Statistical Analysis Plan

Protocol Title	Clinical investigation study to evaluate the consistency and reproducibility of two consecutive mosquito feeding assays in adults with varying Plasmodium falciparum gametocyte densities.
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REVISION HISTORY

Version	Date	Summary of revision
v1.0	09MAR2022	First version for approval

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LIST OF ABBREVIATIONS

Acronym	Definition
CSR	Clinical study report
CI	Confidence interval or Credible interval.
DSFA	Direct skin feeding assay
IRB	Institutional review board
KEMRI	Kenya Medical Research Institute
MoH	Ministry of health
OR	Odds ratio
PI	Principal Investigator
PCR	Polymerase chain reaction
qPCR	Quantitative polymerase chain reaction
RDT	Rapid diagnostic test
RT-PCR	Real time polymerase chain reaction
SMFA	Standard membrane feeding assay
TRIs	Transmission reducing interventions
USAMRD-A	United States Army Medical Research Directorate - Africa
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research

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1 INTRODUCTION

This statistical analysis plan (SAP) for "Clinical investigation study to evaluate the consistency and reproducibility of two consecutive mosquito feeding assays in adults with varying Plasmodium falciparum gametocyte densities" (PATH protocol CVIA-085) describes and expands upon the statistical information presented in the protocol.

This document describes all planned analysis and provides reasons and justifications for these analyses, including sample tables, figures and listings. The structure and content of the SAP provide sufficient detail to meet the requirements identified by ICH. Any deviation from this SAP will be described and justified in protocol amendments and/or in the Clinical Study Report (CSR), as appropriate.

1.1 BACKGROUND AND RATIONALE

New tools are needed to accelerate the path toward eventual elimination of *Plasmodium falciparum* malaria. Interventions, such as vaccines, drugs, or biologics which can break the cycle of malaria parasite transmission between humans and mosquitoes, are viewed as being of particular importance in this regard and are endorsed by the WHO (1). Such interventions harbor the potential to prevent mosquitoes from becoming infected with parasites, even after feeding on infectious individuals, thereby breaking the cycle of transmission.

One of the more novel strategies being pursued is the interruption of transmission of malaria parasites through the mosquito vector, thereby reducing the number of secondary infections (2). The transmission of malaria requires the survival and development of *Plasmodium* parasites within the vertebrate host and the mosquito vector. Female anopheline mosquitoes ingest the sexual stage gametocytes when taking a blood meal from infectious vertebrate hosts. Within the mosquito's midgut, the parasite must overcome both the vector's innate defense mechanisms and the vertebrate host's immune mechanisms that include anti-parasite antibodies found within the blood meal following a mosquito bite (3). The conserved nature of the parasite's proteins expressed in the sexual stages, not under natural selective pressure, renders the sexual stages of the parasite attractive targets for transmission reducing interventions (TRIs).

TRIs interfere with this process of parasite transmission from the vertebrate host to the vector in various ways. Anti-malarial drugs could reduce gametocyte carriage or infectivity directly by killing circulating gametocytes in human blood, or human antibodies directed against gametocyte-specific surface proteins could prevent sporogonic development within the mosquito's midgut, preventing sporozoite formation.

There are several methods to measure the transmissibility of parasites to mosquito:

- The Standard Membrane Feeding Assay (SMFA) has been used by groups worldwide, and measures whether a drug or antibody added exogenously to an in vitro assay can completely block the development of *P. falciparum* malaria parasites in the

Anopheles mosquito when quantified early as oocyst stage parasites (days 7 to 9), or later as sporozoites within the mosquito salivary glands (days 14-21). The SMFA was developed from an experimental laboratory protocol that measures in vitro the inhibition of transmission of malaria parasites to their vectors (4,5) when a test drug, biologic, or antibody-containing sera are introduced. Although the SMFA assay is considered to be a surrogate assay that would recapitulate the activity as it would occur in vivo in a human host given the intervention, the assay does not directly involve the testing within a human volunteer provided a drug, biologic, or vaccine, and therefore direct linkage between the SFMA and an effect in vivo would need to be evaluated in future trials comparing and bridging the in vitro SMFA to assays that measure the same intervention in vivo. The present study does not include SMFA testing.

