN	Upper limit of normal
Usual Social & Functional Activities	Activities which adults and children perform on a routine basis and those which are part of regular activities of daily living, for example: Adults Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby. Young Children Activities that are age and culturally appropriate, such as social interactions, play activities, or learning tasks.
WBC	White blood cell
WHO	World Health Organization
WNL	Within normal limits

DAIDS AE Grading Table Corrected Version 2.1- July 2017
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Introduction

The Division of AIDS (DAIDS) oversees more than 300 clinical trials domestically and internationally, which evaluate the safety and efficacy of therapeutic products, vaccines, and other preventive modalities. Adverse event (AE) data collected during these clinical trials form the basis for subsequent safety and efficacy analyses of pharmaceutical products and medical devices. Incorrect and inconsistent AE severity grading can lead to inaccurate data analyses and interpretation, which in turn can impact the safety and well-being of clinical trial participants and future patients using pharmaceutical products.

Over the years, DAIDS scientific knowledge and experience have expanded, necessitating revisions of the DAIDS grading table which serves as a guide for assessing the severity of AEs (including clinical and laboratory abnormalities) in participants enrolled in DAIDS-sponsored and -supported clinical trials. The *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)* updates and replaces version 2.1 (March 2017).

DAIDS is grateful to the DAIDS Grading Table Working Group, numerous government and non-government affiliated medical subject matter experts and reviewers who were instrumental in the revision of the DAIDS grading table.

Instructions for Use

General Considerations

The *Division of AIDS* (*DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1* consists of parameters, or AEs, with severity grading guidance that are to be used in DAIDS clinical trials for safety data reporting to maintain accuracy and consistency in the evaluation of AEs. The term "severe" is not the same as the term "serious" in classifying AEs. The severity of a specific event describes its intensity, and it is the intensity which is graded. Seriousness, which is not graded, relates to an outcome of an AE and is a regulatory definition.

Clinical sites are encouraged to report parameters in the DAIDS grading table as they are written to maintain data consistency across clinical trials. However, since some parameters can be reported with more specificity, clinical sites are encouraged to report parameters that convey additional clinical information. For example, diarrhea could be reported as neonatal diarrhea; seizures, as febrile seizures; and pain, as jaw pain.

The DAIDS grading table provides an AE severity grading scale ranging from grades 1 to 5 with descriptions for each AE based on the following general guidelines:

- Grade 1 indicates a mild event
- Grade 2 indicates a moderate event
- Grade 3 indicates a severe event
- Grade 4 indicates a potentially life-threatening event
- Grade 5 indicates death (*Note*: This grade is not specifically listed on each page of the grading table).

Other points to consider include:

- Use age and sex values as applicable.
- Unless noted, laboratory values are for term neonates. Preterm neonates should be assessed using local laboratory normal ranges.
- Where applicable, Standard International (SI) units are included in italics.

Selecting and Reporting a Primary AE Term

When selecting a primary AE term to report, sites should select the term that best describes what occurred to the participant. For example, a participant may present with itching, urticaria, flushing, angioedema of the face, and dyspnea. If the underlying diagnosis is determined to be an acute allergic reaction, sites should report "Acute Allergic Reaction" as the primary AE term.

Primary AE terms should be reported using the DAIDS Adverse Experience Reporting System (DAERS) only if they meet expedited reporting criteria. However, all primary AE terms should be reported using protocol-specific case report forms (CRFs). Because the reported information is stored in different databases (i.e., safety and clinical), sites should report primary AE terms using the same terminology for data consistency.

Instructions for Use

When reporting using DAERS, other clinically significant events associated with a primary AE term that more fully describe the nature, severity, or complications of the primary AE term should be entered in the "Other Events" section. However, the severity grade for these events must be lower than or equal to the severity grade of the primary AE term. In the example above, dyspnea and angioedema of the face may be entered in the "Other Events" section, because they are more descriptive and provide additional information on the severity of the acute allergic reaction. However, their severity grades must be lower than or equal to the severity grade of the primary AE term of "Acute Allergic Reaction".

Differences exist in the reporting and recording of information (e.g., signs and symptoms, clinically significant events) in DAERS and CRFs. Therefore, sites should refer to their protocols and CRF requirements for further instructions.

Grading Adult and Pediatric AEs
When a single parameter is not appropriate for grading an AE in both adult and pediatric populations, separate parameters with specified age ranges are provided. If no distinction between adult and pediatric populations has been made, the listed parameter should be used for grading an AE in both populations.

Reporting Pregnancy Outcomes
In the *Pregnancy, Puerperium, and Perinatal* section, all parameters are pregnancy outcomes and should be reported using the mother's participant ID. If an infant is not enrolled in the same study as the mother, any identified birth defects should be reported using the mother's participant ID. However, if an infant is enrolled in the same study as the mother or in another study, any identified birth defects should be reported using the infant's participant ID. Sites should refer to the applicable network standards for reporting abnormal pregnancy outcomes on the CRFs.

Determining Severity Grade for Parameters between Grades
If the severity of an AE could fall in either one of two grades (i.e., the severity of an AE could be either grade 2 or grade 3), sites should select the higher of the two grades.

Laboratory Values
General. An asymptomatic, abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited timeframe unless it meets protocol-specific reporting requirements. Sites should refer to the applicable network standards for reporting abnormal laboratory findings on the clinical case report forms.

Values below Grade 1. Any laboratory value that is between the ULN and grade 1 (for high values) or the LLN and grade 1 (for low values) should not be graded or reported as an AE. Sites should consult the *Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0* and their protocol when making an assessment of the need to report an AE.

Overlap of Local Laboratory Normal Values with Grading Table Ranges. When local laboratory normal values fall within grading table laboratory ranges, the severity grading is based on the ranges in the grading table unless there is a protocol-specific grading criterion for the laboratory

Instructions for Use

value. For example, "Magnesium, Low" has a grade 1 range of 1.2 to < 1.4 mEq/L, while a particular laboratory's normal range for magnesium may be 1.3 to 2.8 mEq/L. If a study participant's magnesium laboratory value is 1.3 mEq/L, the laboratory value should be graded as grade 1.

Appendix Usage
Appendix A takes priority over the main grading table in all assessments of total bilirubin for term and preterm neonates.

Using Addenda 1-3: Grading Tables Used in Microbicide Studies
In protocols involving topical application of products to the female and male genital tracts or rectum, strong consideration should be given to using Addenda 1-3 (see below) as the primary grading tables for these areas. Although these grading tables are used specifically in microbicide studies, they may be used in other protocols as adjuncts to the main grading table (i.e., the *Division of AIDS (AIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0*). It should be clearly stated in a protocol which addendum is being used as the primary grading table (and thus takes precedence over the main grading table) and which addendum is being used in a complementary fashion.

- Addendum 1 – Female Genital Grading Table for Use in Microbicide Studies- *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*
- Addendum 2 – Male Genital Grading Table for Use in Microbicide Studies – *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*
- Addendum 3 – Rectal Grading Table for Use in Microbicide Studies – *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*

Estimating Severity Grade for Parameters Not Identified in the Grading Table
The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

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Major Clinical Conditions
Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities[1]				
Hypertension *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)

[1] Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.

Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

[2] As per Bazett's formula.

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Dermatologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

[3] For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

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Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[4] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.

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Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[5] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

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Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea *≥ 1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)

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Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

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Musculoskeletal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] *≥ 30 years of age*	BMD t-score -2.5 to -1	NA	NA	NA
< 30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] *≥ 30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

[6] BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay *< 18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures ***New Onset Seizure*** *≥ 18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< 18 years of age (includes new or pre-existing febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

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Pregnancy, Puerperium, and Perinatal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal death occurring at ≥ 20 weeks gestation	NA
Preterm Birth (report using mother's participant ID)	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to < 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[7] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

[7] Definition: A pregnancy loss occurring at < 20 weeks gestational age.

Psychiatric

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

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Respiratory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

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Sensory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hearing Loss *≥ 12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

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Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[8]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain[9] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated

[8] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
[9] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

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Systemic

Serum Sickness[10]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight[11] *> 5 to 19 years of age*	WHO BMI z-score < -1 to -2	WHO BMI z-score < -2 to -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
2 to 5 years of age	WHO Weight-for-height z-score < -1 to -2	WHO Weight-for-height z-score < -2 to -3	WHO Weight-for-height z-score < -3	WHO Weight-for-height z-score < -3 with life-threatening consequences
< 2 years of age	WHO Weight-for-length z-score < -1 to -2	WHO Weight-for-length z-score < -2 to -3	WHO Weight-for-length z-score < -3	WHO Weight-for-length z-score < -3 with life-threatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

[10] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.
[11] WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.

Urinary

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Site Reactions to Injections and Infusions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[12] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*
≤ 15 years of age	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

[12] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

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*Laboratory Values**
Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin ***Direct Bilirubin[13], High*** *> 28 days of age*	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High *> 28 days of age*	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
≤ 28 days of age	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates

*Reminder: An asymptomatic abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited time frame unless it meets protocol-specific reporting requirements.

[13] Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.

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Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Calcium, High (mg/dL; *mmol/L*)				
≥ 7 days of age	10.6 to < 11.5 *2.65 to < 2.88*	11.5 to < 12.5 *2.88 to < 3.13*	12.5 to < 13.5 *3.13 to < 3.38*	≥ 13.5 *≥ 3.38*
< 7 days of age	11.5 to < 12.4 *2.88 to < 3.10*	12.4 to < 12.9 *3.10 to < 3.23*	12.9 to < 13.5 *3.23 to < 3.38*	≥ 13.5 *≥ 3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 *≥ 1.8*
Calcium, Low (mg/dL; *mmol/L*)				
≥ 7 days of age	7.8 to < 8.4 *1.95 to < 2.10*	7.0 to < 7.8 *1.75 to < 1.95*	6.1 to < 7.0 *1.53 to < 1.75*	< 6.1 *< 1.53*
< 7 days of age	6.5 to < 7.5 *1.63 to < 1.88*	6.0 to < 6.5 *1.50 to < 1.63*	5.50 to < 6.0 *1.38 to < 1.50*	< 5.50 *< 1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	< LLN to 4.0 *< LLN to 1.0*	3.6 to < 4.0 *0.9 to < 1.0*	3.2 to < 3.6 *0.8 to < 0.9*	< 3.2 *< 0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High **Report only one*	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Creatinine Clearance[14] or eGFR, Low **Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m² OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m² OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m² OR ≥ 50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; *mmol/L*)				
Fasting, High	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*

[14] Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

*Reminder: Choose the method that selects for the higher grade.

