Cover Page

Trial 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

Trial Number: Gates MRI-MAM01-101

NCT #No: NCT05891236

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

Version: Version 4

Last Approval Date: 30 September 2024

Statistical Analysis Plan: Gates MRI-MAM01-101

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Trial Number:	Gates MRI-MAM01-101
Trial Phase:	Phase 1
Sponsor:	Bill and Melinda Gates Medical Research Institute (Gates MRI), One Kendall Square, Building 600, Suite 6-301 Cambridge MA 02139
NCT #No:	NCT05891236
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Confidentiality Statement

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DOCUMENT HISTORY

Document	Date	Change	Rationale
SAP Version 1	27 Oct 2023	Not applicable	Original version
SAP Version 2	01 Mar 2024	Overall Design, IDMC and IA review process, General conventions, Part A SoAs	Protocol Version 5, 26 February 2024
SAP Version 3	21 May2024	Efficacy population and ADA immunogenicity	ADA text change
SAP Version 4	16 August 2024	Part B updated to open-label Added Pre- and Post-CHMI Windows Added New baseline definitions	Part B visits reduced and new information about the treatment gathered from Part A interim analyses Protocol Version 6, 07 June 2024 Replacement infectivity controls participants included in the TEAEs, Overall, pre-CHMI, and post-CHMI study window periods defined for safety analyses Post-CHMI baseline defined for efficacy analyses Analyses populations updated to include replacement infectivity controls and pre- and post-CHMI periods

SIGNATURE PAGE

Trial 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

Trial Number: Gates MRI-MAM01-101

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

% AUC_{ext}	percent AUC extrapolated
λz	terminal Elimination Rate Constant
ADA	anti-drug antibody
ADaM	analysis data model
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ALT	alanine transaminase
ATC	anatomical therapeutic chemical
AUC	area under the curve
$AUC_{0-\infty}$	area under the curve from Time = 0 extrapolated to infinity
AUC_{0-CHMI}	partial AUCs from Time = 0 to the controlled human malaria infection
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
BMI	body mass index
C_{max}	maximum observed blood concentration
C_{CHMI}	concentration at the time of controlled human malaria infection
CBC	complete blood count
CFB	change from baseline
CHMI	controlled human malaria infection
CMP	complete metabolic profile
CSP	circumsporozoite protein
CV	coefficient of variation
DAIDS	Division of Acquired Immune Deficiency Syndrome
eCRF	electronic case report form
EOT	End of Trial
IA	Interim Analysis
IDMC	Independent Data Monitoring Committee
IP	investigational product
IV	intravenous
KM	Kaplan-Meier
LNH	low, normal, high

MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
NA	not applicable
NR	not reportable
PD	pharmacodynamic(s)/protocol deviation(s)
Pf	Plasmodium falciparum
PK	pharmacokinetic(s)
PP	per protocol
PT	preferred term
qRT-PCR	quantitative polymerase chain reaction assay
SAD	single ascending dose
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SDTM	study data tabulation model
SoA	Schedule of Activities
SOC	system organ class
SRT	Safety Review Team
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal half-life
TNR	titer not reportable
TLF	Tables, Listings, and Figures
TEAE	treatment-emergent adverse event
VAMS	Volumetric Absorptive Microsampling
Vz	apparent volume of distribution

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the framework of the statistical analyses, including the planned tables, listings, and figures (TLFs) to assess the safety, tolerability, pharmacokinetics, and protective efficacy of an anti-malaria human monoclonal antibody, MAM01, in healthy, malaria-naive adults. The details in this SAP are based on Final Protocol Version 7.0, 05 September 2024 and Independent Data Monitoring Committee (IDMC) charter, Version 3.0, dated 05 September 2024.

2 TRIAL OBJECTIVES AND ENDPOINTS

The analyses supporting the pharmacokinetic (PK) objectives will be addressed in a separate PK SAP. Additional exploratory analyses may be addressed in an exploratory SAP (ESAP). These are flagged in column "SAP or PK SAP or ESAP."

2.1 Primary Objectives

The following table outlines the endpoints corresponding to the primary trial objectives.

Table 1. Primary Objectives

Objective	Endpoints	SAP, PK SAP, or ESAP
To assess the safety and tolerability of a single dose of MAM01 following intravenous (IV) or subcutaneous (SC) administration	• Solicited local and systemic adverse events (AEs) in the SC cohorts (ie, for injection site reactions) up to 7 days post-dose • Unsolicited AEs up to Day 28 (single dose or multiple dose) • All serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) and adverse events of special interest (AESIs) up to 168 days post-dose (end of trial)	SAP
To assess the safety and tolerability of administration of a repeated SC dose of MAM01	• All SUSARs, SAEs, and AESIs over 378 days for participants that are re-dosed (Part A, Cohorts 2 and 3)	SAP
To characterize safety laboratory parameters of MAM01 following SC or IV administration	• Safety laboratory assessments by grade (Grade 1 and above) up to end of trial	SAP

2.2 Secondary Objectives

The following table outlines the endpoints corresponding to the secondary trial objectives.

Table 2. Secondary Objectives

Objective	Endpoints	SAP, PK SAP, or ESAP
To characterize the pharmacokinetics (PK) of MAM01 following SC or IV administration	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 controlled human malaria infection (CHMI) challenge (AUC_{0-CHMI}) • Concentration at the time of CHMI (C_{CHMI}) • Blood terminal elimination rate constant (λz) • Terminal half-life ($t_{½}$) • AUC from Time = 0 extrapolated to infinity ($AUC_{0-\infty}$) • Percent AUC extrapolated (% AUC_{ext}) • Bioavailability of SC formulation	PK SAP
To characterize the PK of a repeated SC dose of MAM01	• For Part A (Cohorts 2 and 3) (participants that are re-dosed): accumulation ratio $AUC_{0-168}/AUC_{210-378}$	PK SAP
To characterize protective efficacy against *Plasmodium falciparum* (*Pf*) following CHMI challenge	• Presence or absence of *Pf* parasitemia (as determined by quantitative polymerase chain reaction assay [qRT-PCR] or microscopy) after CHMI (up to Day 27 post-CHMI) • Time to parasitemia after CHMI in each cohort	SAP
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 84	SAP

2.3 Exploratory Objectives

The following table outlines the endpoints corresponding to the exploratory trial objectives.