- The Direct Skin Feeding Assay (DSFA) has been developed to measure the transmissibility of parasites directly from human-to-mosquito without an in vitro membrane step as illustrated below. Although DSFA is biologically more relevant with regard to the functional activity that a drug/antibody has on malaria transmission, the assay is complex, requiring human volunteers and the inherent variability in human hosts, parasite strains, and anopheline vector competencies rendering regulatory approval for such an approach untenable. The DSFA is desirable since it closely mimics what would happen in nature, but also has important drawbacks: (i) the number of mosquitoes that can be fed on a human at any one time is restricted (~<30 per skin feed) by volunteer acceptability. (ii) it is difficult to quantify the number of gametocytes circulating in the human blood and in blood meal from a mosquito after they have fed on the human host. (iii) the DSFA may not be ethically used in certain age groups (i.e. young children) depending upon country-specific and community acceptability; (iv) the DSFA can be affected by inter-individual variation in innate attractiveness to mosquitoes; the DSFA is limited to geographical locations with a source of gametocyte-positive *P. falciparum*-infected persons and advanced laboratory and insectary support.
- The Direct Membrane Feeding Assay (DMFA) is an assay that is positioned between the SMFA and DSFA. In the DMFA, instead of using cultured gametocytes of a single strain of *P. falciparum* as in the SMFA, venous blood samples from gametocytemic individuals previously administered with anti-malarial drugs or antibodies are placed into a membrane feeder and fed to mosquitoes. Such an assay illustrated below is performed in malaria endemic regions with direct access to naturally infected gametocyte carriers and advanced laboratory support and insectary facilities. In the DMFA, oocysts in the mosquito midgut and sporozoites in the salivary glands are quantified.

It is crucial that variation in DSFA and DMFA be measured by quantifying the prevalence of infected mosquitoes and/or oocyst density in the mosquitoes at two sequential time points. The data obtained from this study will inform the methodology for future field studies of TRIs.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 STUDY OBJECTIVES

2.1.1 Primary Objective

- To assess variation in the proportion of infected mosquitoes with at least one oocyst (oocyst prevalence) in DSFA performed at two consecutive time points in the same human subject with *P. falciparum* gametocytemia using microscopy.

- To assess variation in the proportion of infected mosquitoes with at least one oocyst (oocyst prevalence) in DMFA performed at two consecutive time points in the same human subject with *P. falciparum* gametocytemia using microscopy.

2.1.2 Secondary Objective

- To assess variation in oocyst density in DSFA at two consecutive time points in the same subject using microscopy.

- To assess variation in oocyst density in DMFA at two consecutive time points in the same subject using microscopy.

- To assess variation in the proportion of infected mosquitoes with at least one sporozoite (sporozoite prevalence) in DSFA at two consecutive time points in the same subject using microscopy.

  To assess variation in the proportion of infected mosquitoes with at least one sporozoite (sporozoite prevalence) in DMFA at two consecutive time points in the same subject using microscopy.

2.1.3 Exploratory Objectives

- To assess variation in oocyst prevalence in DSFA at two consecutive time points in the same subject using qPCR.

- To assess variation in oocyst density in DSFA at two consecutive time points in the same subject using qPCR.

- To assess variation in sporozoite prevalence in DSFA at two consecutive time points in the same subject using qPCR.

- To assess variation in sporozoite density in DSFA at two consecutive time points in the same subject using qPCR.

- To assess variation in oocyst prevalence in DMFA at two consecutive time points in the same subject using qPCR.

- To assess variation in oocyst density in DMFA at two consecutive time points in the same subject using qPCR.

- To assess variation in sporozoite prevalence in DMFA at two consecutive time points in the same subject using qPCR.

- To assess variation in sporozoite density in DMFA at two consecutive time points in the same subject using qPCR.

- To evaluate persistence of gametocytemia at two consecutive time points

  To evaluate the effect of gametocytemia measured by qPCR in oocyst prevalence in DMFA and DSFA in two consecutive time points in the same subject using optical microscopy

2.2 STUDY ENDPOINTS

2.2.1 Primary Endpoint

- Change in oocyst prevalence between baseline visit DSFA and final visit DSFA performed on the same human using microscopy.

- Change in oocyst prevalence between baseline visit DMFA and final visit DMFA performed on the same human using microscopy.

2.2.2 Secondary Endpoints

- Change in oocyst density between baseline visit DSFA and final visit DSFA performed on the same human using microscopy.

- Change in oocyst density between baseline visit DMFA and final visit DMFA performed on the same human using microscopy.

- Change in sporozoite prevalence between baseline visit DSFA and final visit DSFA performed on the same human using microscopy.

- Change in sporozoite prevalence between baseline visit DMFA and final visit DMFA performed on the same human using microscopy.

2.2.3 Exploratory Endpoints

- Change in oocyst prevalence between baseline visit DSFA and final visit DSFA performed on the same human using qPCR.

- Change in oocyst density between baseline visit DSFA and final visit DSFA performed on the same human using qPCR.

- Change in sporozoite prevalence between baseline visit DSFA and final visit DSFA performed on the same human using qPCR.

- Change in sporozoite density between baseline visit DSFA and final visit DSFA performed on the same human using qPCR

- Change in oocyst prevalence between baseline visit DMFA and final visit DMFA performed on the same human using qPCR.

- Change in oocyst density between baseline visit DMFA and final visit DMFA performed on the same human using qPCR.