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Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glucose, Low (mg/dL; *mmol/L*)				
≥ 1 month of age	55 to 64 *3.05 to <3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
< 1 month of age	50 to 54 *2.78 to < 3.00*	40 to < 50 *2.22 to < 2.78*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL; *mmol/L*)				
Cholesterol, Fasting, High				
≥ 18 years of age	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 *≥ 7.77*	NA
LDL, Fasting, High				
≥ 18 years of age	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥ 190 *≥4.90*	NA
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[15], Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL; *mmol/L*)				
> 14 years of age	2.0 to < LLN *0.65 to < LLN*	1.4 to < 2.0 *0.45 to < 0.65*	1.0 to < 1.4 *0.32 to < 0.45*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*

[15] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

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Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 130*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*

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Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	600 to < 650 *0.600 x 10^9 to < 0.650 x 10^9*	500 to < 600 *0.500 x 10^9 to < 0.600 x 10^9*	350 to < 500 *0.350 x 10^9 to < 0.500 x 10^9*	< 350 *< 0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*)				
> 7 days of age	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9*	750 to 999 *0.750 x 10^9 to 0.999 x 10^9*	< 750 *< 0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	< 1,500 *< 1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[16], Low (g/dL; *mmol/L*)[17]				
≥ 13 years of age (male only)	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*

[16] Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (i.e., a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

[17] The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using appropriate conversion factor for the particular laboratory.

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Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 125,000 *100.000 x 10^9 to < 125.000 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*)				
> 7 days of age	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*

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Urinalysis

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

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Appendix A.
Total Bilirubin Table for Term and Preterm Neonates

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Total Bilirubin[18], High (mg/dL; *µmol/L*)[19]				
Term Neonate[20] *< 24 hours of age*	4 to < 7 *68.4 to < 119.7*	7 to < 10 *119.7 to < 171*	10 to < 17 *171* to < *290.7*	≥ 17 ≥ *290.7*
24 to < 48 hours of age	5 to < 8 *85.5 to < 136.8*	8 to < 12 *136.8 to < 205.2*	12 to < 19 *205.2* to < *324.9*	≥ 19 ≥ *324.9*
48 to < 72 hours of age	8.5 to < 13 *145.35 to < 222.3*	13 to < 15 *222.3 to < 256.5*	15 to < 22 *256.5* to < *376.2*	≥ 22 ≥ *376.2*
72 hours to < 7 days of age	11 to < 16 *188.1 to < 273.6*	16 to < 18 *273.6 to < 307.8*	18 to < 24 *307.8* to < *410.4*	≥ 24 ≥ *410.4*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 ≥ *427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Preterm Neonate[20] *35 to < 37 weeks gestational age*	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).
32 to < 35 weeks gestational age and < 7 days of age	NA	NA	10 to < 14 *171 to < 239.4*	≥ 14 ≥ *239.4*
28 to < 32 weeks gestational age and < 7 days of age	NA	NA	6 to < 10 *102.6 to < 171*	≥ 10 ≥ *171*
< 28 weeks gestational age and < 7 days of age	NA	NA	5 to < 8 *85.5 to < 136.8*	≥ 8 ≥ *136.8*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 ≥ *427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

[18] Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.

[19] A laboratory value of 1 mg/dL is equivalent to 17.1 µmol/L.

[20] Definitions: Term is defined as ≥ 37 weeks gestational age; near-term, as ≥ 35 weeks gestational age; preterm, as < 35 weeks gestational age; and neonate, as 0 to 28 days of age.

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APPENDIX 6 VERSION HISTORY

SUMMARY OF CHANGES (Version 7 to Version 8)

Protocol Version 8 was updated to 1) Note that women of child-bearing potential may be contacted by site staff at the end of the required contraception period ie, 10 months post-dosing; 2) Added details regarding the collection of AEs during the CHMI; 3) Added details clarifying what is required for follow-up, collection, and recording of contraception use and if applicable, pregnancy information and potential risks if becoming pregnant, for WOCBP participants in the trial. [Note in the table below ***bold italic*** represents newly added text]

Section Number	Change from Version 7	Rationale
Overall	Unsubstantial edits, updating, and formatting modifications consistent with the following modifications as needed.	Document clarity
Section 7.2	For women of child-bearing potential (WOCBP) participants who discontinue or withdraw from the trial, added text specifying that they need to continue contraception. *If possible, a discontinuation visit should be scheduled for any participant who wishes to discontinue or withdraw from the study. At this visit, topics around participant safety* ***including the need for ongoing contraception for women of child-bearing potential (see Section 10.5),*** *as well as the use of already collected biospecimens, will be discussed.*	To ensure safety of WOCBP participants and their offspring.
Section 10.4.7	For Recording of Follow-up of AEs (Including SAEs, SUSARs, and AESIs), added the following bullet regarding the CHMI part of the trial: ***During the CHMI assessments, expected symptoms from the malaria infection and/or the antimalarial rescue therapy will be queried by site personnel using a structured list, followed by an open-ended question for other symptoms. Expected symptoms may be attributed to the malaria infection and/or malaria medications. Severity of symptoms and concomitant medications will be recorded. Other (unexpected) symptoms will be recorded as a separate AE as outlined in this section.***	Clarified correct methods of capturing AEs during the CHMI.

Section Number	Change from Version 7	Rationale
Section 10.5 Appendix 1, Table 9	For Contraception Guidance, added the following to Section 10.5: ***At the completion of 10 months after last IP dosing, no scheduled visit for follow-up or pregnancy testing is required. However, the site may contact the participant to assess the effectiveness of contraception to prevent pregnancy.*** For Collection and Reporting Pregnancy Information, added the following: *In the event of a confirmed or self-reported pregnancy by a female participant, the processes outlined below must be followed:* ***If the Investigator is notified of a pregnancy either during the trial or after the last scheduled study visit, the Investigator should remind the participant that the risks of MAM01 to the fetus/child are currently unknown, and request consent to collect pregnancy outcome data as outlined below.*** Added the following footnote In Tables 9 and 10 (Schedules of Assessments): ***Participant may be contacted at the end of the contraception window.***	Clarified what is required for follow-up, collection, and recording of contraception use and if applicable, pregnancy information and potential risks if becoming pregnant, for WOCBP participants in the trial.

SUMMARY OF CHANGES (Version 6 to Version 7)

Protocol Version 7 was updated to 1) change the total duration that females of child-bearing potential shall remain on approved contraception from at least 5 months following study drug dosing to at least 10 months following study drug dosing, and 2) in the event of a participant pregnancy during the trial, provides site procedures for obtaining separate informed consent to review and consider for monitoring outcomes of the pregnancy and health of the neonate through 6 weeks post-delivery. In addition, the Schedule of Assessments was updated to note that VAMS PK sampling was discontinued during Part A.

Section Number	Change from Version 6	Rationale
Overall	Unsubstantial edits, updating, and formatting modifications consistent with the following modifications as needed.	Document clarity
Section 5.1 Section 8.4.4 Section 10.1.6.2	Modified the duration that females of child-bearing potential shall remain on approved contraception from 5 months following study drug administration to 10 months following study drug administration.	Per FDA guidance.

Section Number	Change from Version 6	Rationale
Section 10.4.9.2 Section 10.5	*Female participants physically capable of pregnancy….agree to use effective contraception to avoid pregnancy from 28 days before enrollment* ***through 10 months after last administration of investigational product*** *are eligible to participate.* Added the following New Section (10.1.6.2): Informed Consent for Pregnancy Follow-up ***If a positive pregnancy test result is reported during trial participation or if a pregnancy is reported within the necessary contraception window (screening through 10 months post MAM01 or placebo treatment), participants are asked to contact the Principal Investigator. Participants who become pregnant after receiving any dose of MAM01 or placebo will be provided a separate informed consent to review and consider for monitoring outcomes of the pregnancy and health of the neonate through 6 weeks post-delivery.*** ***To follow the participant and neonate the informed consent should be reviewed and signed prior to further data collection. A copy of the informed consent should be provided to the participant to explain the importance of the follow-up with the site and details on the birth of neonate through 6 weeks post-delivery. Please refer to the Manual of Procedures on the necessary steps for pregnancy follow-up, especially if the final trial visit has already been completed and captured in the CRF or will be completed prior to collection of the pregnancy outcomes.***	
Appendix 1 Table 8 and Table 9	Footnotes #14 and #9 in Tables 8 and 9, respectively in the SAD and Repeat Dose Schedules of Assessments were updated to note that VAMS PK sampling was discontinued: ***After Week 32 of Cohort 1 and corresponding visits for other cohorts, PK capillary blood (via VAMS collection) in Part A was discontinued.***	Clarified operational change made during prior protocol amendment.

SUMMARY OF CHANGES (Version 5 to Version 6)

Document was updated to reflect modifications to Part B of the trial, including Part B dose selection following Part A unblinded results review and design modifications to allow for interrogation of additional MAM01 concentrations. Verbatim revised text is presented *in italic*.

Section Number	Change from Version 5	Rationale
Overall	Unsubstantial edits, updating, and formatting modifications consistent with the following modificationsas as needed.	Document clarity
Section 1.1.2 Rationale Section 1.1.5.3 Part B	Added rationale for the revised doses to be evaluated in Part B: *Based on the interim analysis from Part A, the effective MAM01 concentration leading to 80% maximal protective response (EC80) falls between 35 and 100 µg/mL, but lack of challenge data in that range of MAM01 concentrations limits further clarification. This is critical information for further development, as it is the range of expected concentrations for infants and children to achieve the target 4 to 6 months of malaria protection.* *A total of 18 participants will be randomized into one of 3 dose groups with 86 participants each randomized to receive a single fixed SC dose of either MAM01 or placebo. For Part B (Cohort 6) with the expansion cohort, at Visit 1 trialopen-label MAM01.*	Justification for the evaluation of doses in Part B
Section 1.1.3 Objectives and Endpoints	[redacted]	[redacted]
Section 1.1.5 Overall Design Section 6.4.2 Masking (Blinding) Section 6.4.3 Masking Break	Clarified that Part B of the study will be open-label, with a cohort that will not be treated who will serve as infectivity controls during the CHMI. Specified as appropriate that the Investigator would be blinded through completion of safety assessments in Part A. *Part A will have a double-blind, placebo-controlled design. Part B will randomize participants to one of three open-label MAM01 dose groups; a separate non-randomized group will be enrolled to include participants who will receive no treatment and act as infectivity controls.*	Description of the change to open-label dosing for Part B and the inclusion of a group of infectivity controls who will not receive treatment for Part B.
Section 1.1.8 Total Duration of Trial Participation	Trial participation for part B was changed from approximately 168 days (24 weeks) to approximately 84 days (12 weeks) as the 3 dose groups will be dosed in parallel. Trial Schema was updated to reflect trial design changes.	Description of the change to duration of dosing, which was deemed acceptable based on the results observed in Part A of the trial. Trial schema was updated to reflect the parallel dosing schedule, reduced overall duration, inclusion of untreated infectivity control participants, and changes to doses to be evaluated.
Section 2.4.2 Previous Human Experience	Unblinded results of Part A were summarized and it was noted that the results were consistent with published results from other mAbs targeting different sites on *Pf*CSP. *In Part A of the trial, 24 participants received MAM01 doses ranging from 1.5 mg/kg to 40 mg/kg given IV, and 6 participants received two separate doses of 5 mg/kg SC. An additional 7*	The Part A results were presented as they inform design and dosing changes for Part B.