Table 3. Exploratory Objectives

3 TRIAL DESIGN CONSIDERATIONS

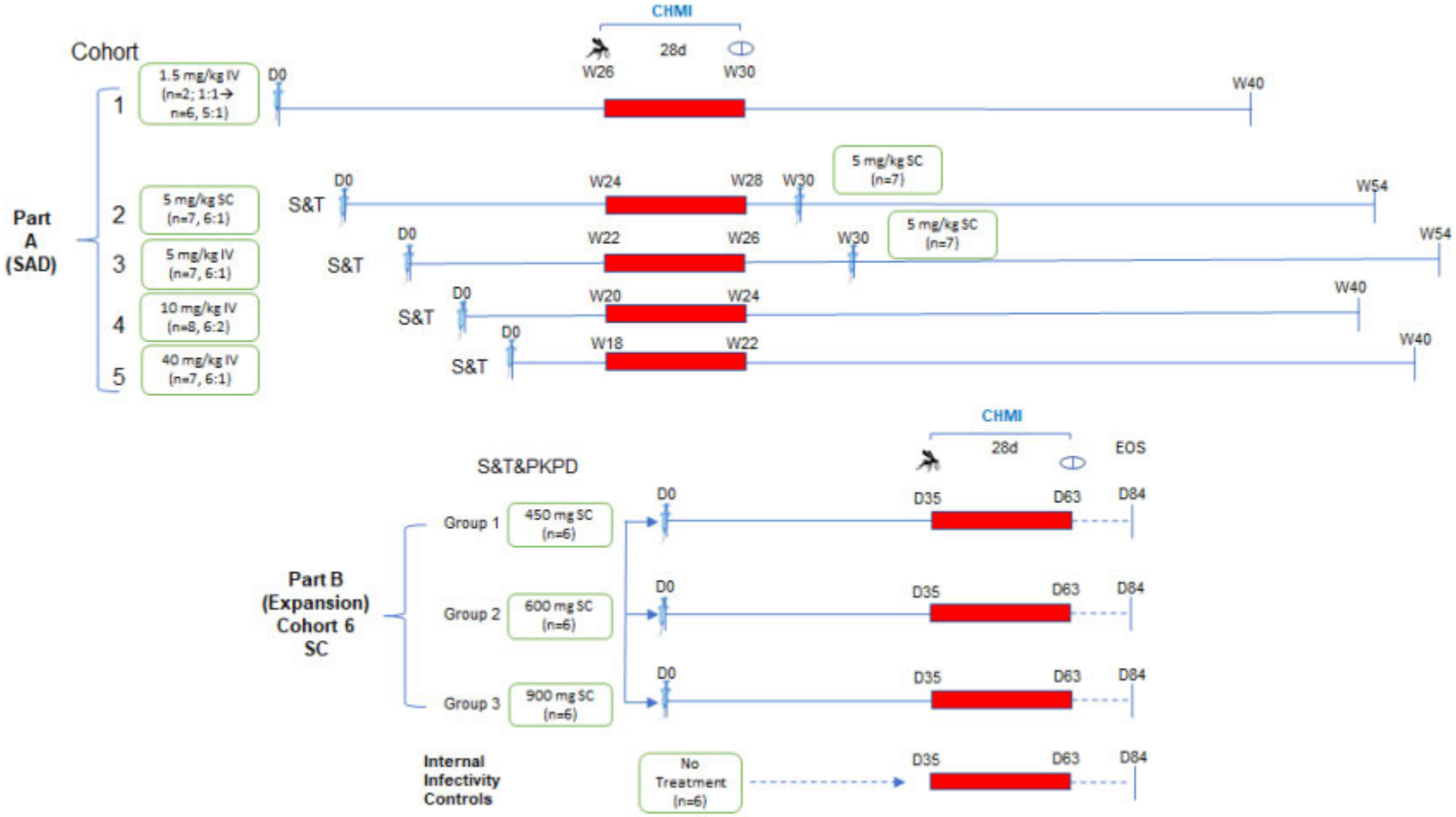
3.1 Trial Design

This clinical trial is a Phase 1, interventional, 5-cohort single ascending dose (SAD) and repeated dose (Part A) trial followed by a single-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. Both Part A and Part B are followed by an assessment of efficacy by using CHMI by mosquito bite. Each of the 2 screening windows (for Part A and Part B) can last up to 60 days, and screening for replacement infectivity controls can occur at the discretion of the Investigator.

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. In Part B, 6 infectivity controls (untreated) will be recruited. 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 replacement 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, approximately 7 participants will receive placebo, and approximately 6 participants will be untreated.

The trial schema is shown below in Figure 1.

Figure 1. Trial Schema



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

3.1.1 Part A

In Part A, the SAD component of the trial will have 5 dosing cohorts with approximately 37 participants in total. The cohorts are as follows and will be staggered by 2 weeks to allow an adequate safety assessment per cohort.

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 assessment period, and favorable safety review team (SRT) assessment, 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).

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

Cohort 3: 7 participants will be randomly assigned 6:1 to receive MAM01 5 mg/kg IV (n = 6) or placebo (n = 1).

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

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

The 7 placebo participants in Cohorts 1 to 5 will serve as replacement infectivity controls for the CHMI procedure. Participants who withdraw from the trial before CHMI procedure will be replaced with participants who will undergo CHMI procedure but not receive MAM01 or placebo. These untreated replacement infectivity controls will be pooled with the placebo participants in the CHMI analyses.

Table 4. Part A – Dose Escalation

Gates MRI-MAM01-101: Part A – Dose Escalation											
		MAM01 Administration									
		Day 0		Week 30 (Day 210) (± 7 days)		CHMI					
Cohort	Participants	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) (± 2 days)	Week 18 (Day 127) (+ 7 days)	Enrolled only in 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.

Prior to the Part A CHMI procedure in Cohorts 1 to 5, participants will have a blood sample drawn for MAM01 concentration determination on the day prior to the CHMI mosquito-bite procedure. CHMI will be initiated simultaneously for Cohorts 1, 2, 3, 4, and 5 at approximately Day 181, after dosing for the main cohort of participants in Cohort 1. Cohort 5 participants will receive the highest dose, 40 mg/kg IV, MAM01 or placebo.

All participants of Cohorts 2 and 3 will receive an open-label second dose of MAM01 5 mg/kg SC (including initial placebo participants) at least 210 days (± 7 days) post the first dose (and after the initial CHMI procedure). This is the multiple ascending dose (MAD) portion of the trial.

3.1.2 Part B

Part B is an open-label expansion cohort, to further assess the safety and tolerability of SC administration of the targeted dose of MAM01 selected from Part A results. This part consists of a single cohort with 3 dosing groups and a total of approximately 18 participants, each group with 6 participants receiving a single fixed SC dose of open-label MAM01. The expansion cohort doses will be defined following review of the Part A unblinded interim analyses (IAs).

In addition to the 18 participants receiving MAM01, 6 infectivity controls for CHMI will be recruited and will not receive any trial intervention. If any Part B Cohort 6 participants drop out prior to CHMI procedures, these participants will be replaced by malaria-naïve replacements to serve as infectivity controls in the CHMI procedure.

The dose for Part B (Cohort 6) were selected by applying a PK/PD 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.

Participants in Part B Cohort 6 dosing groups will take part in the CHMI procedure at the same time.

Groups 1 to 3 participants are expected to complete the trial by approximately 12 weeks post IP administration. Each participant per cohort will have up to 25 visits (including the possible CHMI visits) over 84 days. A CHMI procedure will be conducted 35 days after receiving SC dose of MAM01.

Table 5. Part B – Dose Expansion

Gates MRI-MAM01-101: Part B – Dose Expansion					
		MAM01 Administration		CHMI	
Group Within Cohort 6	Participant	Dose (mg/kg)	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				
IIC	N = 6	Not Dosed			

CHMI = controlled human malaria infection; IIC = Internal Infectivity Controls; SC = subcutaneous.

3.1.3 Controlled Human Malaria Infection

Participants in Part A, Cohorts 1 to 5, and in Part B, will take part in the CHMI challenge and related follow-up according to the Schedule of Activities (SoA) (Appendix 1). Participants in Part A randomized to receive placebo (IV or SC) will serve as infectivity internal reference for the CHMI procedures. Confirmation of malaria infection (and subsequent initiation of rescue anti-malarial therapy) is defined as 2 positive qRT-PCR results or a positive thick blood smear. Those who remain negative malaria infection will be given empiric anti-malarial therapy on Day 27 of the CHMI procedure.

If a participant in Part A Cohorts 1 to 5, or any Cohort 6 Group 1 to 3 MAM01 dosed participant in Part B drops out of the trial before either CHMI procedure starts, the participant may be replaced by an additional malaria naïve participant; they will not be treated with MAM01 or placebo. These untreated participants serve as replacement infectivity controls to ensure at least 6 volunteers in Part A and 6 volunteers in Part B validate the infectivity of the CHMI procedure. The replacement infectivity control participants will not receive administration of MAM01 or placebo.

3.2 Justification of Sample Size

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. The 7 planned placebo participants in Cohorts 1 to 5 will serve as controls for the CHMI procedure. Participants who withdraw from the trial before CHMI procedure will be replaced with participants who will undergo CHMI procedure but not receive MAM01 or placebo. These untreated replacement infectivity controls will be pooled with the placebo participants in the CHMI analyses. Such replacement will ensure minimum of 6 participants to serve as the infectivity controls for each CHMI procedure, as historical data suggest that the rate of infection in the reference group may occasionally be < 100% Epstein et al, 2007.

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 will not receive treatment and will serve as infectivity controls.

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.

3.3 Masking/Blinding

Part A of the trial has a double-blind design in which participants, Investigator, and all site personnel will be blinded to the randomization, except the unblinded pharmacist(s) at the trial site. Protocol Section 9.2.7 provides a description of the planned interim analyses for Part A and extent of unblinding that will take place for each IA. NOTE: The protocol states that the Investigative site personnel will remain blinded to the second interim analysis results, but in fact the unblinded results will be included in the Investigator Brochure. This discrepancy will be documented as a protocol deviation.

Participants in Cohorts 2 and 3 will be re-dosed with MAM01 open-label, without placebo as the comparative trial arm. Participants in Part B will be randomized to receive open-label MAM01 in one of 3 dose groups.

Though access to unblinded results from the first IA for Part A 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 IA. 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.

3.4 Safety Review Team and Independent Data Monitoring Committee

The SRT is comprised of Sponsor staff, the site PI, and CRO medical monitor. The SRT is responsible for blinded safety review prior to dose escalation and dose expansion (Part B) Go/No Go decisions for the trial. This team will review blinded safety data to assess if an *a priori* pausing rule is met and make further recommendations to the Sponsor on further dosing. Details are outlined in the SRT charter.

IDMC team members are identified in the IDMC charter. The role of the IDMC will be to review unblinded safety data in case the SRT determines a pausing rule has been met and make recommendations to the Sponsor. The IDMC will also review unblinded individual and safety data in a closed meeting, after IA #1 to recommend expansion of the clinical development program. The IDMC will further review the IA data from Part A after CHMI (IA #2) and make recommendations to the Sponsor. Separate TLFs will be developed for use in IDMC sessions according to the IDMC charter. A watermark will be used to distinguish between open and closed TLF.

3.5 Planned Analyses for the Trial

3.5.1 Interim Analyses

Two IAs are planned in Part A.