- Change in sporozoite prevalence between baseline visit DMFA and final visit DMFA performed on the same human using qPCR.

- Change in sporozoite density between baseline visit DMFA and final visit DMFA performed on the same human using qPCR

- Estimation of the proportion of subjects that continue being positive for gametocytemia at baseline and at baseline and final visit

  Evaluate the relationship between the presence of detectable gametocytemia by qPCR before the assay and the oocyst prevalence using microscopy.

3 INVESTIGATIONAL PLAN

3.1 TRIAL DESIGN

This is a clinical study with an entomological component. Study participants will be recruited to participate in mosquito feeding assays. The proposed trial design has been developed to assess the consistency and reproducibility of two consecutive direct skin feeding assays (DSFA and DMFA) across a 24-hour interval. The Figure 1 shows the experimental medicine clinical study design and the Table 1 shows the procedures for each one of the three planned visits.

Figure 1: Experimental medicine clinical study design

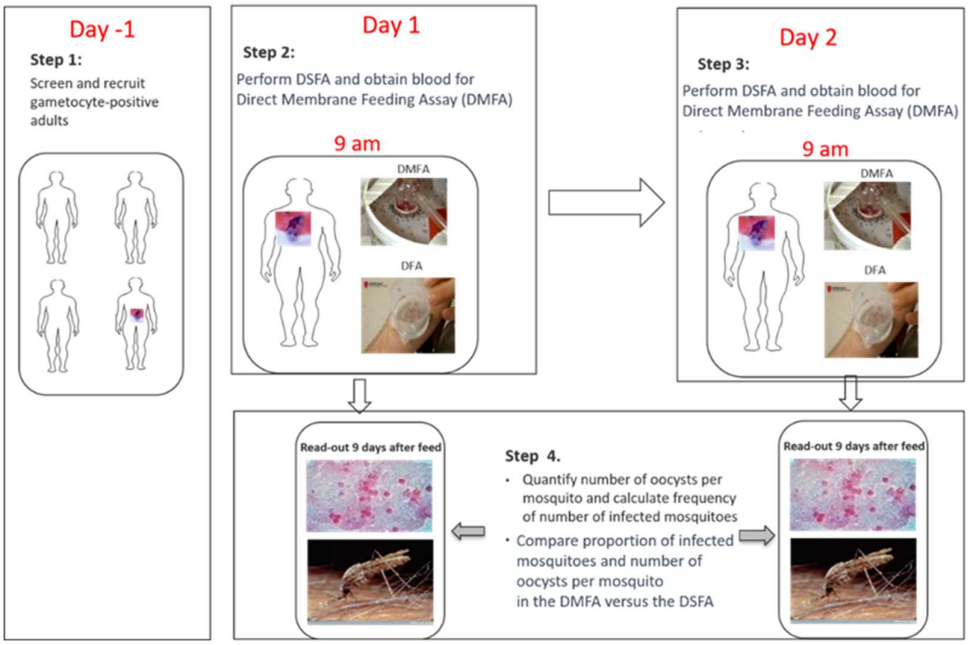

Table 1 Procedures and visits

Procedures	Visit Day -1 to 0 (Screening)	Visit Day 1 (Baseline/Enrollment)	Visit Day 2 (Final)
Window (hours)	–	–	+/-3
Obtain informed consent of potential participant	●		
Obtain demographic information	●		
Obtain medical history	●		
Obtain medications history	●		
Perform medical examinations	●	●	●
Collect blood for gametocyte detection tests (2 mL) by PCR	●		
In females, urine pregnancy test	●		●
Verify inclusion/exclusion criteria	●	●	●
Verify gametocyte detection (RT-PCR) test results		●	
Record vital signs	●	●	●
Blood sample for serology – 5 mL*		●	
Blood sample for DMFA and microscopy (1ml)		●	●
DSFA		●	●
Admit the study participant for observation overnight		●	
Record local and unsolicited AEs as reported by participant or observed by investigator before DSFA and 30 minutes after DSFA		●	●
Administer low dose primaquine* and first dose of Coartem® and give remaining Coartem® dose with instructions			●

3.2 SELECTION OF STUDY POPULATION

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Provision of signed or thumb printed and dated informed consent form.
- Stated willingness to comply with all study procedures and availability for the duration of the study.
- Male or female aged between 18 years and 55 years inclusive.
- Resident within the study area.
- In good general health as evidenced by medical history and clinical examination before entering the study.
- Ability to take oral Coartem and low dose primaquine anti-malarials upon conclusion of day 2 (2nd direct skin feed) and be willing to adhere to the medication regimen.
- For females, she must be of non-childbearing potential or use appropriate measures to prevent pregnancy for 30 days after receiving Coartem and primaquine. Non-childbearing potential means she is surgically sterilized or at least one year post-menopausal. Appropriate measures to prevent pregnancy include abstinence or adequate contraceptive precautions (i.e., intrauterine contraceptive device; oral contraceptives; diaphragm or condom in combination with contraceptive jelly, cream, or foam; Norplant or Depo-Provera).
- For males, he must be willing to ensure that he does not get his partner(s) pregnant for at least 3 months after treatment with primaquine. Appropriate measures to prevent pregnancy include abstinence or adequate contraceptive precautions in either the participant or the partner.
- Positive for P. falciparum gametocytes as measured by PCR with CT value < 31.