Section Number	Change from Version 5	Rationale
	participants received placebo. MAM01 was generally well tolerated with mild systemic solicited symptoms reported on the memory aid card, which generally resolved within 48 hours. No fever or allergic reactions have been noted, and no AEs or SAEs related to the study drug were reported. No local reactions were recorded after SC injection up to 300 mg.	
Section 2.4.3 Rationale for Design	Added text: *This randomized, two-part, dose-escalation design trial will evaluate the safety, tolerability, PK, and protective efficacy of MAM01, as well as safety and PK of repeat SC dosing. Part A will have a double-blind, placebo-controlled design. Part B will randomize participants to one of three open-label MAM01 dose groups; a separate non-randomized group will be enrolled to include participants who will receive no treatment and act as infectivity controls.*	To differentiate Part A and modified Part B.
Section 2.4.4 Justification for Dose	Added text to support new doses based on population model: *A population model was developed to characterize the PK profiles from Part A participants (second interim analysis). This model was then applied in a simulation mode to predict the doses necessary to achieve the target exposures at the time of the CHMI for Part B.*	Explanation of how population modeling was used to inform dose selection for Part B.
Secrtion 4.2 Design Overview Section 4.2.2 Part B Section 9.2.2 Power and Statistical Considerations	Revised Part B design, including updated Table 5 Part B Dose Expansion with revised doses and corresponding estimated CHMI concentrations and number of participants (24) including 18 who will receive MAM01 and 6 who will serve as untreated infectivity controls. *Part B (Cohort 6) will evaluate three fixed doses of MAM01 delivered by SC injection to achieve desired MAM01 concentrations at CHMI. The doses for Part B (Cohort 6) were selected by applying a PKPD model from the Part A data to estimate a (data-driven) protection threshold at CHMI. The maximum dose for Part B of the trial will not exceed the dose(s) of MAM01 determined to be safe in Part A*	Presentation and explanation of the overall revised Part B design of the trial.
Section 4.2.4 Follow-Up through End of Trial	Changed duration of Part B participation from 24 to 12 weeks	Clarification of Part B design change.

Section Number	Change from Version 5	Rationale
Section 5.4.2 Re-Screening	Part A screen failures may be rescreened for Part B, and will not be required to repeat sickle cell testing if performed during their initial screening.	Change made to eliminate potential unnecessary assessment at screening.
Section 6.1 Trial Drug Administration	For Part B where the SC dose volumes are greater, up to 3 injections may be required to administer the dose, compared to 1 SC injection for the originally planned doses.	Up to 3 SC injections are required to administer revised doses.
Section 6.3.1.3 Accountability	Detail was added to clarify how unused supplies, including MAM01 and placebo, should be addressed by clinical sites: *Unused supplies may be destroyed or returned to the Sponsor per Sponsor decision. Sponsor will provide specific instructions to the clinical site on handling of unused supplies. If supplies are to be destroyed, this will be conducted as per the facility's institutional policy or per local regulations.*	To clarify for sites how to dispose of unused trial supplies.
Section 6.4.1 Randomization	Time between Part B participant randomization and dosing was expanded from up to 24 hours to up to 72 hours	Enhanced participant and site flexibility
Section 7.2 Participant Discontinuation or Withdrawal from the Study	Clarified that participants will be followed for safety *unless they withdraw consent* if they choose to withdraw and/or will be dosed with curative antimalarial medication should the withdrawal occur post-CHMI.	Clarification
Section 8.4.3 Vital Signs Table 12 Schedule of Assessments for CHMI for Part B	For Part B, specified that vital signs are to be taken before and after CHMI on Day 0.	Clarification
Section Blood Sampling and Sample Storage	Modified blood sampling and storage. In addition to venous samples collected by phlebotomy, PK and ADA samples will be collected by a volumetric absorptive microsampling method (VAMS) from capillary blood collected after fingerprick *for Part A only. In Part B, VAMS devices will be used for the ADA sample collection, but capillary PK samples will be collected using a fingerstick sample into a serum-separator microtainer tube in addition to the venous samples.*	VAMS use was deemed most appropriate for ADA sample collection following review of Part A results.
Section 8.6 Pharmacokinetic Assesments	This section was revised as follows: *In Part A, serum from venous blood samples will be collected for measurement of MAM01 PK per the SoA (Appendix 1). Blood concentrations of MAM01 will be measured using a validated immunoassay. In Part B, serum from venous and capillary blood samples (via microtainer) will be collected (Appendix 1).*	Specified changes for Part B PK analyses to allow for future bridging of venous and capillary samples for PK modelling.

Section Number	Change from Version 5	Rationale
	Additionally, selected venous and capillary (matched) samples in Part B will be used to provide bridging data to support use of data from both sample types in modeling efforts in this and future studies.	
Section 9.2.3 Pharmacokinetic Analyses	Specified PK parameters to be summarized by dose group in Part B: *For Part B, the following PK parameters will be summarized by dose group: $AUC_{0\text{-}last}$, C_{min}, C_{max}, C_{D84}, C_{CHMI}, $AUC_{0\text{-}CHMI}$, and T_{max}*	To specify specific PK parameters to be summarized.
Section 9.2.6 Pharmacodynamic Analyses	Removed pharmacodynamic assessment from Part B:	No deemed necessary following Part A analysis
Section 9.2.7 Interim Analyses	Specified that an interim analysis may be performed for Part B of the study and that in this event, details will be provided in the Statistical Analysis Plan.	Revision for additional flexibility for analysis
Section 10.4.7.3 Assessment of Expectedness	Added the following text regarding the CHMI: *For the P. falciparum NF54 strain of mosquitoes utilized in the CHMI, no serious adverse reactions are considered to be expected by the Sponsor for the purpose of expedited reporting of SUSARs.*	Added CHMI-specific detail regarding expectedness of serious adverse reactions
Table 10: Schedule of Activities for Dose Expansion Cohort (Part B; Cohort 6)	Updated the table to reflect changes from this amendment for Part B, including revision of table footnotes	Clarity
Table 12: Schedule of Activities for CHMI for Part B (Cohort 6)	Added new Table of Assessments specific for the Part B CHMI	To provide additional detail regarding the Part B CHMI portion of the trial.

SUMMARY OF CHANGES (Version 4 to Version 5)

Document was updated to reflect revised vendor for CHMI.

Section Number	Text in Version 4	Text in Version 5
Overall	~~Version 4, 05 February 2024~~	**Version 5, 26 February 2024**
List of Abbreviations	~~WRAIR – Walter Reed Army Institute of Research~~	
Document History		Added Protocol version 5.0 – 26 Feb 2024
Section 1.1.5 Overall Design	The trial will be conducted at the University of Maryland School of Medicine in the United States of America (USA) and the CHMI mosquito bite challenge will be supported by the ~~Walter Reed Army Institute of Research (WRAIR)~~.	The trial will be conducted at the University of Maryland School of Medicine in the United States of America (USA) and the CHMI mosquito bite challenge will be supported by **Sanaria Inc. (Rockville, MD).**
Section 1.1.5.4 Controlled Human	Each CHMI procedure will be conducted using *Anopheles stephensi* mosquitoes reared by an experienced insectary at ~~WRAIR, Silver~~	Each CHMI procedure will be conducted using *Anopheles stephensi* mosquitoes reared by an experienced insectary at **Sanaria Inc.,**

Section Number	Text in Version 4	Text in Version 5
Malaria Infection (CHMI)	~~Spring,~~ Maryland, USA and entomologic staff who travel to University of Maryland to conduct the mosquito bite challenge. Mosquitoes are infected via membrane feeds of pathogen-free blood containing the cultured *P. falciparum* ~~3D7~~ strain (~~lot#1887~~) and reared per standardized procedures until they are infectious (containing mature sporozoites in the salivary glands).	**Rockville,** Maryland, USA and entomologic staff who travel to University of Maryland to conduct the mosquito bite challenge. Mosquitoes are infected via membrane feeds of pathogen-free blood containing the cultured *P. falciparum* **NF54** strain and reared per standardized procedures until they are infectious (containing mature sporozoites in the salivary glands).
Section 6 Trial Intervention	Additionally, most study participants will undergo a CHMI challenge (see Appendix 1) whereby he/she will be bitten by 5 mosquitoes infectious with the ~~3D7~~ strain of *Pf* to initiate malaria infection (see Section 6.5).	Additionally, most study participants will undergo a CHMI challenge (see Appendix 1) whereby he/she will be bitten by 5 mosquitoes infectious with the **NF54** strain of *Pf* to initiate malaria infection (see Section 6.5).
Section 6.5.1 CHMI Agreements and Regulatory Considerations	The trial site and ~~WRAIR~~ are required to complete a written agreement to allow ~~WRAIR~~ personnel to conduct the CHMI procedures and mosquito infectivity assessments within the trial site location. Each CHMI procedure will be conducted using An. stephensi mosquitoes reared by an experienced insectary at ~~WRAIR (Walter Reed Army Institute of Research, Silver Spring, Maryland, USA)~~ under their ~~Drug~~ Master File. The WRAIR entomologic staff will travel ~~transport~~ the infectious mosquitoes to University of Maryland for the mosquito bite challenge and prepare cups of infected ~~mosquites~~ for challenge, and then dissect the mosquitoes to determine their sporozoite burden. The actual mosquito bite challenge will be conducted by University of Maryland staff.	The trial site and **Sanaria** are required to complete an agreement to allow **Sanaria** personnel to conduct the CHMI procedures and mosquito infectivity assessments within the trial site location. Each CHMI procedure will be conducted using *An. stephensi* mosquitoes reared by an experienced insectary at **Sanaria** under their **Biologic** Master File. The **Sanaria** entomologic staff will travel **ship** the infectious mosquitoes **and travel** to University of Maryland for the mosquito bite challenge and prepare cups of infected **mosquitoes** for challenge, and then dissect the mosquitoes to determine their sporozoite burden. The actual mosquito bite challenge will be conducted by University of Maryland staff.
Section 6.5.2 Description of Parasite Strain	Mosquitoes are infected via membrane feeds of pathogen-free blood containing the cultured Pf ~~3D7~~ strain (~~lot #1887~~) and reared per standardized procedures until they are infectious (containing mature sporozoites in the salivary glands). The ~~3D7~~ strain of Pf is drug sensitive to atovaquone/proguanil, chloroquine, ~~mefloquine~~ and artemether/lumefantrine.	Mosquitoes are infected via membrane feeds of pathogen-free blood containing the cultured *Pf* **NF54** strain and reared per standardized procedures until they are infectious (containing mature sporozoites in the salivary glands). The **NF54** strain of Pf is drug sensitive to atovaquone/proguanil, chloroquine, and artemether/lumefantrine.
Section 6.5.3.1 Preparation and Handling	The preparation of infected mosquitoes will be performed according to a Type II Master Files, ~~DMF #033797 (Pf 3D7)~~ Malaria Challenge Model, SOPs for the Pf model used. Emerged females (~ 4 days old) will be fed with mature gametocyte cultures of *Pf* (~~3D7, Lot#1887~~), via artificial membrane feeding system.	The preparation of infected mosquitoes will be performed according to a Type II Master Files, **BMF #14118 (Pf NF54)** Malaria Challenge Model, SOPs for the Pf model used. Emerged females (~ 4 days old) will be fed with mature gametocyte cultures of *Pf* (**NF54**), via artificial membrane feeding system.
6.5.3.2 Transport and Storage	The ~~WRAIR~~ entomology team will ~~transport~~ the infectious mosquitoes to the trial site at University of Maryland.	The **Sanaria** entomology team will **ship** the infectious mosquitoes to the trial site at University of Maryland.