The first IA will focus on safety and tolerability up to a point triggered when Cohort 1 participants have had their Week 16 visit, which is planned to occur just prior to the CHMI procedure in Cohorts 1 to 5. This will focus on all cohorts, ensuring 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 to 5) collected up to the date of mosquito challenge and all available safety and tolerability data from all cohorts 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 IA will focus on safety, efficacy and PK modelling following the CHMI procedures. Post completion of CHMI (Day 27), two output analyses will be created for IA #2.

- Pharmacokinetic data 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 PK SAP. The Sponsor will review unblinded data at the participant level. The purpose of this second IA is to inform dose selection for Part B.
- 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. Investigator will remain fully blinded through safety assessments (Day 28) post Cohort 2 and 3 re-dosing (MAD), while the Sponsor will be unblinded at participant level. The purpose of this unblinded interim will be to develop the individual and population PK and PK/PD modes and aid in dose selection for future clinical trials.

3.5.2 Final Analysis

The final analysis will be conducted after both Part A and Part B of the trial have been completed and the final database lock has occurred.

3.6 Efficacy Measures

3.6.1 PCR Analysis for *P. falciparum* Parasitemia

A sensitive qRT-PCR will be used for the detection of *Pf* parasites. Parasitemia monitoring will occur during CHMI visits starting on Day 6 after mosquito bite as defined in the SoA (see Appendix 1). A thick blood smear will be prepared for microscopic analysis aside from the qRT-PCR but will be read microscopically only when the first PCR sample becomes positive. Monitoring parasitemia evaluations will continue daily until a participant has a confirmed initial positive qRT-PCR. A first positive qRT-PCR will trigger analysis of a second PCR or a microscopic analysis of the blood smear until either two tests are positive, then rescue therapy will be initiated.

A confirmed positive malaria infection is defined as 2 positive qRT-PCR (> 12 hours but < 60 hours apart) or a positive blood smear result(s) prior to or on Day 27 of the CHMI. Further parasitemia checks will not be needed after confirmed diagnosis and initiation of rescue therapy until test of cure visit (Day 49 of CHMI). If a missing assessment is followed immediately by a non-missing assessment with a positive result, then the missing assessment will be considered positive for the purpose of determining time to *Pf* parasitemia.

qRT-PCR will be reported qualitatively to the trial site and recorded. A data file with quantitative assessment of the qRT-PCR recorded as cycle times will be prepared and transferred as a datafile at the end of the trial. Microscopy will be recorded both qualitatively (positive or negative) and quantitatively (number of parasites seen) and reported to the trial site.

Time to infection will be defined as the time to the first of the 2 positive qRT-PCR assays or positive thick blood smear.

In the listing, the serum concentration of MAM01 at the time of CHMI will be included.

3.6.2 Actual Antibody Concentration

The efficacy of MAM01 based on actual antibody concentration will be performed for all participants in Cohorts 1 to 5 at the time of CHMI, and all participants in Cohort 6 at the time of CHMI.

The analyses supporting the antibody objectives will be addressed in a separate ESAP.

3.7 Safety Measures

3.7.1 Clinical Safety Laboratory Assessments

Blood samples for clinical safety laboratory assessments will be performed at Day -1, and throughout the trial at timepoints specified in the SoA (Appendix 1). Additional tests may be performed at any time during the trial as determined necessary.

Clinical safety laboratory parameters will include:

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

Serum chemistry: alanine transaminase (ALT) and creatinine

Complete metabolic profile: sodium, potassium, total CO_2, chloride, blood urea nitrogen, creatinine, glucose (random), ALT, aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, total protein, albumin, alanine aminotransferase.

For participants in Cohorts 2 and 3, who will receive a second dose of MAM01, CMP and CBC with differential will be repeated at the visit prior to second treatment administration as per the SoA (Appendix 1).

Refer to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 DAIDS 2017 for the toxicity table for grading of each clinical laboratory test.

3.7.2 Physical Examinations and Vital Signs

A full physical exam with vital signs and medical history (including medication use) will be obtained at Screening. Focused physical examination may be performed on Day -1 pre-dose and all subsequent visits to check for changes in health throughout the trial, as indicated in the SoA (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.

Vital signs (body temperature, percent oxygen saturation on room air by pulse oximetry, pulse, and resting blood pressure) and weight (Part A only) will be repeated at the Day -1 pre-dose visit. The vital signs will be collected for all visits through Day 28 after trial intervention administration and during the CHMI procedure (as outlined in Appendix 1).

3.7.3 Adverse Events

Adverse events are defined as any unexpected medical occurrence in a participant which are temporally associated with the trial intervention, whether or not considered related. Adverse events will be collected from the Screening visit throughout the trial, to the end of trial (EOT). Adverse events reported include adverse drug reactions (ADRs), defined as a noxious or unintended response to a trial intervention which occurs at any dose and can also result in an overdose, misuse or abuse of the trial intervention. Other reported AE assessments collected include the AE intensity, AE causality, AE expectedness, and AE outcome.

Participants will be instructed to contact a trial team member to report new or worsening AEs, as well as new diagnoses, and to come to the trial clinic if medical attention is needed during the 60 days after trial intervention administration. Participants will be asked about the occurrence of SAEs, AESIs, receipt of 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 (Appendix 1).

3.7.3.1 Collection of Solicited Adverse Events

A memory aid card will be utilized by participants to collect solicited and unsolicited AEs beginning at discharge from the clinic after infusion/injection, up to Day 7 (or EOT 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 a SC dose will also receive a ruler to measure the diameter of redness and/or swelling at the injection site, if present.

The memory aid card will be used by the trial participants to record the duration and intensity of solicited injection site AEs (for participants who receive a SC dose) and solicited systemic AEs up to Day 7 following injection or infusion for all participants.

3.7.3.2 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.

Systemic solicited AEs will be assessed in 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.

3.7.3.3 Unsolicited Adverse Events

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

- From product administration to Day 28 (Week 4) visit
- From CHMI Day 0 up to Day 27 post-CHMI visit or Day 49 post-CHMI visit, depending on the diagnosis of malaria infection

3.7.3.4 Adverse Events of Special Interest

Adverse events of special interest will be collected for all participants from Screening up to EOT. The following AEs will be collected and reported as AESIs:

- Infusion reactions requiring permanent discontinuation of the trial intervention
- Anaphylaxis (see DAIDS 2017)
- Other severe (Grade 3 to 4) hypersensitivity reactions
- Immune complex disease

3.7.3.5 Suspected Unexpected Serious Adverse Reaction

SUSARs are AEs that occur in a clinical trial participant, which is assessed by the Sponsor and/or trial Investigator as being unexpected, serious, and as having a reasonable possibility of a causal relationship with the trial intervention. SUSARs will be collected for all participants from Screening up to EOT.

3.7.3.6 Adverse Drug Reaction

An ADR is defined as a reaction as a result of trial intervention, which may occur at any dose. These will be collected from the date of trial intervention administration up to EOT. Serious ADR are ADRs that are judged as serious, and these will be reported even after the trial is over, if the Sponsor Medical Monitor and Investigator are made aware.

3.7.3.7 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that meets at least one of the following criteria:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent disability/incapacity
- Is a congenital anomaly/birth defect
- Is a medically significant/important event or reaction

Serious adverse events will be collected for all participants from Screening up to EOT.

3.8 Anti-Drug Antibody Assessments

Capillary blood samples and selected serum samples will be collected on volumetric absorptive microsampling (VAMS) devices as per the SoA (see Appendix 1). Pre dose samples on Day 1 and re-dosing (Week 30) will be collected prior to MAM01 administration. The detection of ADA to MAM01 antibodies will be performed using a qualified tiered immunoassay.

The detection of ADA to MAM01 will be performed using a qualified immunoassay method with tiered testing of screening, confirmatory, and titration, ie:

1. All samples will undergo a screening test.
2. If the screening test is positive for ADA, the sample will undergo a confirmatory test. A sample that has a negative or not reportable (NR) screening result will not undergo further testing.
3. If the confirmatory test is positive, the sample will be analyzed to determine the titer. A titer result can be a quantifiable number or not reportable (titer not reportable [TNR]). A sample that has a negative or not reportable (NR) confirmatory result will not undergo further testing.

3.9 Pharmacokinetic and Pharmacodynamic Measures

3.9.1 Pharmacokinetic Assessments

The analyses supporting the PK objectives will be addressed in a separate PK SAP.

In Part A, serum from venous blood samples will be collected for measurement of MAM01 PK per the SoA (Appendix 1). The protocol planned for capillary blood samples (VAMS) collection for PK analysis in Part A: following Part A interim analysis these will not be analyzed due to failure of assay validation. Additional blood samples and selected serum samples for ADA will be collected starting on Day 7. 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 of each sample will be recorded to calculate the actual time elapsed since dose administration.