An individual who meets any of the following criteria will be excluded from participation in this study:

- Presence of any signs or symptoms of malaria.
- Presence of contraindications to administration of Coartem and primaquine as indicated in the respective drug package inserts.
- History of severe allergic reactions to mosquito bites (other than pruritus and local swelling).
- Pregnant (i.e., a positive pregnancy test).
- Current or recent (within the preceding 2 weeks) use of antimalarial treatment.
- Current participation in a malaria vaccine study.
- Any other findings that the investigator feels would increase the risk of having an adverse outcome from participation in the trial.

3.3 RANDOMIZATION AND TREATMENT ASSIGNMENT

Not Applicable: No investigational product is used on this trial. All enrolled subjects will follow the same procedures.

3.4 BLINDING

Not Applicable. This is an open-label study. The number of survival mosquitoes and prevalence of oocysts and sporozoites using microscopy have been monitored through the study to inform on the quality of the entomological assays.

3.5 PROTOCOL DEVIATIONS

Protocol deviations will be reported by the principal investigator (PI) in a cumulative summary report with each continuing review/progress report and with the study closeout report. Protocol deviations will be classified as Major/Significant if they may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being, or Minor/non-significant otherwise. Protocol deviation will be also classified as subject-specific or not (deviations not related specifically to a subject but rather to an incorrect process, procedure, or issue at the clinic/facility level). A Data Review Meeting attended by the sponsor and investigator representatives before the topline analysis of the primary and secondary endpoints will review the protocol deviations that will exclude participants from the Per Protocol population.

3.6 VARIABLES

3.6.1 Parasitological outcomes on mosquitoes

- Oocyst prevalence: defined as the proportion of mosquitoes in a cup with at least one oocyst detected in the mid-gut among the surviving mosquitoes (in the same cup) that underwent the feeding assays. It will be estimated by optical microscopy and by PCR. Negative PCR will have as a value equal or greater than 39. (CT≥39 or CT = Undetermined)

- Oocyst density: defined as the mean number of oocysts detected in the surviving mosquitoes that underwent feeding assays on the same subject. Non-infected mosquitos will be included as having zero density (CT≥39 or CT = Undetermined) It will be measured by optical microscopy and PCR. By microscopy, the numerator will be the sum of observed oocysts. By PCR, the numerator will be the sum of each mosquito number of cycles minus the number of maximum of cycles in the assay plus one:
  by Optical microscopy: $(\sum oocysts)/(\sum surviving\ mosquitoes)$
  by PCR: $(\sum(38 - Number\ of\ cycles + 1))/(\sum surviving\ mosquitoes)$

- Sporozoite prevalence: defined as the proportion of mosquitoes in a cup with at least one sporozoite detected in the salivary glands among the surviving mosquitoes (in the same cup) that underwent the feeding assays. It will be estimated by optical microscopy and by PCR. Negative PCR will have as a value equal or greater than 39. (CT≥39 or CT = Undetermined)

- Sporozoite density: Defined as the mean number of sporozoites detected in surviving mosquitoes that underwent feeding assays on the same subject. Not infected mosquitoes will be included as having zero density (CT≥39 or CT = Undetermined). It will be measured by qPCR. The numerator will be the sum of each mosquito number of cycles minus the number of maximum of cycles in the assay plus one: PCR: $(\sum(38 - Number\ of\ cycles + 1))/(\sum surviving\ mosquitoes)$

3.6.2 Parasitological outcomes on the participant

- Gametocytemia Prevalence: Defined as the proportion of subject with gametocytes detected in peripheral blood by qPCR. Positive qPCR is defined as having CT < 39 for PLU gen and either pf16 or pf25 gens.

3.6.3 Safety Variables

3.6.3.1 Adverse events

Local solicited AEs, as defined in this protocol, include pruritus and erythema at the site of the mosquito bite in a study participant following DSFA on days 1 and 2.

Unsolicited AEs will be AEs captured in study participants after informed consent is obtained and until the subject completes all study procedures.

For AEs, the following guidelines will be used to describe severity.

- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events prevents a participant's usual daily activity.

3.6.3.2 Serious Adverse events

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Serious adverse events will be classified as expected or unexpected and related or unrelated to the study procedures.