Section Number	Text in Version 4	Text in Version 5
6.5.3.3Accountability	Any mosquitoes not used for malaria challenge are the responsibility of the ~~WRAIR entomology team, who which can designate the trial team to discard under SOP be repurposed for research use only or destroyed~~. ~~WRAIR~~ personnel will provide reports of each mosquito-bite CHMI in support of the University of Maryland, Baltimore (UMB) IND for CHMI.	Any mosquitoes not used for malaria challenge are the responsibility of the **Sanaria entomology team, who may repurpose, dispose of, or destroy the mosquitos in accordance with Sanaria SOPs.** **Sanaria** personnel will provide reports of each mosquito-bite CHMI in support of the University of Maryland, Baltimore (UMB) IND for CHMI.
Section 10.1.2 Trial Oversight	~~The WRAIR is~~ not engaged in human subjects research, but is supplying infected mosquitoes under their ~~Cooperative Research and Development Agreement (CRADA) with Gates MRI, and is subject to the Department of Defense (DoD) regulatory reporting requirements are outlined in Section 10.1.3.~~	**Sanaria** staff are not engaged in human subjects research, but is supplying infected mosquitoes under their **contract with Gates MRI**.
Section 10.1.3 Sanaria Reporting Requirements to Human Subjects Protection	~~**Initial Protocol Review**~~ ~~The entomologists from WRAIR, the facility that will conduct the CHMI mosquito bite challenge, will have no interaction with study participants during the administration of the CHMI. WRAIR Human Subjects Protection Branch (HSPB) will perform an administrative review of the protocol to assess the engagement of their entomology staff in human subjects research.~~ ~~As this is a first in human trial using the DoD infectious challenge agent, headquarters level review will be conducted as appropriate.~~ ~~**Reporting requirements to both the WRAIR HSPB, United States Army Medical Research and Development Command (USAMRDC) Office of Human and Animal Research Oversight (OHARO):**~~ **Unanticipated Problems Involving Risks to Subjects or Others** Unanticipated problems involving risk to participants or others related to the CHMI ~~procedure~~ should be promptly reported (48 hours) to ~~the WRAIR HSPB~~. A complete written report should follow the initial notification within 10 working days. **Pregnancies and Serious Adverse Events** All pregnancies, ~~SUSARs~~, SAEs and deaths related to the CHMI should be reported to ~~the WRAIR HSPB~~ within ~~48~~ hours by telephone, email or fax. A ~~complete~~ written report should follow the initial notification within ~~10~~ working days. ~~**Major Protocol Deviations**~~ ~~All major protocol deviations involving the CHMI that adversely affect the safety and rights of a participant or scientific integrity of the study will be reported to the WRAIR HSPB within 48 hours. A complete written report should follow the initial notification to the~~	**Unanticipated Problems Involving Risks to Subjects or Others** Unanticipated problems involving risk to participants or others related to the **use of** the CHMI **material** should be promptly reported (48 hours) to Sanaria. A complete written report should follow the initial notification within 10 working days. **Pregnancies and Serious Adverse Events** All pregnancies, SAEs and deaths related to the **use of** the CHMI material should be reported to Sanaria within **24** hours by telephone, email or fax. An **initial** written report should follow the initial notification within **2** working days. **Sanaria will be notified about all other adverse events incurred during or as a result of the use of the CHMI material as part of the Final Clinical Study Report. Additionally, the following actions should be promptly reported to Sanaria:**

Section Number	Text in Version 4	Text in Version 5
	~~WRAIR-HSPB within 10 working days. Additionally, the following actions should be promptly reported to the WRAIR-HSPB and the USAMRDC-OHARO:~~ ~~**WRAIR-HSPB Contact Information**~~ ~~Director, Human Subjects Protection Branch~~ ~~503 Robert Grant Avenue, Silver Spring MD 20910~~ ~~Telephone: 301-319-9940 Fax: 301-319-9961~~ ~~Email: usarmy.detrick.medcom-wrair.mbx.hspb@health.mil~~ ~~**USAMRDC-OHARO Contact Information**~~ ~~US Army Medical Research and Development Command, ATTN: MCMR-RP~~ ~~810 Schreider Street, Fort Detrick, Maryland 21702-5000.~~ ~~Telephone: 301-619-2165 Fax: 301-619-7803~~ ~~Email: usarmy.detrick.medcom-usamrmc.oharo.hrpo@health.mil~~	**Sanaria Contact Information** [redacted], **M.S.** **Managing Director, Regulatory Affairs** **Sanaria Inc.** **9800 Medical Center Drive, Suite A209** **Rockville, MD 20850** **Tel:** [redacted] **Fax:** [redacted] **Email:** [redacted]
Appendix 6 Version History		Added summary of changes from Version 4.0 to Version 5.0

SUMMARY OF CHANGES (Version 3 to Version 4)

Document was changed to clarify pharmacokinetic sampling logistics and shift in the window to conduct the CHMI.

Section Number	Text in Version 3	Text in Version 4
Overall	Version 3, 22 August 2023	Version 4, 05 February 2024
1.1.3 Objectives and Endpoints	Secondary Endpoint • Maximal observed ~~blood~~ concentration (C_{max}) • For Part A (Cohorts 2 and 3) (participants that are redosed): accumulation ratio $AUC_{0\text{-}168}$/~~$AUC_{169\text{-}336}$~~ • ~~Blood titers~~ of ADAs to MAM01 Exploratory Endpoint • [redacted] •	Secondary Endpoint • Maximal observed concentration (C_{max}) • For Part A (Cohorts 2 and 3) (participants that are redosed): accumulation ratio $AUC_{0\text{-}168}$/$AUC_{210\text{-}378}$ • **Titers** of ADAs to MAM01 Exploratory Endpoint • [redacted] •
1.1.5.1 Trial Participants	CHMI will be initiated for Cohorts 1, 2, 3, and 4 at approximately Day ~~112, Day 98, Day 84 and Day 70~~ ~~(respectively)~~ after mAb dosing for the main cohort of participants in Cohort 1. ~~Cohort 5 participants will receive 40 mg/kg IV MAM01 or placebo, but this cohort *will not* undergo CHMI and provide opportunity for safety/tolerability assessment~~ only. All participants of Cohorts 2 and 3 will receive a second dose of MAM01 (open label) at least ~~168~~ days (± 7 days) post-dose (and after the initial CHMI procedure).	**Cohort 5 participants will receive the highest dose, 40 mg/kg IV, MAM01 or placebo.** CHMI will be initiated for Cohorts 1, 2, 3, **4** and **5** at approximately Day **181** after mAb dosing for the main cohort of participants in Cohort 1. All participants of Cohorts 2 and 3 will receive a second dose of MAM01 (open label) at least **210** days (± 7 days) post-dose (and after the initial CHMI procedure).
1.1.5.4 Controlled Human Malaria Infection (CHMI)	Trial participants ~~(except Cohort 5)~~ will have additional visits related to the CHMI procedures. If any participant in Cohort 1-~~4~~ in Part A or any Cohort in Part B drops out of the trial before either CHMI procedure start, the participant ~~will~~ be replaced by an additional malaria-naïve participant to serve as infectivity control. The replacement infectivity control participants will not receive administration of MAM01 or placebo.	If any participant in Cohort 1-5 in Part A or any Cohort in Part B drops out of the trial before either CHMI procedure start, the participant **may** be replaced by an additional malaria-naïve participant to serve as infectivity control **to ensure at least 6 volunteers validate the infectivity of the CHMI procedure**. The replacement infectivity control participants will not receive administration of MAM01 or placebo.
1.1.7 Interim Analyses	~~Three~~ interim ~~analysis~~ are planned: a blinded interim analysis of safety and tolerability after ~~day 28~~ of Part A (dose escalation), an unblinded assessment of efficacy after the first CHMI procedure, and a unblinded analysis of PK from Part A participants prior to the ~~re-dosing of Cohorts 2 & 3~~.	**Two** interim **analyses** are planned: a blinded interim analysis of safety and tolerability after **a minimum of 56 days for all of the cohorts** of Part A (dose escalation), and an unblinded assessment of efficacy after the first CHMI procedure, and a unblinded analysis of PK from Part A participants prior to the **CHMI**.

<table>
<tr><th>Section Number</th><th>Text in Version 3</th><th>Text in Version 4</th></tr>
<tr><td>1.1.8
Total Duration of Trial Participation</td><td>Part A repeat dosing (Cohorts 2 and 3) will remain active for approximately ~~336~~ days (48 weeks).</td><td>Part A repeat dosing (Cohorts 2 and 3) will remain active for approximately 378 days (48 weeks).</td></tr>
<tr><td>Figure 1</td><td>Removed figure</td><td>Added updated figure</td></tr>
<tr><td>2.4.4
Justification for Dose</td><td>The lowest dose (1.5 mg/kg) was selected to achieve concentrations below the targeted protective titer at the time of CHMI ~~(amounting to 14% of simulated virtual population above~~ the 10 mg/mL threshold). Intermediary doses were chosen to assess the absolute bioavailability (5 mg/kg SC and IV) and explore the ranges of exposures ~~which are projected to lead to 27-51% population above the threshold~~ at 6 months after the infection. The dose justification for the highest antibody exposure is outlined in Appendix 2.

The projected drug levels (based on a virtual participant population with weight at baseline between 45 and 90 kg) at the time of CHMI are outlined in Table 3.</td><td>The lowest dose (1.5 mg/kg) was selected to achieve concentrations below the targeted protective titer (estimated at an EC80 of 10 mg/mL) at the time of CHMI to evaluate the dose response. Intermediary doses were chosen to assess the absolute bioavailability (5 mg/kg SC and IV) and explore the ranges of exposures near the target EC80 at 6 months after the infection. The dose justification for the highest antibody exposure is outlined in Appendix 2.