[redacted]

4 TRIAL POPULATIONS

4.1 Analysis Populations

Replacement infectivity control participants will form part of the cohorts in case of dropouts, but they will not receive trial intervention (neither MAM01 nor placebo). They will undergo CHMI procedure to ensure there are adequate infectivity controls to evaluate the efficacy of the infectious challenge. Replacement infectivity control participants who underwent CHMI procedure will be included in the Safety and Efficacy populations as described below. These participants may be considered for the Per Protocol, PK and Immunogenicity populations.

4.1.1 Randomized Population

The Randomized population includes all participants randomly assigned to trial intervention, with a randomization number and date. A participant will be programmatically included in the Randomized population if the participant has a randomization number and date. Participants will be analyzed according to the treatment they were randomized to.

4.1.2 Safety Population

The Safety population includes all participants who were randomly assigned to trial intervention and received the trial intervention, and the replacement infectivity control participants. Participants will be analyzed according to the treatment they received. Replacement infectivity control participants will be included only in the Safety population for the post-CHMI and overall safety presentations. See Section 6.9 for definitions of pre-CHMI, post-CHMI, and overall safety reporting windows.

Participants in Cohorts 2 and 3 who receive the second dose will be identified by a flag for the re-dose safety presentation.

4.1.3 Efficacy Population

The Efficacy population includes all participants who were randomly assigned to trial intervention, received the trial intervention or acted as replacement infectivity (untreated) control, and completed CHMI procedure. Completion of CHMI procedure is defined as having undergone the mosquito bite challenge and meeting any of the following criteria: (1) documented to be *Pf* infection-free through Day 27; (2) documented to have breakthrough *Pf* infection; or (3) received anti-malarial treatment at any time on or before Day 27. Participants will be analyzed according to the treatment they received, with replacement infectivity controls included with pooled placebo.

4.1.4 Per Protocol Population

The “per protocol (PP)” population includes 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 treatment they received.

4.1.5 PK Population

The PK population includes all participants who were randomly assigned to trial intervention, received the trial intervention, and have baseline and on-trial concentration-time data available. Participants will be analyzed according to the treatment they received.

4.1.6 Immunogenicity Population

The Immunogenicity population includes all participants who were randomly assigned to trial intervention, received the trial intervention, and have at least 1 valid ADA result. Participants will be analyzed according to the treatment they received.

4.2 Subgroups

There are no subgroups to be considered.

5 CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

In Part B, where a participant is randomized and assigned a randomization number and does not show up for the dosing visit, a new participant will be randomized and assigned a new randomization number. This participant may be assigned a different treatment from that of the participant that did not show up. Replacement infectivity control replacement participants will be assigned new randomization number.

The protocol states that the Investigative site personnel will remain blinded to the second interim analysis results, but in fact the unblinded results will be included in the Investigator Brochure. This discrepancy will be documented as a protocol deviation.

The protocol planned for capillary blood samples (VAMS) collection for PK analysis in Part A: following Part A interim analysis these will not be analyzed due to failure of assay validation.

6 OVERALL STATISTICAL CONSIDERATIONS

6.1 General Conventions

Number (n) and percentages (%) will be used to summarize categorical variables.

Unless otherwise specified, the denominators for percentages will be the number of participants in each treatment group with non-missing data for the variable of interest at the summarized visit.

Percentages will be displayed with one decimal place. Percentages for zero counts will be omitted from the presented results, ie, only the number, '0' will be displayed.

Descriptive statistics will be presented for continuous data with applicable decimal precision as follows in relation to the actual source data, mean and median one decimal place regardless of the value being an integer or not, two decimal places will be displayed for standard deviation (SD) regardless of the value being an integer or not. Decimals for minimum and maximum will be, no decimals if value is integer and one decimal maximum if not integer.

Decimal precisions for specific laboratory parameters will be presented as follows, two decimal places for mean and range, and three decimal places for SD unless otherwise specified for laboratory parameters.

6.2 Baseline Definition

Unless otherwise specified, baseline is defined as the last non-missing assessment (scheduled or unscheduled) prior to the trial intervention in Part A and Part B separately. This baseline applies to the overall and pre-CHMI safety assessments.

Change from Baseline is calculated as:

$$\text{CFB} = \text{Observed Value} - \text{Baseline Value}$$

if baseline and post-baseline observed values are not missing.

6.2.1 Efficacy and Replacement Infectivity Controls Post-CHMI Changes

For replacement infectivity controls, changes from pre-CHMI baseline will be calculated using pre-CHMI values, which are defined as the most recent non-missing assessment (scheduled or unscheduled) conducted before the CHMI procedure. This calculation is performed separately for Part A and Part B.

Efficacy (post-CHMI) changes from pre-CHMI baseline will be calculated as the difference between the last available pre-CHMI assessment and the post-CHMI assessments. This pre-CHMI baseline assessment is defined as the most recent non-missing evaluation, whether scheduled or unscheduled, conducted before the CHMI procedure. This method is applied separately for Part A and Part B.

Changes from pre-CHMI baseline values will be highlighted in each respective section, with clear descriptions provided to distinguish between changes from baseline and changes from pre-CHMI assessments.

6.3 Calculation of Trial Day and Time

Although the protocol defines the first day of administration of trial intervention as Day 0, for datasets and trial results reporting, the first day of administration of trial intervention will be defined as Day 1. All other trial days will be computed relative to Day 1. Visit Day 0 in the SoA (Appendix 1) is on relative Day 1.

For events on or after the date of trial intervention administration (defined as Day 1), trial day for a particular event or visit will be calculated as:

$$Date_{event} - Date_{first\ dose} + 1$$

For events before Day 1, trial day for a particular event will be calculated as:

$$Date_{event} - Date_{first\ dose}$$

For participants in Part B, trial day since expansion dose will be calculated as:

$$Date_{event} - Date_{expansion\ dose} + 1$$

The exception to this convention is the calculation of time to infection, which is described in Section 7.5.1.

6.4 Handling of Partial Dates

6.4.1 Missing or Partial Dates for Adverse Events

Missing or partial AE start dates will be imputed for the purpose of determining whether the AEs started post-trial intervention administration. Data handling rules for missing or partial start/stop date for AEs are detailed in Appendix 2. The missing or partial dates will be displayed in the data listings as reported on the electronic case report form (eCRF) rather than the imputed dates.

6.4.2 Missing or Partial Dates for Prior and Concomitant Medications

Missing or partial medication start or stop dates will be imputed for the purpose of determining whether the medications are taken concomitantly. Data handling rules for missing or partial start/stop date medications are detailed in Appendix 2. The missing or partial dates will be displayed in the data listings as reported on the eCRF rather than the imputed dates.

6.5 Handling of Missing Data

Missing data will not be imputed, unless otherwise specified in the specific analysis methods section.

6.6 Interim Analysis

Two IAs are planned for this trial, as described in Section 3.5.1.

6.7 Pooling Strategy for Trial Sites

Not applicable, as this is a single-site trial.

6.8 Visit Windows/Unscheduled Visits

Additional visit windowing will not be applied in this trial, and nominal visit names will be used as entered on the eCRF. Unscheduled visits will not be included in by-visit summaries or analyses but will contribute to the baseline value and worst value determinations and will be included in the listings.

6.9 Safety Reporting Windows

All safety summaries will be reported for three periods: the pre-CHMI period, the post-CHMI period, and overall. These periods are defined as follows:

- Overall period includes all safety assessments from start of trial through end of trial, regardless of whether participants underwent CHMI procedure.
- Pre-CHMI period includes assessments/events collected from the start of the trial up to the last available assessments/event collected prior to the CHMI procedure start date for participants who began the CHMI procedure. For participants who did not start the CHMI procedure but were treated, include all assessments/events through end of trial.
- Post-CHMI period includes assessments/events collected from the start date of CHMI procedure through end of trial.

Replacement infectivity controls (ie, untreated participants who completed CHMI) are included in the Overall and Post-CHMI safety populations.

7 STATISTICAL ANALYSIS METHODS

Data from Part A and Part B of the trial will be analyzed and presented separately. Placebo participants from each cohort will be pooled and presented together as "Pooled Placebo" per trial part. All collected data will be presented in by-participant listings; therefore, listings will not be mentioned in this section unless any clarifications to listings need to be addressed.

7.1 Participant Disposition

The following will be presented in a summary table by treatment group and overall, for disposition:

- Number of participants:
  - Screened (including number and percentage of screen failures with reason[s])
  - Randomized (Randomized population)
- Number and percentage of participants:
  - Re-screened
  - Eligible and not randomized
  - Randomized or replacement infectivity control
    - Randomized population
    - Randomized but not treated
    - Replacement Infectivity Controls
  - Randomized and treated
    - Overall
    - Pre-CHMI (actual or planned)
    - Post-CHMI
    - Received two doses (Cohorts 2 and 3)
  - Efficacy population
  - Per Protocol population
  - PK population
  - Immunogenicity population
  - Completed the trial
  - Ongoing participation
  - Discontinued the trial with reason(s)

Percentages for screen failures and participants re-screened will be calculated using the number of participants screened as the denominator. Percentages for participants replaced, analysis populations, and those who underwent CHMI procedures will be calculated using the Randomized population as the denominator.