4 SAMPLE SIZE AND POWER CONSIDERATIONS

This is a clinical investigation study where there is no prior knowledge related to the oocyst prevalence or density on a repeated DSFA or DMFA in a human subject. As such, the sample size chosen for this study was primarily based on logistical and budgetary considerations that would estimate the variability in DSFA. The results of this experimental medicine trial would be to ascertain the feasibility of using a paired "before-after" study design in same individual in a future trial when a TRI that have a result observed in less than 24h is introduced.

There are two unknowns and a major constraint in arriving at a meaningful sample size for the current trial challenging. First, there are no prior data in metrics of DSFA in same person at 2 consecutive time points. Secondly, there is a wide range of initial gametocyte densities in persons at baseline screening which may markedly influence the transmission and development of parasites from man-to-mosquito and detection of oocysts in the mosquito midgut 9 days after a blood meal. Prior data obtained from the same site and same investigators in Kenya indicate that:

Approximately 25% of persons at any one time will have positive *P. falciparum* gametocytes by PCR

Of those that are positive *for P. falciparum* gametocytes and who have undergone DSFA, there will be a distribution of oocyst-positive mosquitoes (defined as positive event) detected 9 days after a mosquito feed as shown in Figure 2.

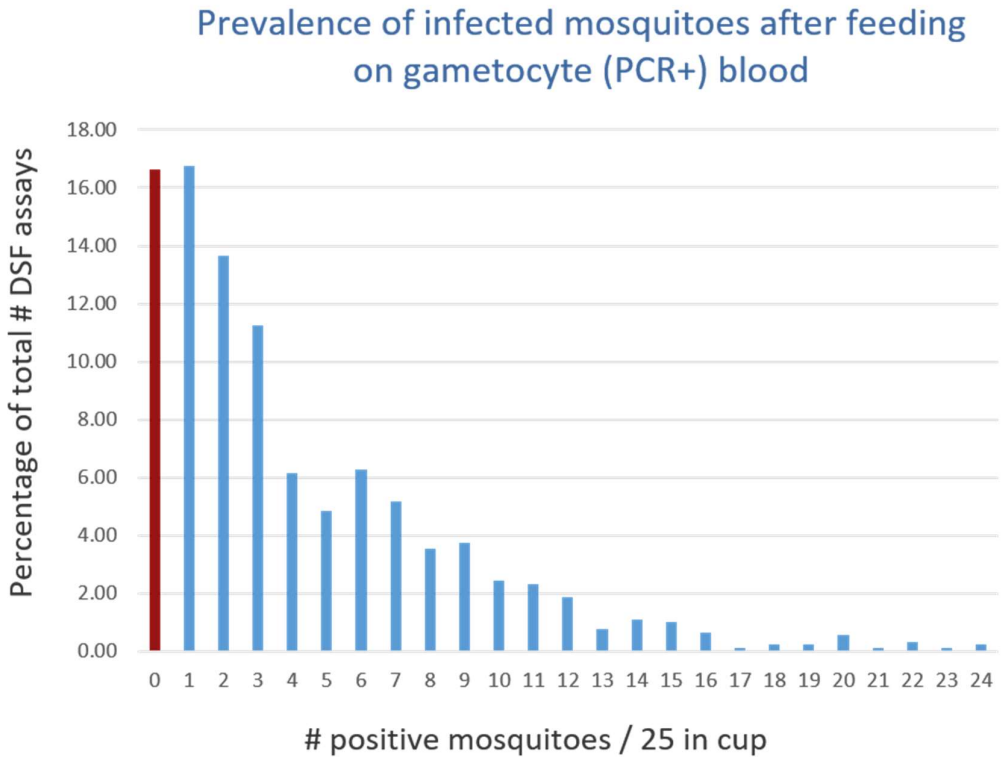

Figure 2: Prevalence of infected mosquitos(6).

As the budget for the trial is constrained, we estimate a sample size below that will have 45 consented individuals out of 180 screened with positive *P. falciparum* gametocytes of whom will have an estimated transmissibility on day 1 indicated in the figure below. It is unknown whether the same level of transmissibility occurs on day 2 in the same person which is the subject of the proposed trial. The sample size proposed below provides for a reasonable and logistically feasible number of subjects (n=36) that will have two consecutive DSFA performed across a range of positive events.

5 GENERAL STATISTICAL CONSIDERATIONS

5.1 GENERAL PRINCIPLES

In general, all analysis will be grouped by day and by method of mosquito feeding. In general, all data will be listed by subject id, day and method of mosquito feeding and when appropriate by visit number within subject. All summary tables will be annotated with the total population size relevant to that table including any missing observations.

Except where otherwise indicated, summary statistics will be composed of the mean, standard deviation, median and the minimum and maximum for continuous variables. For categorical variables, the count and proportion will be presented.