The projected drug levels (based on a virtual participant population with weight at baseline between 45 and 90 kg) at the time of the revised CHMI schedule are outlined in Table 3.</td></tr>
<tr><td>Table 3</td><td>Table 3: Phase 1 Part A Drug Concentration Estimations at Time of CHMI
<table>
<tr><th>Cohort #</th><th>Dose</th><th>Route of Administration</th><th>Interval Between Dose and CHMI</th><th>Estimated Concentration at Time of CHMI
Median [5th percentile – 95th percentile]</th></tr>
<tr><td>1</td><td>1.5 mg/kg</td><td>IV</td><td>16 weeks</td><td>6.75 [3.21-11.64] µg/mL</td></tr>
<tr><td>2</td><td>5 mg/kg</td><td>SC</td><td>14 weeks</td><td>19.03 [10.06 - 31.07] µg/mL</td></tr>
<tr><td>3</td><td>5 mg/kg</td><td>IV</td><td>12 weeks</td><td>31.53 [18.16 - 49.58] µg/mL</td></tr>
<tr><td>4</td><td>10 mg/kg</td><td>IV</td><td>10 weeks</td><td>74.63 [44.32 - 112.56] µg/mL</td></tr>
<tr><td>5</td><td>40 mg/kg</td><td>IV</td><td>Safety only; No CHMI</td><td>Not applicable</td></tr>
</table>
Assumption: Based on similar PK to L9LS mAb given IV and SC</td><td>Table 3: Phase 1 Part A Drug Concentration Estimations at Time of CHMI*
<table>
<tr><th>Cohort #</th><th>Dose</th><th>Route of Administr-ation</th><th>Interval Between Dose and CHMI</th><th>Estimated Concentration at Time of CHMI
Median [5th percentile – 95th percentile]</th><th>Estimated percent of participants >10 µg/mL</th></tr>
<tr><td>1</td><td>1.5 mg/kg</td><td>IV</td><td>26 weeks</td><td>3.07 [0.92 – 6.8] µg/mL</td><td>0.5</td></tr>
<tr><td>2</td><td>5 mg/kg</td><td>SC</td><td>24 weeks</td><td>8.15 [2.69 – 18.02] µg/mL</td><td>36.9</td></tr>
<tr><td>3</td><td>5 mg/kg</td><td>IV</td><td>22 weeks</td><td>14.08 [4.72 – 28.23] µg/mL</td><td>72.3</td></tr>
<tr><td>4</td><td>10 mg/kg</td><td>IV</td><td>20 weeks</td><td>32.97 [12.55 – 61.15] µg/mL</td><td>97.9</td></tr>
<tr><td>5</td><td>40 mg/kg</td><td>IV</td><td>18 weeks</td><td>151.77 [59.84 – 282.25] µg/mL</td><td>99.9</td></tr>
</table>
Assumption: Based on similar PK to L9LS mAb given IV and SC
*Based on the adjusted CHMI date, whereby Cohort 1 will be 6 months after IP dosing.</td></tr>
<tr><td>4.2 Design Overview (Part A)</td><td>Cohort 5 participants will receive 40 mg/kg IV MAM01 or placebo~~, but this cohort *will not* undergo CHMI and provide opportunity for safety/tolerability assessment only.~~</td><td>Cohort 5 participants will receive the highest dose, 40 mg/kg IV, MAM01 or placebo.</td></tr>
<tr><td>Table 4</td><td>Table 4: Part A - Dose Escalation
<table>
<tr><th colspan="11">Gates MRI-MAM01-101: Part A – Dose Escalation</th></tr>
<tr><th rowspan="3">Cohort</th><th rowspan="3">Participant</th><th colspan="4">MAM01 Administration</th><th colspan="5" rowspan="2">CHMI</th></tr>
<tr><th colspan="2">Day 0</th><th colspan="2">Week 24 (Day 168) (± 7 days)</th></tr>
<tr><th>Dose (mg/ kg)</th><th>Route</th><th>Dose (mg/ kg)</th><th>Route</th><th>Week 16 (Day 112) (± 7 days)</th><th>Week 14 (Day 98) (± 7 days)</th><th>Week 12 (Day 84) (± 7 days)</th><th>Week 10 (Day 70) (± 2 days)</th><th>Enrolled only to CHMI</th></tr>
<tr><td>1</td><td>N=8 (6:2)</td><td>1.5</td><td>IV</td><td></td><td></td><td>X</td><td></td><td></td><td></td><td></td></tr>
<tr><td>2</td><td>N=7 (6:1)</td><td>5</td><td>SC</td><td>5</td><td>SC</td><td></td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>3</td><td>N=7 (6:1)</td><td>5</td><td>IV</td><td>5</td><td>SC</td><td></td><td></td><td>X</td><td></td><td></td></tr>
<tr><td>4</td><td>N=8 (6:2)</td><td>10</td><td>IV</td><td></td><td></td><td></td><td></td><td></td><td>X</td><td></td></tr>
<tr><td>5</td><td>N=7 (6:1)</td><td>40</td><td>IV</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>IIC</td><td>As needed</td><td colspan="4">Not dosed</td><td></td><td></td><td></td><td></td><td>X</td></tr>
<tr><td>Total</td><td>37 (30:7)</td><td colspan="9"></td></tr>
</table>
CHMI=Controlled Human Malaria Infection; IIC= Internal Infectivity Controls; IV=intravenous; SC=subcutaneous</td><td>Table 4: Part A - Dose Escalation
<table>
<tr><th colspan="12">Gates MRI-MAM01-101: Part A – Dose Escalation</th></tr>
<tr><th rowspan="3">Cohort</th><th rowspan="3">Participant</th><th colspan="4">MAM01 Administration</th><th colspan="6">CHMI</th></tr>
<tr><th colspan="2">Day 0</th><th colspan="2">Week 30 (Day 210) (± 7 days)</th><th colspan="6" rowspan="2"></th></tr>
<tr><th>Dose (mg/ kg)</th><th>Route</th><th>Dose (mg/ kg)</th><th>Route</th><th>Week 26 (Day 181) (± 7 days)</th><th>Week 24 (Day 168) (± 7 days)</th><th>Week 22 (Day 154) (± 7 days)</th><th>Week 20 (Day 140) (± 7 days)</th><th>Week 18 (Day 127) (± 7 days)</th><th>Enrolled only to CHMI</th></tr>
<tr><td>1</td><td>N=8 (6:2)</td><td>1.5</td><td>IV</td><td></td><td></td><td>X</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>2</td><td>N=7 (6:1)</td><td>5</td><td>SC</td><td>5</td><td>SC</td><td></td><td>X</td><td></td><td></td><td></td><td></td></tr>
<tr><td>3</td><td>N=7 (6:1)</td><td>5</td><td>IV</td><td>5</td><td>SC</td><td></td><td></td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>4</td><td>N=8 (6:2)</td><td>10</td><td>IV</td><td></td><td></td><td></td><td></td><td></td><td>X</td><td></td><td></td></tr>
<tr><td>5</td><td>N=7 (6:1)</td><td>40</td><td>IV</td><td></td><td></td><td></td><td></td><td></td><td></td><td>X</td><td></td></tr>
<tr><td>IIC</td><td>As needed</td><td colspan="4">Not dosed</td><td></td><td></td><td></td><td></td><td></td><td>X</td></tr>
<tr><td>Total</td><td>37 (30:7)</td><td colspan="10"></td></tr>
</table>
CHMI=Controlled Human Malaria Infection; IIC= Internal Infectivity Controls; IV=intravenous; SC=subcutaneous</td></tr>
</table>

Section Number	Text in Version 3	Text in Version 4
4.2 Design Overview (Part A Dose Escalation)	In Step 6, participants from Cohort 2 and Cohort 3 (including initial placebo recipients) will receive an unblinded second dose of MAM01, 5 mg/kg SC, approximately ~~168~~ days (~~24~~ weeks) post the first dose and well after the Part A CHMI procedure. *~~The 6 control~~ participants in Cohorts 1-~~4~~ will serve as the infectivity controls for the CHMI procedure* At least ~~168~~ days (± 7 days) post-dose (and after the initial CHMI procedure and unblinding), these participants will receive a second MAM01 dose of 5 mg/kg SC regardless of the initial assignment and administration route and assignment used for the initial dose. Approximately ~~168~~ days following administration, participants from Cohort 2 and from Cohort 3 will return to the clinic to receive 5 mg/kg MAM01 SC.	In Step 6, participants from Cohort 2 and Cohort 3 (including initial placebo recipients) will receive an unblinded second dose of MAM01, 5 mg/kg SC, approximately **210** days (**30** weeks) post the first dose and well after the Part A CHMI procedure. *The **7 placebo** participants in Cohorts 1-**5** will serve as the infectivity controls for the CHMI procedure* At least **210** days (± 7 days) post-dose (and after the initial CHMI procedure and unblinding), these participants will receive a second MAM01 dose of 5 mg/kg SC regardless of the initial assignment and administration route and assignment used for the initial dose. Approximately **210** days following administration, participants from Cohort 2 and from Cohort 3 will return to the clinic to receive 5 mg/kg MAM01 SC.
4.2.3.1 Overview of Parasitemia Management	The intent of the CHMI is to evaluate if MAM01 can prevent *Pf* infection among all participants ~~(except Cohort 5 who will have very high antibody concentrations)~~ thru a consistent *Pf* sporozoite inoculation delivered via the bites of infectious laboratory-reared *An. stephensi* mosquitoes.	
4.2.4 Follow-Up through End of Trial	Trial follow-up will continue via clinic visits through approximately 40 to ~~48~~ weeks (depending on Cohort in Part A) after the IP administration or 24 weeks in Part B.	Trial follow-up will continue via clinic visits through approximately 40 to **54** weeks (depending on Cohort in Part A) after the IP administration or 24 weeks in Part B.
5.2 Exclusion Criteria #16	ECG abnormalities determined by ~~a cardiologist~~ to be clinically insignificant as related to trial participation do not preclude trial enrollment	ECG abnormalities determined by **an investigator** to be clinically insignificant as related to trial participation do not preclude trial enrollment. **Consultation may be sought by a cardiologist at investigator discretion.**
6.1 Trial Drug Administration	Additionally, participants from Cohort 2 and 3 will receive a second dose of MAM01 5 mg/kg at least ~~168~~ days (+/- 7 days) regardless of the administration route or product received initially.	Additionally, participants from Cohort 2 and 3 will receive a second dose of MAM01 5 mg/kg at least **210** days (+/- 7 days) regardless of the administration route or product received initially.
6.4.2 Masking (Blinding)	For the ~~second and third~~ interim analyses only, the Sponsor will be unblinded to ~~aggregate summaries by dose cohort~~ and ~~treatment group~~ .	For the **first** interim **analysis, the Sponsor will review unblinded aggregate PK** analyses **and will remain blinded to clinical data. For the second interim analysis,** the Sponsor will be unblinded to PK, safety and **efficacy results at the participant level after completion of the CHMI.**
8.4.7 Electrocardiogram	For participants in the Dose Escalation Phase, an additional ECG will be taken at the 24 hours post-dose visit on Day 1.	For participants in the Dose Escalation Phase, an additional ECG will be taken at the 24 hours post-dose visit on Day 1 **after the first dose**.
8.6 Pharmacokinetic Assessments	Blood concentrations of MAM01 will be measured using a ~~validated~~ immunoassay.	Blood concentrations of MAM01 will be measured using a **qualified** immunoassay.