The denominator for the percentage of participants who completed the trial and discontinued the trial with reasons will be obtained from the Randomized population.

7.1.1 Protocol Deviations

Important protocol deviations (PDs) are a subset of PDs that may significantly impact the completeness, accuracy and/or reliability of trial data or that may significantly affect a participant's rights, safety or well-being. Important PDs will be presented in a summary table by treatment group and overall, for the Safety population. A participant with multiple occurrences of an important PD in the same deviation category will only be counted once. The procedures for identifying and classifying PDs will be described in a PD Management Plan.

7.2 Demographics and Baseline Characteristics

Demographics and other baseline characteristics will be summarized by using descriptive statistics by treatment group and overall. The denominators for percentages will be the number of participants in each cohort with non-missing data for the variable of interest for the Randomized and Safety populations.

The following demographic data will be summarized and listed:

- Age (years)
- Age (years) categories: (18 - 30, 31 - 40, and 41 - 50)
- Sex (Male, Female)
- Childbearing potential (if female: Yes, No)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown)
- The following baseline characteristics will be summarized:
  - Weight (kg)
  - Height (cm)
  - Body mass index (BMI) (kg/m^2) (as collected in the eCRF)

A listing of the above demographic data will be produced, which includes all infectivity controls.

7.2.1 Medical History

Medical history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.1 or higher. The number and percentage of participants reporting any medical history will be summarized by system organ class (SOC) and preferred term (PT), by treatment group and overall, for the Safety population. A participant with multiple medical conditions will be counted once per SOC and PT. For computing percentages, the denominator will be the number of participants for the Safety population for each treatment group. The summary table will be sorted alphabetically by SOC, then by descending number based on the overall column of PT (within the treatment group) within each SOC (then alphabetically for ties).

7.3 Prior and Concomitant Medications

Prior medications are defined as medications with a start and an end date prior to the date of the first dose. Concomitant medications are defined as medications that either started prior to the first dose and ended on/after the first dose of trial intervention, ongoing at Baseline or, having started on/after the first dose of trial intervention.

All prior and concomitant medications will be coded using the World Health Organization Drug Dictionary, September 2022, or later version. The anatomical therapeutic chemical (ATC) level 3 and preferred name will be used to summarize the data, by treatment group and overall, for the Safety population, separately for prior and concomitant medications. A participant with multiple prior or concomitant medications will be counted once per ATC level 3 and preferred name. The summary table will be sorted alphabetically for ATC level 3, then by descending number based on the overall column of preferred name within each ATC level 3, and then alphabetically for ties.

7.4 Treatment Exposure and Memory Aid Card Compliance

Three treatment exposure listings will be produced for the Safety population and will include date and start/end time of administration, route of administration, whether the complete dose was administered (and reason, if no), the total dose (and unit) administered, number of syringes used and location of administration from each syringe. This listing will be created for:

- Part A, first dose administration, sorted by treatment group and participant number
- Part A, repeat-dose administration for Cohorts 2 and 3 only, sorted by treatment group and participant number
- Part B, sorted by treatment group and participant number

7.4.1 Memory Aid Card Compliance

The number of participants who returned the memory aid card will be summarized for the Safety population. The reason for not returning the memory aid card will be listed for the Safety population. The results will be presented separately for Part A and B. For any given day, the memory aid card will be considered as complete if all expected data are available (ie, a non-missing response is available). If any of the items in the diary are missing on a specific day, the diary is considered incomplete.

Memory aid card compliance will be derived as follows:

- Compliance per day: the numerator is the number of participants who completed the memory aid card on a given day (Day 0 to Day 7) and the denominator is the total number of participants who received the applicable dose and memory aid card.
- Compliance at least x days for x = 1, 2, … 8: the numerator is the number of participants who completed the memory aid card for x days out of the 8 days and the denominator is the total number of participants who received the applicable dose and memory aid card.

7.5 Efficacy Analysis

7.5.1 Evaluation of Protective Efficacy Against *P. falciparum* Parasitemia

Protective efficacy against *Pf* parasitemia delivered by mosquito bite will be tested for participants from Cohorts 1 to 5 in Part A of the trial, and for participants in all groups in Part B of the trial for the Efficacy population, defined in Section 4.1.3.

Determination of *Pf* parasitemia will be defined as:

1. Two positive qRT-PCR results with the second positive result occurring > 12 hours and < 60 hours relative to the first positive; OR
2. A single thick blood smear with 2 confirmed parasites.

The following CHMI-related parameters will be summarized separately for each cohort in Part A and Part B:

1. qRT-PCR results
    - Proportion of participants with at least one positive qRT-PCR result
    - Proportion of participants with two positive qRT-PCR results within the given window
2. Proportion of participants with a positive blood smear result
    - Descriptive statistics for the number of parasites
    - Descriptive statistics for the number of parasites per microliter
3. Proportion of participants with a confirmed *Pf* parasitemia after CHMI by Day 27 post-CHMI (*Pf* parasitemia)

The time to *Pf* parasitemia will be defined as the time to the first of the 2 positive qRT-PCR assays or positive thick blood smear. See Section 3.6.1 for an all-inclusive definition.

The time to *Pf* parasitemia will be calculated as date of *Pf* parasitemia - CHMI procedure date. This convention reflects post-CHMI study day. Participants who are infection-free will be censored at the date of the last non-missing qRT-PCR or thick blood smear assessment (Day 27 for the Efficacy population). Time to censoring will be similarly calculated as date of visit Day 27 or Lost to Follow-up - CHMI procedure date.

A Kaplan-Meier (KM) plot, with study days since CHMI on the x-axis and probability of being infection-free on the y-axis, will be created for each cohort in Part A (with separate lines for each of the 5 treatment doses in Cohorts 1 to 5, and a line for pooled placebo) and Part B (with separate lines for each of the 3 treatment times in Groups 1 to 3, and a line for pooled placebo).

Participants that withdraw consent or are lost to follow-up prior to Day 27 will be censored.

The quartiles of the infection-free curve, point estimates and 95% CIs will be reported by treatment group.

By-participants listings will be produced as follows:

- For the CHMI Challenge includes date of CHMI, total mosquitoes used, total mosquitoes fed, number fed with qualifying bites and average gland rating.
- Local parasitemia evaluation includes sample collection date, qRT-PCR results, Ct Values and Thick Blood Smear, including Number of Parasites and Parasites per Microliter.
- Confirmed malaria infections, includes participants with at least one positive qRT-PCR result, two positive qRT-PCR results, positive blood smear, *Pf* parasitemia criteria met, time to *Pf* parasitemia in days and whether participants received anti-malaria medication.
- Time to *Pf* parasitemia in days, includes the CHMI procedure date, *Pf* parasitemia results, date of diagnosis or censoring, time to *Pf* parasitemia in days, MAM01 serum concentrations results at Day -1 pre-CHMI and MAM01 blood concentration at CHMI.

7.5.2 Evaluation of MAM01 Efficacy at CHMI

The analyses supporting MAM01 levels evaluated at the time of CHMI among all participants in Cohorts 1 to 5, using the estimate EC80 of the antibody, will be addressed in a separate ESAP.

7.6 Immunogenicity Analysis

ADA assessments will be conducted as defined in Section 3.8.

The ADA status per sample will be performed on all individual results. Listings and pre-existing immunogenicity incidence will the conducted on the Safety population. ADA Status and subsequent analyses will be performed on the Immunogenicity population.

Participants with no baseline ADA assessment are assumed to be negative at baseline. Participants will be analyzed according to the intervention they received.

7.6.1 Terms and Definitions

The following terms and definitions will be applied in the immunogenicity analyses.

ADA status of a sample

- ADA negative sample: Screening or confirmatory test of the sample indicates ADA is not detected.

- ADA NR sample: Screening or confirmatory test of the sample indicates ADA is not reportable.
- ADA sample missing: No sample was available for testing.
- ADA positive sample: Screening and confirmatory tests of the sample indicate ADA is detected. The numeric titer will be reported unless the titer result is NR, which would be reported as positive TNR.

Pre-existing immunogenicity incidence (Safety population):

- Percentage of valid baseline samples that are ADA positive samples.

ADA status of a participant (Immunogenicity population):

- ADA Never positive: No ADA positive samples at baseline or post-baseline.
- ADA Pre-existing Treatment Boosted: An ADA positive sample at baseline with at least one post-baseline reportable titer ≥ 8-fold increase above baseline titer. Note that the baseline sample and at least one post-baseline sample must have reportable titer met the criterion for treatment-boosted.
- ADA Pre-existing Not Treatment Boosted: An ADA positive sample at baseline that doesn't have any post-baseline reportable titer ≥ 8-fold increase above baseline titer. Note that all participants with positive-TNR at baseline fall into this category by default.
- ADA Treatment-Induced: A negative, missing, or NR ADA sample at baseline and at least one post-baseline ADA positive sample (either numeric or positive TNR).