All confidence intervals presented will be 95% and two-sided. For Bayesian analysis, 95% credible interval from the simulated posterior distribution will be presented, as result of at least 10000 simulations and having an effective sample size of at least 1000. P-value below 0.05 will be considered statistically significant. CI will be the abbreviation for credible intervals for Bayesian analysis or confidence intervals otherwise.

P-values will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001" and p-values greater than 0.999 will be reported as ">0.999". The median (except for ties), minimum and maximum will be reported on the same scale as the original value. The mean, standard deviation and CIs will be reported to one additional decimal place. Proportions and percentages will be reported to one decimal and corresponding 95% CIs will be two decimals.

5.2 TIMING OF ANALYSIS

Upon completion of the second DSFA and DMFA for the final participant, a topline analysis will be initiated to include the results of the oocyst prevalence and density analysis, after data lock of this data. Following collection of the remainder of the data and final database lock, all results will be described and presented in a peer reviewed publication.

No interim analysis is planned. No stopping rules are defined for this trial.

5.3 ANALYSIS POPULATION

5.3.1 Enrolled Population

All screened participants who provide informed consent will be included in the Enrolled Population

5.3.2 Full Analysis Population

All participants in the Enrolled Population who participated in at least one direct skin feed will be included in the Full Analysis Population. The population will be dynamically adjusted to the population with responses for the outcomes analyzed. For summaries occurring specifically on day 2, the Full Analysis Population is limited only to those with at least one feed on day 2. For summaries of cross-timepoint differences, only subjects contributing an assay result at both time points will be included. Similarly, for cross-assay results at a given timepoint, only subjects contributing a result for both assays will be included.

5.3.3 Per Protocol Population

All participants in the full analysis population who have no major protocol violations that are determined to potentially interfere with DSFA or DMFA. The criteria for exclusion of participants from the Per Protocol population will be based on review of the protocol deviations and the number of mosquitoes surviving for evaluation at a Data Review Meeting attended by the sponsor and investigator representatives before the topline analysis of the primary and secondary endpoints. If no subjects are excluded from the Per Protocol population, only the Full Analysis population results will be presented

5.4 MISSING DATA AND OUTLIERS

In this experimental medicine study, missing data will be assumed to be missing completely at random, and only observed data collected from participants and available in the appropriate study population will be used for analysis. Graphic inspection for outliers will be performed. Outliers will not be excluded from primary or secondary analysis.

6 STUDY SUBJECTS

6.1 DISPOSITION OF SUBJECTS

{[S]Table 1} Presents the summary of subject disposition including number of subjects that signed informed consent and the summary of the enrollment status including the number of eligible subjects, that undergo assays by day and undergo final visit. A consort diagram will be prepared {[S]Figure 1]}. {[S]Table 2} Summarize the eligibility criteria for subjects screened but not enrolled. The list of subjects that do not meet the inclusion/exclusion criteria is presented in {[S]Listing 1}. The composition of analysis populations is presented in {[S]Listing 2}. A list of subjects by visits is presented in {[S]Listing 3]}

6.2 PROTOCOL DEVIATIONS

Protocol deviation will be listed in {[S]Listing 4]} categorized as major/minor and summarized in {[S]Table 3}

6.3 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Baseline characteristics will be presented for full analysis population. The following variables will be summarized as categorized in the CRF, except age that will use the already calculate variable of age in years from the CRF if available or calculated as the number of complete years since date of birth and the date of screening {[S]Table 4}

- Age
- Gender
- Ever had malaria?
- Time since last episode of malaria
- Was last episode of malaria confirmed by an RDT or any other laboratory test?
- Mode of treatment
- Malaria treatment taken for last episode of malaria.
- Time since last malaria medication taken.

7 ANALYSIS OF ENTOMOLOGICAL OUTCOMES

7.1 PRIMARY AND SECONDARY ANALYSIS

For each pair of entomological observations within each participant, the difference in prevalence will be estimated, and 95% CI obtained using the Agresti and Caffo method (7). To evaluate the hypothesis that the average mean difference in the prevalence between two assays within the same subject is zero, combined estimates (weighted mean and variance) will be obtained using as weight the inverse of the variance of each paired difference obtained from the Agresti and Caffo method (See Annex 1 for details on the calculation of the confidence intervals and the weights for the combined estimation)

The {[S]Table 5}summarizes the oocyst's prevalence by day and feeding method. The Intra Class Correlation (ICC) is estimated by maximum likelihood as the overdispersion parameter of a beta-binomial distribution. The {[S]Figure 2, [S]Figure 3, [S]Figure 4 and [S]Figure 5]} show the scatterplot of the prevalence by day and by feeding method. The {[S]Table 7, [S]Table 8, [S]Table 9, [S]Table 10}presents the paired differences between days by method. The {[S]Table 11} presents the summary of the combined estimations for each comparison. Forest plot for the estimated differences is presented in {[S]Figure 6, [S]Figure 7, [S]Figure 8, [S]Figure 9]}.