Section Number	Text in Version 3	Text in Version 4
	~~In Cohorts 2 and 3 in Part A~~, selected venous whole blood will be collected for measurement of MAM01 PK per the Schedules of Assessment (Appendix 1) and processed to serum. Serum concentrations of MAM01 will be measured using a validated immunoassay. The matched venous serum and capillary blood samples ~~from Cohorts 2 and 3~~ in Part A will provide bridging data to support use of data from both sample types in modeling efforts.	**Additionally,** selected venous whole blood will be collected for measurement of MAM01 PK per the Schedules of Assessment (Appendix 1) and processed to serum. Serum concentrations of MAM01 will be measured using a validated immunoassay. The matched venous serum and capillary blood samples in Part A will provide bridging data to support use of data from both sample types in modeling efforts.
8.7 Anti-drug Antibody Assessments	Capillary blood samples will be collected on VAMS microsampling devices per the SoA (Appendix 1). Samples on Day 1 and redosing (Week 24) will be collected prior to MAM01 administration. Additional blood samples for ADA will be collected starting on day 7 as per Appendix 1.	Capillary blood samples will be collected on VAMS microsampling devices per the SoA (Appendix 1). Samples on Day 1 and redosing (Week 24) will be collected prior to MAM01 administration. Additional blood **samples and selected serum** samples for ADA will be collected starting on day 7 as per Appendix 1.
9 Statistical Analysis Plan Summary	This section contains a brief description of the statistical analyses for this trial, ~~details~~ will be further specified in the full ~~protocol and the~~ SAP.	This section contains a brief description of the statistical analyses for this trial. **Details** will be further specified in the full **statistical analysis plan** (SAP).
9.2.1.1 Power and Sample Size Considerations	In Cohorts 2 and 3, at least ~~168~~ days (± 7 days) post-initial dose, participants will receive a second dose of MAM01 dose of 5 mg/kg SC. Cohort 4 includes 2 placebo participants to ensure that the ~~total~~ number of infectivity controls in Part A is 6, as noted above.	**The infectivity controls are comprised of the placebo recipients in the cohorts.** In Cohorts 2 and 3, at least **210** days (± 7 days) post-initial dose, participants will receive a second dose of MAM01 dose of 5 mg/kg SC. Cohort 4 includes 2 placebo participants to ensure that the **minimum** number of infectivity controls in Part A is 6, as noted above.
9.2.2 Safety Analyses	For Part A, Cohort 2 and Cohort 3 participants who receive repeat dosing, the analysis of safety will occur when all participants reach at least Day 336 and will include all available data at the time of analysis.	For Part A, Cohort 2 and Cohort 3 participants who receive repeat dosing, the analysis of safety **after the second dose** will occur when all participants reach at least Day 336 and will include all available data at the time of analysis.
9.2.3 Pharmacokinetic Analyses	All available PK data will be summarized at the time of the primary analysis, when all participants reach last PK sample. MAM01 blood concentrations and the following PK parameters, $AUC_{0-\infty}$, C_{min}, C_{max}, CD168, CCHMI, AUC_{0-CHMI}, T_{max}, λz, $t_{1/2}$, clearance (CL), SC Bioavailability, and apparent volume of distribution (Vz), will be summarized by treatment group. For Part A (Cohorts 2 and 3) participants that are redosed additional PK parameters will be calculated: AUC_{0-168}, ~~$AUC_{169-336}$~~ , accumulation ratio AUC_{0-168}/~~$AUC_{169-336}$~~ , and C_{min}, C_{max}, T_{max}, $t_{1/2}$,	All available PK data will be summarized at the time of the primary analysis, when all participants reach last PK sample. MAM01 blood **and serum** concentrations and the following PK parameters, $AUC_{0-\infty}$, C_{min}, C_{max}, CD168, CCHMI, AUC_{0-CHMI}, T_{max}, λz, $t_{1/2}$, clearance (CL), SC Bioavailability, and apparent volume of distribution (Vz), will be summarized by treatment group. For Part A (Cohorts 2 and 3) participants that are redosed additional PK parameters will be calculated: AUC_{0-168}, **$AUC_{210-378}$**, accumulation ratio AUC_{0-168}/ **$AUC_{210-378}$**, and C_{min}, C_{max}, T_{max}, $t_{1/2}$,

Section Number	Text in Version 3	Text in Version 4
	ratio of clearance to bioavailability (CL/F) following the second dose and will be summarized (i) by cohort and (ii) combined The MAM01 blood concentration data obtained in this trial will be used to develop individual and population PK models that will aid in the prediction of dose levels in trial participants and assess potential covariates. [redacted]	ratio of clearance to bioavailability (CL/F) following the second dose and will be summarized (i) by cohort and (ii) combined The MAM01 blood **and serum** concentration data obtained in this trial will be used to develop individual and population PK models that will aid in the prediction of dose levels in trial participants and assess potential covariates. [redacted]
9.2.5 Efficacy Analyses		**The efficacy of MAM01 based on actual antibody concentration at the time of CHMI is described in Section 9.2.6.**
9.2.6 Pharmacodynamic Analyses	MAM01 levels at the time of CHMI will be used to ~~assess~~ the ~~IC80~~ of the antibody.	MAM01 levels at the time of CHMI **among all participants in Cohorts 1-5** will be used to **estimate** the **EC80** of the antibody.
9.2.7.1 Part A *Interim Analyses*	~~Three~~ interim analyses are planned in Part A. The first interim analysis will focus on safety up to ~~the~~ time of the CHMI ~~procedures for each dose group (Cohort 1-4)~~ in Part A. The Sponsor and SRT will review blinded safety data (from Cohorts 1-~~4) collected up to the date of mosquito challenge and all available safety data from Cohort~~ 5 to inform whether to proceed to Part B of this trial. • The second interim analysis will focus on efficacy following the CHMI procedures. PK at the time of CHMI will be paired with the parasitologic outcome (Day 27) at CHMI by the Sponsor's unblinded pharmacometrics team. A detailed description will be provided in the PK SAP. The Sponsor will ~~review unblinded summaries by dose cohort, but will not~~ be unblinded at the participant level; the Investigators will remain fully blinded. The purpose of this ~~second interim analysis~~ is to inform dose selection for Part B and the broader development program. • ~~The third interim analysis in Part A will focus on PK modelling. It will occur when participants in the 5 mg/kg SC cohort have had their Week 24 visit (prior to re-dosing).~~ This interim analysis will include all ~~available safety data and~~ PK samples, ~~which will range from 18 to 26 weeks~~ of ~~follow up after treatment across the dose cohorts~~. The Sponsor will ~~review unblinded summaries by dose cohort, but will not~~ be unblinded at the participant level; the Investigators will remain fully blinded. The purpose of this unblinded interim analysis will be	**Two** interim analyses are planned in Part A.The first interim analysis will focus on safety **for all cohorts up to a point triggered when cohort 1 is 16 weeks post dose** (time of the **initial planned** CHMI **procedure). This will ensure a minimum of 56 days of safety data for all cohorts** in Part A. The Sponsor and SRT will review blinded safety data (from Cohorts 1-5) to inform whether to proceed to Part B of this trial. **The IDMC will review unblinded individual and aggregate safety data in a closed meeting.** The second interim analysis will focus on **safety and** efficacy following the CHMI procedures **and PK modelling. This will occur after completion of the CHMI (Day 27). There will be two outputs form this analysis:** • PK at the time of CHMI will be paired with the parasitologic outcome (Day 27) at CHMI by the Sponsor's unblinded pharmacometrics team. A detailed description will be provided in the PK SAP. The Sponsor will be unblinded at the participant level; the Investigators will remain fully blinded. The purpose of this **output** is to inform dose selection for Part B and the broader development program. • This interim analysis **output** will include all PK samples drawn up to the time of the **CHMI (including the pre-CHMI sample). It will explore the MAM01 pharmacokinetic profile and explore MAM01 concentrations at or around the time that any additional safety events (relevant SAEs or AESIs)**

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	to develop the individual and population PK and PK/PD models and aid in dose selection for future clinical trials. Though access to unblinded results from the second and third interim analyses will be limited within the Sponsor team, such reviews of aggregated data could lead to unblinding of the treatment received by individual participants.	**occurred**. The Sponsor will be unblinded at the participant level; the Investigators will remain fully blinded. The purpose of this unblinded interim analysis will be to develop the individual and population PK and PK/PD models and aid in dose selection for future clinical trials. **MAM01 (open label; without placebo comparator) will be given for the re-dosing of all participants in Cohorts 2 & 3.** Though access to unblinded results from the second interim analyses will be limited within the Sponsor team, such reviews of data could lead to unblinding of the treatment received by individual participants.
10.1.2 Trial Oversight		[IDMC will] **(c) review the unblinded safety data from Interim Analysis #1 to recommend expansion of the clinical development program**.
Appendix 1 Table 8	Footnote 7: Weeks 24, 32, and 40 assessments are only applicable for participants in Cohorts 1, 4, and 5. Assessments for Cohorts 2 and 3 ~~beyond week 20~~ are detailed in Table 9. Footnote 16: PK Serum samples will ~~only~~ be collected for participants in ~~Cohorts 2 and 3~~. Footnote 21: Cohorts 1,2,3, and ~~4~~ will undergo the CHMI procedures, See Table 11 for the CHMI procedure SoA. ~~Cohort 5 will not undergo CHMI procedure.~~ One CHMI procedure will be performed per participant.	Added PK Serum at Week 20 and Week 24. Footnote 7: Weeks 24, 32, and 40 assessments are only applicable for participants in Cohorts 1, 4, and 5. Assessments for Cohorts 2 and 3 **after CHMI** are detailed in Table 9. Footnote 16: PK Serum samples will be collected for **all** participants in **Part A**. Footnote 21: Cohorts 1,2,3,4 and **5** will undergo the CHMI procedures, See Table 11 for the CHMI procedure SoA. One CHMI procedure will be performed per participant. **The window for CHMI is +2 weeks starting on the time post dose listed in Table 4.**
Appendix 1 Table 9	Footnote #10: Memory Aid card will be provided to participants after product administration (WK ~~24~~ D0 post-dose and will be reviewed at each visit following administration of the product until day 7 (Wk ~~25 visit~~)	Updated number of weeks and number days designations. Added PK Serum at Week 24 and Week 40. Footnote #10: Memory Aid card will be provided to participants after product administration (WK **30** D0 post-dose and will be reviewed at each visit following administration of the product until day 7 (Wk **31visit**)
Appendix 1 Table 11	Days After CHMI: Day 7-~~13~~	Days After CHMI: Day 7-17 Added to Footnote #10: **Extra serum will be stored per lab manual**

SUMMARY OF CHANGES (Version 2 to Version 3)

Document was changed to address modifications based on proposed team responses to FDA non-hold comments (6 July 2023) and internal clinical review.