7.6.2 Derivation Rules

Immunogenicity results will be collected prior to dose administration and at post-treatment follow-up visits. Sample-level and participant-level derivations are shown in Table 6 and Table 7, respectively.

Table 6. Algorithm for Deriving Anti-Drug Antibody Sample-Level Results

SDTM Raw Data			Derived ADaM Sample Result
ADA Screening Result (ISTSTOPO = Screen)	**ADA Confirmatory Result (ISTSTOPO = Confirm)**	**ADA Titer Result (ISTSTOPO = Quantity)**	
Negative	NA	NA	Negative
NR	NA	NA	NR
Missing	NA	NA	Negative
Positive	Negative	NA	Negative
Positive	NR	NA	NR
Positive	Positive	Number	Number
Positive	Positive	NR	Positive TNR

ADaM = analysis data model; NA = not applicable; NR = not reportable; SDTM = study data tabulation model; TNR = titer not reportable.

Table 7. Algorithm for Deriving Anti-Drug Antibody Participant-Level Results Across All Derived Sample Results From Participant

Baseline ADA Result	Post-baseline ADA Results	Participant Immunogenicity Status
Negative or NR or Missing	No Number or Positive TNR, at least one Negative result	ADA Never Positive
Negative or NR or Missing	All NR or Missing	Not evaluable
Negative or NR or Missing	At least one Positive TNR or Number	ADA Treatment-Induced
Positive TNR	At least one Negative, no Number of Positive TNR	ADA Pre-existing Not Treatment Boosted
Positive TNR	All NR or Missing	Not evaluable
Positive TNR	At least one Positive TNR or Number	ADA Pre-existing Not Treatment Boosted
Number	At least one Negative, no Number or Positive TNR	ADA Pre-existing Not Treatment Boosted
Number	All NR or Missing	Not evaluable
Number	At least one Positive TNR, no Number	ADA Pre-existing Not Treatment Boosted
Number	At least one Number, but none ≥ 8-fold increase above baseline titer	ADA Pre-existing Not Treatment Boosted
Number	At least one Number ≥ 8-fold increase above baseline titer	ADA Pre-existing Treatment Boosted

ADA = anti-drug antibody; NA = not applicable since not included in assessing participant status since no valid post-baseline result; NR = not reportable; TNR = titer not reportable.

The number and percentage of baseline samples will be reported by treatment group as follows:

- ADA positive sample vs. ADA negative sample vs ADA missing sample vs ADA NR sample

For the subset of the Immunogenicity population that has at least one valid post-baseline result, the number and percentage of participants will be reported as follows:

- No Treatment-Emergent ADA
    - ADA Never positive
    - ADA Pre-existing Not Treatment Boosted
- Treatment-Emergent ADA
    - ADA Pre-existing Treatment Boosted
    - ADA Treatment-Induced

Listings will be prepared for the ADA sample-level and participant-level results by treatment group.

7.6.3 Potential Association of Immunogenicity With Adverse Events

A summary table showing number and percentage of participants with AEs will be produced by treatment group for the following categories:

- Any ADA detected
- No ADA detected

This analysis illustrates a potential association between outcomes and is not indicative of causation.

7.7 Pharmacokinetic Analyses

The analyses supporting the PK objectives will be addressed in a separate PK SAP.

7.7.1 Evaluation of PK Parameters After Initial and Repeat Dosing

MAM01 concentrations below the limit of quantification will be set to 0 for all summaries. For participants in the PK population, MAM01 blood and serum concentrations will be summarized by treatment group, separately, for:

- Part A; by nominal time relative to first dose
- Part A; Cohorts 2 and 3 only, by nominal time relative to repeat dose
- Part B; by nominal time relative to expansion dose

Number, arithmetic mean, SD, median, minimum, maximum, geometric mean, and geometric percent coefficient of variation (CV) will be presented for blood and serum concentrations. Linear and semi-log plots of individual and mean concentrations versus nominal time will be presented by the treatment group. Plasma concentrations of MAM01 having value 0 will be excluded from semi-log plots.

The following PK parameters will be derived using a non-compartmental model, as described in a separate PK SAP:

- C_{max} – maximum observed blood and serum concentration
- C_{min} – minimum observed blood and serum concentration
- T_{max} – time to maximum blood and serum concentration
- $AUC_{0\text{-}t}$ – area under the blood and serum concentration-time curve from time 0 up to the last measurable concentration
- $AUC_{0\text{-}CHMI}$ – area under the blood and serum concentration-time curve from time 0 up to Day -1 CHMI measurable concentration
- C_{CHMI} – blood and serum concentration at the time of CHMI challenge
- C_{D168} – plasma concentration up to Week 24 Day 168

- λz – elimination rate constant. The elimination rate constant will be calculated as the negative of the slope of the terminal log-linear segment of the plasma concentration-time curve
- $t_{½}$ – terminal half-life, calculated as ln (2)/λz
- $AUC_{0-\infty}$ – AUC extrapolated to infinity. $AUC_{0-\infty} = AUC_{0-t} + C_{last}/\lambda z$, where C_{last} is the last measurable concentration and λz is the terminal phase rate constant
- % AUC_{ext} – percent AUC extrapolated
- CL – Clearance
- Vz – Apparent volume of distribution. The apparent volume in which a drug is distributed.
- F – Bioavailability of SC formulations

The following PK parameters will be calculated following the repeat dose and summarized in the same manner for participants in Part A, Cohorts 2 and 3, by treatment group and combined:

- AUC_{0-168} – area under the plasma concentration-time curve from time 0 up to Day 168 measurable concentration.
- $AUC_{210-378}$ – area under the plasma concentration-time curve from Week 30 Day 210 up to Week 54 Day 378 measurable concentration.
- $AUC_{0-168}/AUC_{210-378}$ – Accumulation ratio. A division of area under the plasma concentration-time curve from time 0 up to Week 24 Day 168 measurable concentration and area under the plasma concentration-time curve from Week 30 Day 210 up to Week 54 Day 378 measurable concentration, Part A (Cohorts 2 and 3) only for participants that are re-dosed.
- C_{max} – maximum plasma concentration
- C_{min} – minimum plasma concentration
- T_{max} – time to maximum plasma concentration
- $t_{½}$ – terminal half-life, calculated as ln (2)/λz
- CL/F – Ratio of clearance to bioavailability. This ratio will be calculated following the second dose and will be summarized by the treatment group.

The following PK parameters will be calculated following Part B and summarized in the same manner for participants in Part A and Cohorts 2 and 3, by the treatment group:

- AUC_{0-t} – area under the blood and serum concentration-time curve from time 0 up to the last measurable concentration
- C_{max} – maximum plasma concentration
- C_{min} – minimum plasma concentration
- C_{CHMI} – blood and serum concentration at the time of CHMI challenge

- C_{D84} – plasma concentration up to Week 12 Day 84
- $AUC_{0\text{-}CHMI}$ – area under the blood and serum concentration-time curve from time 0 up to Day -1 CHMI measurable concentration
- T_{max} – time to maximum plasma concentration

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 are described in an independent analysis plan and reported separately.

An SDTM file will be created for these data to support the PK SAP.

7.8 Pharmacodynamic Analyses

[redacted]

7.9 Safety and Tolerability

Safety and tolerability of Part A SAD and MAD phases and Part B of the MAM01 compared to placebo will be assessed using various safety measures within the pre-CHMI, post-CHMI, and overall reporting periods (see Section 6.9).

7.9.1 Adverse Events

Overall, AEs reported from Screening up to EOT, will be evaluated as per Section 3.7.3 definitions and per reporting windows specified below.

AEs reported in Part A, SAD, and MAD cohorts:

In the SAD cohorts, ADRs are evaluated from Day 1 to Day 28. SUSARs, AESIs, and SAEs are reported from Screening up to EOT. In the MAD cohorts, ADRs will be reported from Day 211 up to Day 238, and SUSARs, AESIs, and SAEs reported from Screening to EOT.

Solicited AEs for the SAD and MAD cohorts including injection site and systemic body symptoms will be evaluated from Day 0 of trial intervention administration up to Day 7. Ongoing solicited events will be reported within the EDC and flagged as ongoing solicited events, post Day 7 up to EOT. Unsolicited AEs for the SAD and MAD cohorts will be evaluated from Day 1 up to Day 28.

AE Category	Cohort Types	Collection Period
ADR	SAD	From Day 1 to Day 28
	MAD	From Day 211 to Day 238
SUSAR, SAE, and AESI	SAD	From Screening to EOT
	MAD	From Screening to EOT
Solicited AE	SAD and MAD	From Day 1 post-trial intervention administration to Day 7
Unsolicited AE	SAD and MAD	From Day 1 to Day 28

AE evaluated in Part B

From Day 1 post-trial intervention administration up to EOT, the SUSARs, AESIs, and SAEs will be evaluated. ADRs will be evaluated from Screening up to Day 28.