For each assay, the confidence intervals of the difference of proportion between days will indicate if there is any systemic difference between days within each assay, while the coefficient of variation of the within-assay between-day differences will provide information on assay repeatability.

The prevalence of sporozoites by optical microscopy will be analyzed using the methods described for the prevalence of oocysts {[S]Table 5, [S]Table 12, [S]Table 13, [S]Table 14, [S]Table 15, [S]Table 16}

A descriptive analysis by time point and assay of the oocyst density estimated by Optical microscopy will be presented {[S]Table 5}. Difference between days will be evaluated using zero inflated Poisson regression models having as outcome the number of oocysts, as offset the number of surviving mosquitoes, a random effect by subject at the intercept and day as fixed effects, with independent models for each assay {[S]Table 17}. If the model does not fit because characteristics of the data, alternative methods will be evaluated and explained.

Entomological results by optical microscopy will be listed in [[S]Listing 5]

7.2 EXPLORATORY ANALYSIS

Prevalence and density of oocysts and sporozoites determined by PCR will be analyzed using the same methodology described for the primary and secondary endpoint {[S]Table 18, [S]Table 19, [S]Table 20, [S]Table 21, [S]Table 22, [S]Table 23, [S]Table 24, [S]Table 25, [S]Table 26, [S]Table 27, [S]Table 28}. Zero inflated Poisson models will be fitted for the Oocyst density and for the Sporozoite density {[S]Table 29}. Entomological results by PCR will be listed in [[S]Listing 6].

The proportion of positive subjects with gametocytemia at baseline visit and at both baseline visit and final visit, accompanied with Clopper-Pearson confidence intervals are presented in {[S]Table 30}. Results of the gametocytemia are listed in {[S]Listing 7}. Descriptive analysis of the Oocyst Prevalence and density will be stratified by the presence of gametocytemia before the assay{[S]Table 6}

The probability of a mosquito infection and the dispersion of the probability within assay may vary by day or by method of feeding, and it can be dependent or independent by day within the same subject. To analyze at the same time the difference between methods of feeding, the difference between days and the association between days, as well as to consider that the number of surviving mosquitos, the probability of infection and the dispersion of the probability of infection may vary between assays, a beta-binomial model of number of infected mosquitos by subject, assay and day will be fitted using a Bayesian framework. In this Bayesian analysis, the prevalence of oocyst will allow the estimation of the probability of mosquito infection by day and by feeding method.

The Bayesian model is described in the Annex 2. Additional exploratory models assuming constant dispersion between assays and days as well as considering the effect of gametocytemia positivity before the assay in the probability of infection will be fitted and presented. The mean, median and their corresponding 95% credible intervals will be obtained from the simulated posterior distribution of parameters, based on at least a total of 10000 iterations of the model, using 4 chains with different starting point, and having at least 1000 effective sample size. 95% credible intervals will be based on the 2.5 and 97.5 centile of the posterior distribution. Models will be presented following the {[S]Table 31}. Convergence of

the models will be inspected using trace plots by chain, density plot by chain comparing partial and full chains Running mean by chain, Potential scaling factor, Shrinkage of potential scale reduction factors and Geweke Diagnostics {[S]Figure 10]}. If necessary, more iterations will be run.

This Bayesian model complements the analysis of the primary objective as it will inform the change of the prevalence within each subject considering the number of surviving mosquitos and will provide insight on the distribution of the probability of mosquito infection.

8 ANALYSIS OF SAFETY DATA

All safety assessments will take place in the Full Analysis Population. All subject-level percentages will be supplemented with two-sided 95% CIs computed via the Clopper-Pearson method. Summaries will include all events occurring on or after the date of first skin feed until final visit. When an AE occurs more than once for a subject, the subject will be only counted once for the corresponding preferred term according to the maximum severity of the event. All unsolicited AEs, including serious and/or severe AEs will be coded according to the according to the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 or later.

Overall safety profile is presented in {[S]Table 32} Summaries and lists are presented also for Solicited adverse events (Pruritus and Erythema on the site of mosquito bite) {[S]Table 33, [S]Table 33, [S]Table 34, [S]Table 35}, unsolicited adverse events {[S]Table 36, [S]Table 37, [S]Table 38}, serious adverse events {[S]Table 39}, adverse events by system and preferred term {[S]Table 40}, Vital Signs {[S]Table 41, [S]Listing 9}, and signs and symptoms {[S]Table 42, [S]Listing 10, [S]Listing 11}. Results of pregnancy test and dispensed Coartem® and Primaquine will be listed {[S]Listing 12] and [[S]Listing 13]} respectively.