Section Number	Text in Version 2	Text in Version 3
Overall	Version 2, 30 July 2023	Version 3. 22 August 2023
Section 4.2.2 Design Overview, Part B	No text.	The maximum dose for Part B of the trial will not exceed the dose(s) of MAM01 determined to be safe in Part A.
Section 4.2.3.2.4 CHMI Day 6, Outpatient Post-malaria Challenge Surveillance Initiation	Parasitemia monitoring by qRT-PCR will commence.	Parasitemia monitoring by qRT-PCR **and microscopy** will commence.
Section 4.2.3.2.5 CHMI Day 7-17, Daily Post-malaria Challenge Surveillance	Participants will be checked daily for the presence of falciparum malaria in their blood (qRT-PCR) during the period of time they are most at risk for the development of falciparum malaria. A small quantity of blood (~2 mL) will be obtained daily for malaria diagnostics (qRT-PCR with and without a thick blood smear). Microscopic analysis of the thick blood smear is required along with all qRT-PCR samples once the blood sample for which an initial qRT-PCR test is positive until a diagnosis of *Pf* parasitemia is confirmed.	Participants will be checked daily for the presence of falciparum malaria in their blood (qRT-PCR) during the period of time they are most at risk for the development of falciparum malaria. A small quantity of blood (~2 mL) will be obtained daily for malaria diagnostics (qRT-PCR **and a** thick blood smear). Microscopic analysis of the thick blood smear will **commence on the blood sample for which an initial qRT-PCR test is positive, and continue with all samples until a diagnosis of *Pf* parasitemia is confirmed**.
Section 4.3.2.1 Safety Review Team (SRT)	The SRT recommendation will be communicated to the Sponsor Chief Medical Officer for information.	The SRT recommendation will be communicated to the Sponsor Chief Medical Officer for approval.
Section 4.3.2.1 Safety Review Team (SRT)	No text. The pausing rules were included in the next section with the individual discontinuation rules.	Pausing rules for the cohort (as further described in the SRT charter) include: 1. At least participant experiences a ≥ Grade 3 AE assessed as related to study product (except Grade 3 solicited local injection reaction lasting less than 48 hours); 2. At least 2 participants in a cohort experience systemic Grade 2 AE of a similar nature assessed as related to study product by the SRT; 3. A SAE of any grade assessed as related to study product;

Section Number	Text in Version 2	Text in Version 3
		4. Any occurrence of infusion reactions requiring discontinuation of study drug, a Grade 3-4 immediate hypersensitivity reaction or immune complex disease associated with study product;
Section 4.3.2.2 Trial Intervention Discontinuation Rules for Individual Participants	• Grade 3 AE assessed as related to study product (except Grade 1 solicited reactogenicity lasting less than 48 hr; • Grade 4 AE assessed as related to study product; • A SAE of any grade assessed as related to study product;	Text deleted. Cohort pausing rules separated into section 4.3.2.1.
Section 5.1 Inclusion Criteria	4.a. Female participants physically capable of pregnancy, have at least one negative pregnancy test during Screening, on the day of enrollment, prior to IP administration, prior to CHMI and at the start of antimalarial treatment, and who agree to use effective contraception to avoid pregnancy from 28 days before enrollment through completion of trial visits are eligible to participate.	4.a. Female participants physically capable of pregnancy, have at least one negative pregnancy test during Screening, on the day of enrollment, prior to IP administration, prior to CHMI and at the start of antimalarial treatment, and who agree to use effective contraception to avoid pregnancy from 28 days before enrollment **through 10 months after last administration of investigation product** are eligible to participate.
Section 5.1 Inclusion Criteria	**Laboratory criteria within range at Screening:** 22. White Blood Cell (WBC) 2,500-12,000/mm^3	**Laboratory criteria within range at Screening:** 1. White Blood Cell (WBC) **3,500**-12,000/mm^3
Section 8.4.7 Electrocardiogram	For participants in the Dose Escalation and Dose Expansion Phase, an additional ECG will be taken at the 24 hours post-dose visit on Day 1.	For participants in the Dose Escalation Phase, an additional ECG will be taken at the 24 hours post-dose visit on Day 1.
Section 8.4.8 Clinical Safety Laboratory Assessments	b. Serum chemistry: ALT and creatinine or CMP. (see Appendix 1) For participants in Cohort 2 and 3 who will receive a 2nd dose of MAM01, CMP will be repeated at the visit prior to second drug administration as per the SoA (Appendix 1).	b. Serum chemistry: ALT and creatinine or CMP. (see Appendix 1) For participants in Cohort 2 and 3 who will receive a 2nd dose of MAM01, CMP **and CBC with differential** will be repeated at the visit prior to second drug administration as per the SoA (Appendix 1).
Section 8.4.9 Memory Aid Card	A Memory Aid card will be utilized by participants to collect unsolicited AEs beginning at discharge from the clinic after infusion/injection	A Memory Aid card will be utilized by participants to collect **solicited and unsolicited AEs** beginning at discharge from the clinic after infusion/injection
Section 8.7 Anti-drug Antibody Assessments	Additional blood samples for ADA will collected starting on day 7 for participants in Cohort 6, Part B (Appendix, Table 10)	Additional blood samples for ADA will be collected starting on day 7 as per Appendix 1.
Section 8.9.1 Blood Stage Parasites	After CHMI, a parasite infection that escapes the MAM01 antibody targeting sporozoites will progress to blood stage	After CHMI, a parasite infection that escapes the MAM01 antibody targeting sporozoites will progress to blood stage (merozoite) infection, which cause illness at higher **parasite** concentrations.

Section Number	Text in Version 2	Text in Version 3
	(merozoite) infection, which cause illness at higher concentrations.	
Section 8.9.2 PCR Analysis for *P. falciparum*	Each sample will be run in triplicate along with a water control. The data will be analyzed using the Applied Biosystem 7300 Absolute Quantification Software.	Each sample will be run in **duplicate** along with a water control. The data will be analyzed using the Applied Biosystem 7300 Absolute Quantification Software.
Section 8.9.3 Microscopic Visualization of Parasites by Blood Smear	A small aliquot of blood (10 µL) will be placed upon microscope slides for the creation of thick malaria smears. The thick smear will be allowed to dry, lysed with distilled water and stained with Giemsa for analysis of intra-erythrocytic ring forms consistent with malaria. The thick blood smears will be examined if either the participant is symptomatic or a qRT-PCR signal is identified.	A small aliquot of blood (10 µL) **from the same EDTA tube** will be placed upon microscope slides for the creation of thick malaria smears. The thick smear will be allowed to dry, lysed with distilled water and stained with Giemsa for analysis of intra-erythrocytic ring forms consistent with malaria. The thick blood smears will be **examined for parasites** if either the participant is symptomatic or a qRT-PCR signal is identified **(see section 4.2.3.2).**
Section 9.2.7.2 Part B	The efficacy outcomes after the 2nd CHMI of the 3 cohorts in Part B may also be shared with the Sponsor aggregated by dose cohort by the unblinded statistician.	**There will be no planned interim analysis for Part B of the study.**
Section 10.1.6.1 Informed Consent for Trial Participation	No text.	**A separate ICF will be used for participants in Part B of the trial.**
Section 10.4.7.2 Assessment of AE Causality (Relatedness)	No text.	**Causality may be due to a study procedure, the investigational product (MAM01 or placebo), the controlled human malaria infection (CHMI), antimalarial rescue therapy or none of these study activities.**
Section 10.4.7.3 Assessment of AE Expectedness	Expected AEs are AEs consistent with the applicable product information provided by the Sponsor (i.e., Investigator's brochure for MAM01).	Expected AEs are AEs consistent with the applicable product information provided by the Sponsor (i.e., Investigator's brochure for MAM01 **or package inserts for approval antimalarial drugs**).
Section 10.5 Contraception Guidance and Collection of Pregnancy Information	Female participants physically capable of pregnancy or who are lactating, have at least one negative pregnancy test during Screening, on the day of enrollment, prior to IP administration, prior to CHMI and at the start of antimalarial treatment, and who agree to use effective contraception to avoid pregnancy from 28 days before enrollment through completion of the trial are eligible to participate.	Female participants physically capable of pregnancy or who are lactating, have at least one negative pregnancy test during Screening, on the day of enrollment, prior to IP administration, prior to CHMI and at the start of antimalarial treatment, and who agree to use effective contraception to avoid pregnancy from 28 days before enrollment **through 10 months after the administration of investigational product** are eligible to participate.
Appendix 1, Table 8	Safety Labs on Day 28	**CMP, CBC with diff** added on day 28 follow-up and Safety Labs deleted on Day 28 **ADA, capillary blood added on day 7 and day 14 follow-up**
Appendix 1, Table 9	Safety Labs on Day 196	**CMP, CBC with diff** added on day 196 follow up

Section Number	Text in Version 2	Text in Version 3
Appendix 1, Table 10	Safety Labs on Day 28	**CMP, CBC with diff** added on day 28 follow up and Safety Labs deleted on day 28 **ADA, capillary blood added on day 7 follow up**
Appendix 1, Table 11	Parasitemia evaluations should continue daily until a participant has a confirmed positive qRT-PCR. A first positive qRT-PCR should trigger both a PRC and a blood smear each visit until either subsequent test is positive.	[8] Parasitemia evaluations with qRT-PCR coupled with preparation of a thick blood smear should continue daily until a participant has a confirmed initial positive qRT-PCR. A first positive qRT-PCR should trigger analysis of the blood smear from that sample and both a PCR and a microscopic analysis of the blood smear at each visit until either subsequent test is positive. A confirmed positive malaria infection is defined as either two positive qRT-PCR or one positive blood smear results prior to or on Day 27. Further parasitemia checks are not needed after confirmed diagnosis and initiation of rescue therapy until test of cure visit (Day 49).
Appendix 3, Criteria For Assessing Risk Of Cardiovascular Disease For CHMI Screening	Study ECGs will be reviewed by a study Investigator and a study cardiologist.	Study ECGs will be reviewed by a study Investigator and a study cardiologist **(if required)**.

SUMMARY OF CHANGES (Version 2.0 to Version 2.1)

Document was changed to address requests from FDA reviewers on 7 May 2023.

Section Number	Text in Version 2.0	Text in Version 2.1
Overall	Version 2.0; Version 23 May 2023	**Version 2.1; Version 08 Jun 2023**
Section 2.4.4 Justification for Dose	Furthermore, the doses for Part B of the trial will be selected based on the clinical PK profile of MAM01 in Part A of the trial, and will be added as a protocol amendment.	Furthermore, the doses for Part B of the trial will be selected based on the clinical PK profile of MAM01 in Part A of the trial, and will be added as a protocol amendment. **The maximum dose for part B of the trial will not exceed the dose(s) of MAM01 determined to be safe in part A.**
Section 4.2.2 Part B	The dose for Part B (Cohort 6) will be selected by applying a PKPD model from the Part A data to estimate a (data-driven) protection threshold. Details on the criteria for progressing to Part B and how the dose predictions will be derived from the data generated in Part A will be featured in the Statistical Analysis Plan (SAP).	The dose for Part B (Cohort 6) will be selected by applying a PKPD model from the Part A data to estimate a (data-driven) protection threshold. **The maximum dose for part B of the trial will not exceed the dose(s) of MAM01 determined to be safe in part A.** Details on the criteria for progressing to Part B and how the dose predictions will be derived from the data generated in Part A will be featured in the Statistical Analysis Plan (SAP).
Section 4.2.3.2.4 CHMI Day 6, Outpatient Post-malaria Challenge Surveillance Initiation	Parasitemia monitoring by qRT-PCR will commence.	Parasitemia monitoring by qRT-PCR **and microscopy** will commence.
Section 4.2.3.2.5 CHMI Day 7-17, Daily Post-malaria Challenge Surveillance	Participants will be checked daily for the presence of falciparum malaria in their blood (qRT-PCR) during the period of time they are most at risk for the development of falciparum malaria. A small quantity of blood (~2 mL) will be obtained daily for malaria diagnostics (qRT-PCR without or without a thick blood smear). Microscopic analysis of a thick blood smear is required along with all qRT-PCR samples once an initial qRT-PCR test is positive, until a diagnosis of Pf parasitemia is confirmed.	Participants will be checked daily for the presence of falciparum malaria in their blood (qRT-PCR) during the period of time they are most at risk for the development of falciparum malaria. A small quantity of blood (~2 mL) will be obtained daily for malaria diagnostics (qRT-PCR **and a thick blood smear**). Microscopic analysis of **the thick blood smear will commence on the blood sample for which an initial qRT-PCR test is positive, and continue with all samples** until a diagnosis of Pf parasitemia is confirmed.
Section 8.9.1 Blood Stage Parasites	After CHMI, a parasite infection that escapes the MAM01 antibody targeting sporozoites will progress to blood stage (merozoite) infection, which cause illness at higher concentrations. The presence of pathogens will be detected with a validated quantitative ultrasensitive RT-PCR assay and/or microscopic assessment of thick blood films.	After CHMI, a parasite infection that escapes the MAM01 antibody targeting sporozoites will progress to blood stage (merozoite) infection, which cause illness at higher **parasite** concentrations. The presence of pathogens will be detected with a validated quantitative ultrasensitive RT-PCR assay **and** microscopic assessment of thick blood films.