Solicited AEs, including injection site and systemic body symptoms, will be evaluated from Day -1 of trial intervention administration up to Day 7. Ongoing solicited events will be reported within the EDC and flagged as ongoing solicited events, post Day 7 up to EOT. Unsolicited AEs will be evaluated from Day 1 up to Day 28.

Group 1 participants not found to be positive for *Pf* parasitemia (remain qRT-PCR negative) will be considered as "completed the trial" by end of Week 24. Participants in Group 1 found to have a positive *Pf* parasitemia will be considered as "completed the trial" once considered cured, if at Day 49 a cure negative test of qRT-PCR is documented.

AE Category	Collection Period
ADRs	From Day 1 to Day 28
SUSARs, SAEs, and AESIs	From Day 1 post-trial intervention administration to EOT
Solicited AE	From Day 1 post-trial intervention administration to Day 7
Unsolicited AE	From Day 1 to Day 28

AE evaluated in CHMI Procedure

AESIs and SAEs will be reported from Day 6 and SUSAR from Day 7 up to Day 49 of the CHMI procedure.

Ongoing solicited events will be reported within the EDC and flagged as ongoing solicited events, post Day 7 up to EOT. Unsolicited AEs will be evaluated from Day 1 up to Day 27 post-CHMI visit or Day 49 post-CHMI visit, depending on the diagnosis of malaria infection.

AE Category	Collection Period
AESI and SAE	From Day 6 to Day 49
SUSAR	From Day 7 to Day 49
Unsolicited AE	From Day 27 post-CHMI visit or Day 49 post-CHMI visit

AEs will be recorded from the time a participant signs the Informed Consent until EOT. All SAEs and non-serious AESIs will be followed until resolution or stabilization, or the event is otherwise explained, or the participant is lost to follow-up.

AEs will be coded using the most recent version of MedDRA Version 26.1 or higher. Adverse events intensity (severity) will be graded using the DAIDS 2017 table for grading the severity of adult and pediatric adverse events, as Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), or Grade 4 (Potentially Life-threatening) on the eCRF. Missing and partial AE dates will be imputed as specified in Appendix 2.

Treatment-emergent AEs (TEAEs) are defined as AEs that have started on or after the date of the first dose of trial intervention administration up to the EOT. AEs for replacement infectivity control participants will be included and considered as TEAEs.

All AE summary tables will be reported for the overall treatment period, the pre-CHMI period and the post-CHMI period:

- Overall AEs are defined as AEs observed from start of trial through the end of trial, regardless of whether participants underwent the CHMI procedure.
- Pre-CHMI AEs are defined as AEs that started on or after the start of the IP regardless of whether participants completed the CHMI procedure. For participants who started the CHMI procedure, these AEs will be included up to the last date prior to the CHMI procedure start date.
- Post-CHMI AEs are defined as AEs that started on or after the start date of CHMI procedure and continued up to discontinuation or through the end of trial.
- Replacement infectivity controls AEs (ie, these are for untreated participants who completed CHMI) will be included in the Overall and Post-CHMI AEs summary tables.

The following AESIs will be reported for this trial:

- Infusion reactions requiring permanent discontinuation of the trial intervention
- Anaphylaxis (standardized MedDRA query [SMQ]: Anaphylactic reaction)
- Other severe (Grade 3 to 4) hypersensitivity reactions (SMQ: Hypersensitivity)
- Immune complex disease (SMQ: Immune-mediated/autoimmune disorders)

An overview table of TEAEs, containing the number and percentages of TEAEs with number of reported events, will be summarized by treatment group and by the following categories for the Safety population. Replacement infectivity control participants will be included in overall and post-CHMI TEAE summaries and pooled with the placebo participants, despite not receiving trial treatment. Each of the following categories specified will be summarized in separate tables by SOC/SMQ and PT and by treatment group for the Safety population.

- Any TEAE
- Serious TEAEs
- TEAEs with highest intensity (Grade 1, 2, and ≥ 3 [severe])
- TEAEs related to trial intervention
- TEAEs of special interest

- TEAE SUSARs
- Serious TEAEs leading to death
- TEAEs leading to trial discontinuation

Adverse events summarized by SOC and PT will be sorted by SOC/SMQ (alphabetical order), then PT by decreasing number, displayed by treatment group. If a participant has more than one AE at a given level (eg, SOC/SCM and PT), the participant will only be counted once within that level.

The following listings will be presented:

- All AEs
- All TEAEs
- Serious TEAEs
- TEAEs of special interest
- TEAEs leading to trial discontinuation
- TEAEs leading to death
- All SUSARs

Adverse events will be sorted by treatment group, participant ID, start date of AE, SOC, and PT. Adverse event table with SMQ will be sorted by treatment group, participant ID, start date of AE, SMQ, and PT.

Adverse drug reactions to MAM01/placebo or anti-malarial treatment will be included in the AE listing only.

7.9.1.1 Solicited AEs

Solicited AEs will be reported in a listing by participant ID, and treatment group, for the Safety population. The listing will contain; the dose (whether first or repeat dose, for participants in Part A), days of memory aid card, category (injection site or systemic body symptoms), symptoms and results, and/or integrator's assessment of serious symptoms. Injection site and systemic symptoms will be further summarized as stipulated below.

7.9.1.1.1 Injection Site Symptoms

Injection site symptoms will be evaluated for participants receiving treatment via SC dosing for the Safety population. Redness and swelling, 'mild,' 'moderate,' and 'severe' categories are based on the largest diameter of the redness or swelling reported in mm: Mild = 25 to < 50 mm; Moderate = ≥ 50 to < 100 mm; Severe = ≥ 100 mm (refer to the 'Site Reactions to Injections and Infusions' table [DAIDS 2017]).

The following summaries will be generated for injection site symptom events within 8 days post-dose:

1. At least one symptom with highest intensity over the 8 reporting days
    - Number and percentage of participants with injection site symptom events (any intensity) and by intensity grade after first dose for Part A and Part B
    - Number and percentage of participants with injection site symptom events (any intensity) and by intensity grade after second dose for Cohorts 2 and 3
2. Number of participants with symptom events per day
    - Number and percentage of participants with any injection site symptom events at each day after first dose for Part A and Part B
    - Number and percentage of participants with any injection site symptom events at each day after second dose for Cohorts 2 and 3
3. Duration of injection site symptom over the 8 reporting days
    - After first dose for Part A and Part B
    - After second dose for Cohorts 2 and 3
4. Reported redness and swelling diameter values will be summarized descriptively by treatment group and visit

7.9.1.1.2 Systemic Body Symptoms

Systemic body symptoms will be summarized for participants by number and percentage by treatment group in the Safety population, and separately by Part A and Part B. The systemic body symptoms will be summarized by each symptom, and the intensity grading of the symptom and any reported symptom within the 8 days of reporting on the memory aid card.

Grading for fever is as follows: Mild = 38.0 to < 38.6 C; Moderate = ≥ 38.6 to < 39.3°C; Severe = ≥ 39.3 to < 40 C; Life-threatening = ≥ 40°C (refer to the 'Site Reactions to Injections and Infusions' table [DAIDS 2017]).

The following summaries will be generated for systemic body symptom events within 8 days post-dose:

1. At least one symptom with highest intensity over the 8 days post-dose
    - Number and percentage of participants with systemic body symptom event (any intensity) and by intensity grade after first dose for Part A and Part B
    - Number and percentage of participants with systemic body symptom event (any intensity) and by intensity grade after second dose for Cohorts 2 and 3

2. Number of participants with symptom events per day
    - Number and percentage of participants with any systemic body symptom event at each day after first dose for Part A and Part B
    - Number and percentage of participants with any systemic body symptom event at each day after second dose for Cohorts 2 and 3

7.9.2 Clinical Laboratory

Clinical laboratory assessments are collected as described in Section 3.7.1.

For Part A and B respectively, the following summary tables will be created for the Safety population:

- The observed value and change from baseline (CFB) at each scheduled post-baseline visit by treatment group for each parameter
- The observed post-CHMI values and change from pre-CHMI baseline at each scheduled post-CHMI visit by treatment group for each parameter
- Toxicity grade shift tables from baseline (defined as last non-missing assessment prior to first treatment) to worse post-baseline grade (which may occur at an unscheduled visit) by treatment group for each parameter
- Toxicity grade (DAIDS 2017) shift tables from baseline (defined as last non-missing assessment prior to first treatment) to each scheduled post-baseline visit for participants with toxicity grade ≥ 1 at post-baseline
- Shift table with low (L), normal (N), and high (H) results from baseline (defined as last non-missing assessment prior to first treatment) and each scheduled post-baseline visit by treatment group for each parameter

Percentages will be based on the number of participants with both a baseline and post-baseline (at the specified visit) assessment of the summarized laboratory parameter.