Section Number	Text in Version 2.0	Text in Version 2.1
Section 8.9.3 Microscopic Visualization of Parasites by Blood Smear	A small aliquot of blood (10 µL) will be placed upon microscope slides for the creation of thick malaria smears. The thick smear will be allowed to dry, lysed with distilled water and stained with Giemsa for analysis of intra-erythrocytic ring forms consistent with malaria. The thick blood smears will be interpreted if either the participant is symptomatic or a qRT-PCR signal is identified.	A small aliquot of blood (10 µL) **from the same EDTA tube** will be placed upon microscope slides for the creation of thick malaria smears. The thick smear will be allowed to dry, lysed with distilled water and stained with Giemsa for analysis of intra-erythrocytic ring forms consistent with malaria. The thick blood smears will be **examined for parasites** if either the participant is symptomatic or a qRT-PCR signal is identified **(see section 4.2.3.2)**.
Table 11 Schedule of Activities for CHMI	Parasitemia Monitoring (qRT-PCR +/-Thick Blood Smear)[8] Footnote 8: Monitoring parasitemia evaluations should continue daily until a participant has a confirmed positive qRT-PCR. A first positive qRT-PCR should trigger collection of both a PCR and a blood smear at each visit until either subsequent test is positive. A confirmed positive malaria infection is defined as either two positive qRT-PCR or one positive blood smear results prior to or on Day 27.	Parasitemia Monitoring (qRT-PCR **and** Thick Blood Smear)[8] Footnote 8: Parasitemia evaluations **with qRT-PCR coupled with preparation of a thick blood smear** should continue daily until a participant has a confirmed **initial** positive qRT-PCR. A first positive qRT-PCR should trigger **analysis of the blood smear from that sample and** both a PCR and a **microscopic analysis of the** blood smear at each visit until either subsequent test is positive. A confirmed positive malaria infection is defined as either two positive qRT-PCR or one positive blood smear results prior to or on Day 27.

SUMMARY OF CHANGES (Version 1.1 to Version 2.0)

Document version was changed from Version 1.1 (10 May 2023) to Version 2.0 (23 May 2023) in preparation for Ethics Committee submission. Content remained the same as Version 1.1.

SUMMARY OF CHANGES (Version 1.0 to Version 1.1)

Administrative changes, typographical errors, and editorial/formatting changes are not included in this summary. Substantive revisions to the protocol are shown in deleted text in the initial wording (Protocol V1.0, dated 28-Apr-2023) is formatted as strikethrough and revised/new text in Amendment V1.1 (dated 10-May-2023) is bolded.

Section Number	Text in Version 1	Text in Version 1.1
Overall	Version 1.0, 28 April 2023	Version 1.1, 10 May 2023
Section 4.1 Trial Population	Adequate contraceptive precautions include intrauterine contraceptive device, oral contraceptives, diaphragm, or condom in combination with contraceptive jelly, cream, or foam; Norplant® or Depo-Provera®, through 28 days after the malaria challenge injection to minimize any potential risk.	Adequate contraceptive precautions include intrauterine contraceptive device, oral contraceptives, diaphragm, or condom in combination with contraceptive jelly, cream, or foam; Norplant® or Depo-Provera®, through ~~28 days after the malaria challenge injection~~ **completion of the trial visits** to minimize any potential risk.
Section 4.2.3.2.1 Screening for Infectivity Control Participants	Screening laboratory tests, a review of changes in adverse events or medical history, and assessment of concomitant medications.	Screening laboratory tests, **serum pregnancy test for women of child-bearing age**, a review of changes in adverse events or medical history, and assessment of concomitant medications.
Section 4.2.3.2.5 CHMI Day 7-17, Daily Post-malaria Challenge Surveillance	A thick blood smear is required with all samples once an initial qRT-PCR is positive, until a diagnosis of *Pf* parasitemia is confirmed, A focused physical exam will be performed as indicated. Vital signs (oral temperature, blood pressure, pulse) will be recorded. Participants be contacted to initiate a full course antimalarial rescue therapy given by direct observed therapy.	**Microscopic analysis of** a thick blood smear is required **along** with all **qRT-PCR** samples once an initial qRT-PCR **test** is positive, until a diagnosis of *Pf* parasitemia is confirmed. A focused physical exam will be performed as indicated. Vital signs (oral temperature, blood pressure, pulse **and pulse oximetry**) will be recorded. Participants **will** be **promptly** contacted to initiate a full course antimalarial rescue therapy given by direct observed therapy.
Section 5.1 Inclusion Criteria #4a	Female participants physically capable of pregnancy, have at least one negative pregnancy test during Screening, on the day of enrollment, prior to IP administration, prior to CHMI and at the start of antimalarial treatment, and who agree to use effective contraception to avoid pregnancy from 28 days before enrollment through 90 days after they complete the trial are eligible to participate. Adequate contraceptive precautions include intrauterine contraceptive device, oral contraceptives, diaphragm, or condom in combination with contraceptive jelly, cream, or foam;	Female participants physically capable of pregnancy, have at least one negative pregnancy test during Screening, on the day of enrollment, prior to IP administration, prior to CHMI and at the start of antimalarial treatment, and who agree to use effective contraception to avoid pregnancy from 28 days before enrollment through **completion of the trial visits are eligible to participate**. Adequate contraceptive precautions include intrauterine contraceptive device, oral contraceptives, diaphragm, or condom in combination with contraceptive jelly, cream, or foam; Norplant® or

Section Number	Text in Version 1	Text in Version 1.1
	Norplant® or Depo-Provera®, through 28 days after the malaria challenge injection to minimize any potential risk.	Depo-Provera®, through **the completion of study visits to minimize any potential risk.**
Section 8.1 Screening Assessments for Eligibility	Physical examination, including vital signs (supine blood pressure, supine heart rate, pulse oximetry on room air, and temperature), weight and height	Physical examination, including vital signs (blood pressure, heart rate, pulse oximetry on room air, and temperature), weight and height
Section 8.4.9 Memory Aid Card	Throughout section reference to diary card is made.	Diary card has been changed to **memory aid**
Section 8.4.12 Timing of Collection of Adverse Events	The participant may record solicited AEs on the diary card and will be recorded in the study database.	The participant may record solicited AEs on the **Memory Aid** card and **these** will be **reviewed by study investigators for recording in** the study database.
Section 8.9.2 PCR Analysis for *P. falciparum*	A confirmed parasite detection consists of two sequential positive qRT-PCR tests at > 12 hours but < 60 hours, and the time to infection is the time of the first positive qRT-PCR.	A confirmed parasite detection consists of two sequential positive qRT-PCR tests at > 12 hours but < 60 hours, and the time to infection is **recorded as** the time of the first positive qRT-PCR.
Section 10.1.1 Regulatory and Ethical Considerations	The protocol, protocol amendments, ICF, and other relevant documents (e.g., assessment of understanding, diary cards, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the trial is initiated.	The protocol, protocol amendments, ICF, and other relevant documents (e.g., assessment of understanding, **Memory Aid** cards, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the trial is initiated.
Section 10.4.7.1 Assessment of AE Intensity (Severity)	The Investigator will make an assessment of intensity for each AE reported during the study and assign it to 1 of 5 categories (with exception to solicited AEs collected in any diary card completed by the participant):	The Investigator will make an assessment of intensity for each AE reported during the study and assign it to 1 of 5 categories (with exception to solicited AEs collected in any **Memory Aid** card completed by the participant):
Section 10.5 Contraceptive Guidance and Collection of Pregnancy Information	Female participants physically capable of pregnancy or who are lactating, have at least one negative pregnancy test during Screening, on the day of enrollment, prior to IP administration, prior to CHMI and at the start of antimalarial treatment, and who agree to use effective contraception to avoid pregnancy from 28 days before enrollment through 90 days after they complete the trial are eligible to participate. Adequate contraceptive precautions include intrauterine contraceptive device, oral contraceptives, diaphragm, or condom in combination with contraceptive jelly, cream, or foam; Norplant® or Depo-Provera®, through 28 days after the malaria challenge injection to minimize any potential risk.	Female participants physically capable of pregnancy or who are lactating, have at least one negative pregnancy test during Screening, on the day of enrollment, prior to IP administration, prior to CHMI and at the start of antimalarial treatment, and who agree to use effective contraception to avoid pregnancy from 28 days before enrollment **through completion of the trial** are eligible to participate. Adequate contraceptive precautions include intrauterine contraceptive device, oral contraceptives, diaphragm, or condom in combination with contraceptive jelly, cream, or foam; Norplant® or Depo-Provera®, **through completion of the trial** to minimize any potential risk.

Section Number	Text in Version 1	Text in Version 1.1
Appendix 1 Schedule of Activities Table 8	Diary Card	**Memory Aid** Card Added: **Footnote #22: SUSARs are recorded only after administration of Investigational Product.**
Appendix 1 Schedule of Activities Table 9	Diary Card	**Memory Aid** Card
Appendix 1 Schedule of Activities Table 10	Diary Card	**Memory Aid** Card Added: **Footnote #19: SUSARs are recorded only after administration of Investigational Product.**
Appendix 1 Schedule of Activities Table 11	Schedule of Activities for CHMI (Visits C1-C11) Screen (infectivity controls only) Day 7-17 with window ±1 day Day 6 Window was ±1 day Footnote 1: Screening period is for the infectivity controls only, if needed All subsequent visits are applicable to infectivity controls and previously randomized participants. Footnote 9: Empiric antimalarial treatment given on Day 27 for those CHMI participants not previously diagnosed with malaria infection.	**Schedule of Activities for CHMI** Screen **Replacements as Infectivity Controls Only** Day **7-13** with window **+1 day** Day 6 Window is **-1** day Footnote 1: Screening period is for **any participants recruited as replacements to serve as** infectivity controls only, if needed All subsequent visits are applicable to infectivity controls and previously randomized participants. Footnote 9: **Participant will be treated for malaria at any visit where infection is confirmed.** Added: (X) to Antimalarial Treatment on Days 6, 7-13, 20, 23, Added: X^{14} to Antimalarial Treatment for Day 27 Added: Footnote **14: Empiric antimalarial treatment will be given on day 27 for those CHMI participants not previously diagnosed with malaria infection.**

Signature Page for: Gates MRI-MAM01-101 Protocol Version 8

Gateway RIM Document #: MAM01-CLIN-000012 v13.0

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