Box and Whiskers plot will be produced for all laboratory parameters by trial part, treatment group, and time point. Separate plots will be provided for each laboratory category including hematology, serum chemistry, and CMP.

A longitudinal individual spider plot with reference lines for normal range will be produced for selected Hematology, serum chemistry and CMP parameters by treatment group and timepoint. The plots will be presented for both the absolute (actual) values, percentage CFB values and percentage change from pre-CHMI baseline, with the same y-axis number scale for all plots produced.

Additionally, a listing of the CMP data will be reported by treatment group for the Safety population.

7.9.3 Vital Signs

Vital signs are collected as described in Section 3.7.2.

For Part A and Part B separately, observed values and CFB, observed post-CHMI values and change from pre-CHMI baseline will be summarized at each scheduled visit, by treatment group and parameter for the Safety population. Additionally, the number and percentage of participants with potentially clinically important results will be summarized at each visit by treatment group and parameter.

A longitudinal individual spider plot will be produced for selected vital signs parameters by treatment group and timepoint.

The following potentially clinically important criteria will be followed:

Table 8. Criteria for Clinical Importance: Vital Signs and Weight

Parameter	Criterion
Pulse rate	≥ 100 bpm and increase of ≥ 15 bpm and ≥ 30 bpm, ≤ 55 bpm and decrease of ≥ 5 bpm and ≥ 10 bpm
Systolic blood pressure	≥ 140 mmHg and increase of ≥ 10 mmHg and ≥ 15 mmHg, ≤ 90 mmHg and decrease of ≥ 5 mmHg and ≥ 10 mmHg
Diastolic blood pressure	≥ 91 mmHg and increase of ≥ 15 mmHg and ≥ 30 mmHg, ≤ 50 mmHg and decrease of ≥ 5 mmHg and ≥ 10 mmHg
Body Temperature*	> 38.0°C or < 36.0°C
Weight	± 7% relative to baseline
* Overall (CFB) and Post-CHMI windows	

7.9.4 Physical Examinations

Focused physical examinations abnormal findings by body system will be summarized by number and percentage of participants, by treatment group for Part A and B separately. The denominators for percentages will be the number of patients with non-missing data in each cohort for the Safety population.

A shift table with normal, abnormal, clinically significant and abnormal, not clinically significant results from baseline to each scheduled post-baseline visit by treatment group for each parameter will be presented. The denominators for percentages will be the number of patients with non-missing data for both baseline and post-baseline visits.

Focused physical examinations are collected as described in Section 3.7.2.

Full physical examination data and focused physical examination data will be reported in separate listings, by treatment group for the Safety population.

7.9.5 Electrocardiograms

Electrocardiogram will be performed for Part A at the Screening visit and 24 hours post-trial intervention administration, and at the Screening visits for CHMI and Part B. The results will be reported for Part A and B separately in a listing by treatment group, for the Safety population.

For Part A and Part B separately, observed values and CFB will be summarized at each scheduled visit, by treatment group and parameter for the Safety population. Additionally, the number and percentage of participants with potentially clinically important results will be summarized at each visit by treatment group and parameter.

Normal, abnormal, clinically significant and abnormal, not clinically significant results from baseline to each scheduled post-baseline will be presented in a listing by treatment group, for the Safety population.

Normal electrocardiogram ranges are as follows:

Parameter	**Normal Range**
PR Interval	120 - 200 inclusive
QRS duration	≤ 110
QT	< 500
QTcB	(< 430 msec) for males/ (< 450 msec) for females

8 REFERENCES

1. Epstein JE, Rao S, Williams F, et al. 2007. Safety and clinical outcomes of experimental challenge of human volunteers with Plasmodium falciparum-infected mosquitoes: an update. J Inf Diseases, 196:145-154.

2. U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 [July 2017]. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

9 APPENDICES

Appendix 1. Schedule of Assessments and Procedures

Table 9. 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								W1	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 to -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			+ 7 D	+ 10 min	+ 10 min	+ 10 min	± 2 H	± 2 H	± 2 H	± 2D	± 2D	± 2D	± 2D	± 2D	± 2D	± 2 D	± 2 D	± 2 D	± 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																				

Trial Period	Screen	Trial Drug Administration[1]								Follow-up													ED[2]
Weeks[3] in Trial		W 0								W1	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 to -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			+ 7 D	+ 10 min	+ 10 min	+ 10 min	± 2 H	± 2 H	± 2 H	± 2D	± 2D	± 2D	± 2D	± 2D	± 2D	± 2 D	± 2 D	± 2 D	± 7D	± 7D	± 7D	± 7D	
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 after 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 7 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 10.
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 Vital 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 Day 0 EOI, Hr 1, and Hr 3.
16 PK Serum samples will be collected for all participants in Part A.
17 [redacted]
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 diary 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 12 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 AEs related to Screening procedures should be captured and reported.

Table 10. 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 H24	W31 D7	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 D	± 2 H	± 2 H	± 2 D			± 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						
Diary 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

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 7 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.
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 11. Schedule of Activities for Dose Expansion Cohort (Part B; Cohort 6)

Trial Period	Screen	Trial Drug Administration[1]			Follow-Up							ED[2]
No. of Days or Weeks in Trial[3]	D -60 to D -2	D -7 to -1[4] (Pre-dose)	D0	D0 H 2	D 3	W 1 D 7	W 1 D 10	W 4 D 28	W 4[5] D 34	W 9 D 63	W 12 D 84	
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, Weight[6]	X											
HIV Antibody, Hepatitis B & C test	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 Venos Serum[19]		X			X	X	X	X	X[19]	X	X	X
ADA VAMS Capillary Blood [20]		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 7 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 Counselling form when pregnancy tests are performed.
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 Counselling 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 Day 0 post-dose and will be reviewed at each visit following administration of the product up to 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 in the Protocol.
21 Groups 1, 2, and 3 will undergo CHMI procedures on Week 5. See Protocol Table 11 for the CHMI procedure SoA.

Table 12. 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 D**	**± 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 +/- 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 Counselling form when pregnancy tests are performed.

7 Capillary blood PK samples will continue to be collected during this CHMI observation phase as per Protocol Table 8 and Protocol 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 2 positive qRT-PCR or 1 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 CO2, chloride, blood urea nitrogen, creatinine, glucose (random), ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin.

14 Empiric anti-malarial treatment will be given on Day 27 for those CHMI participants not previously diagnosed with malaria infection.

Table 13. 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	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 in the Protocol.

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 anti-malarial treatment will be given on Day 27 for those CHMI participants not previously diagnosed with malaria infection.

Appendix 2. Imputation of Partial Dates

Table 14. Imputation Rules for Partial Dates – Adverse Events

Parameter	Missing	Additional Condition	Imputation
Start Date	D only	M and Y are prior to first trial intervention dosing	First day of indicated month
		M and Y is same as first trial intervention dosing	Date of first trial intervention dosing
		M and Y are after first trial intervention dosing	First day of indicated month
	M and D	Y is prior to first trial intervention dosing	01 Jan of indicated year
		Y is same as first trial intervention dosing	Date of first trial intervention dosing
		Y is after first trial intervention dosing	01 Jan of indicated year
	M, D, and Y	-	assumed to be TEAE
End Date	D only	M and Y are prior to last trial intervention dosing	Last day of indicated month
		M and Y is same as last trial intervention dosing	Date of last observation
		M and Y are after last trial intervention dosing	First day of indicated month
	M and D	Y is prior to last trial intervention dosing	31 Dec of indicated year
		Y is same as last trial intervention dosing	Date of last observation
		Y is after last trial intervention dosing	01 Jan of indicated year
	M, D, and Y	-	TEAE is ongoing
	-	Estimated end date is before a complete or imputed AE start date	Last day of the month of AE start date

Note: The imputation of end date must be later than start date
D = day; M = month; Y= year; TEAE = treatment-emergent adverse event.

Table 15. Imputation Rules for Partial Dates – Prior and Concomitant Medications

Parameter	Missing	Additional Condition	Imputation
Start Date	D only	M and Y same as M and Y of first trial intervention dosing	Date of first trial intervention dosing
		M and/or Y not the same as M and Y of first trial intervention dosing	First day of indicated month
	M and D	Y same as Y of first trial intervention dosing	Date of first trial intervention dosing
		Y not the same as Y of first trial intervention dosing	01 Jan of indicated year
	M, D, and Y	none – date completely missing	Date of first trial intervention dosing
End Date	D only	M and Y same as M and Y of last trial intervention dosing	Date of last trial intervention dosing
		M and/or Y not the same as M and Y of last trial intervention dosing	Last day of indicated month
	M and D	Y same as Y of last trial intervention dosing	Date of last trial intervention dosing
		Y not the same as Y of last trial intervention dosing	31 Dec of indicated year
	M, D, and Y	none – date completely missing and not ongoing	Date of last trial intervention dosing

D = day; M = month; Y = year.

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