9 TECHNICAL DETAILS

Shell Tables, Listing and Figures are presented in the Annex 3. Analysis will be made using the SAS system V 9.4 or later with the exception of the Graphs and the Bayesian models that will be fitted in the R statistical Software (8) using the latest version of the rJags package (9) and goodness of fit of the Bayesian model using the ggmcmc package (10). Graph will be made using the ggplot2 package (11). Libraries from package tidyverse will be use to reshape the data (12). Reports will be produce using the R-Markdown package (13–15). All libraries used in the report will be listed with the corresponding version.

10 SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

Sporozoite density is only evaluated by qPCR due to technical limitations and state-of-art. Therefore, the secondary endpoint defined in the protocol for assessing the sporozoite density by optical microscopy is not analyzed. Only the exploratory endpoint that explores the sporozoite density by PCR is included in this analysis. Densities measured by qPCR are

based on the number of cycles instead of the number of parasites as it was not possible to establish a standard curve with a known number of parasites. The objective/endpoint pair designed to evaluate the persistence of gametocytemia and the effect of gametocytemia in the oocyst prevalence are added beginning with this version, and are to be considered exploratory and post hoc. The remaining endpoints have been adapted to match the study objectives.

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ANNEX 1

ESTIMATION OF CONFIDENCE INTERVALS FOR DIFFERENCE OF PROPORTIONS USING THE AGRESTI – CAFFO METHODOLOGY

Point estimate of the difference in proportion within a subject estimated as:

$$d = \frac{x_2}{n_2} - \frac{x_1}{n_1}.$$

Variance of the difference of proportion within a subject is estimated as:

$$v = \frac{\tilde{p}_1(1-\tilde{p}_1)}{n_1+2} + \frac{\tilde{p}_2(1-\tilde{p}_2)}{n_2+2}$$

Where:

$\tilde{p}_1 = \frac{x_1+1}{n_1+2}$, and $\tilde{p}_2 = \frac{x_2+1}{n_2+2}$

x_1 and x_2 are the number of positives mosquitos in group 1 and 2 respectively and

n_1 and n_2 are the number of surviving mosquitos in group 1 and 2 respectively.

The 100(1-α)% confidence interval is estimated as:

$$(\tilde{p}_2 - \tilde{p}_1) \pm z_{\alpha/2}\sqrt{\frac{\tilde{p}_1(1-\tilde{p}_1)}{n_1+2} + \frac{\tilde{p}_2(1-\tilde{p}_2)}{n_2+2}}$$

and limited to be in the interval [-1,1], where z_c is the 1- C quantile of the Standard Normal distribution.

Following common definition for meta-analysis using as weight the inverse of the variance, the combined estimate for the difference in proportions for K subjects is estimated as:

$$w_k = 1/v_k$$

$cd = \frac{\sum d_k w_k}{\sum w_k}$ where d and w are the difference and the inverse of the variance for each pair k respectively

And the weighted variance of the combined estimation is:

$$vcd = \frac{\sum w_k (d_k - cd)^2}{\frac{(K-1)}{K}\sum w_k}$$

$\frac{cd}{\sqrt{vcd}} \sim Normal(0,1)$

The Q test for heterogeneity is estimated as

$$Q = \sum w_k d_k^2 - \frac{(\sum w_k d_k)^2}{\sum w_k} \sim \chi^2_{df=K-}$$

The I2 measured of heterogeneity is estimated as $i^2 = \max\left(0, \left(1 - \frac{K-1}{Q}\right) * 100\right)$

The coefficient of variation for the difference in proportions is calculated as the square root of the variance of the combined estimation divided by the absolute value of the combined estimated difference:

$$CV = \frac{\sqrt{vcd}}{|cd|}$$

ANNEX 2

BETA BINOMIAL BAYESIAN MODEL

Assume the number of infected mosquitoes n from m exposed mosquitos for the subject i the day j and the assay k follows a $Binomial$ distribution as:

$$n_{i,j,k} \sim Binomial(\pi_{i,j,k}, m_{i,j,k})$$

Where the probability π follows a $Beta$ distributions as:

$$\pi_{i,j,k} \sim Beta(\mu_{j,k}, \phi_{j,k})$$

and

$$logit(\mu_{j,k}) = \alpha + \beta_{day} day_j + \beta_{assay} assay_k + \ldots$$
$$\log(\theta_{j,k}) = \gamma + \delta_{day} day_j + \delta_{assay} assay_k$$

where day_j has values of {0,1} for days 1 and 2, respectively, and $assay_k$ has values of {0,1} for assays 1 and 2, respectively.
The Odds Ratio (OR) for mean probability of infection the day 2 vs day 1 is $e^{\beta_{day}}$
the OR for the mean probability of infection for the assay 2 vs 1 is $e^{\beta_{assay}}$
the Relative Change (RC) for the dispersion parameter for day 2 vs day 1 is $e^{\delta_{day}}$
and the RC of the dispersion parameter for the assay 2 vs 1 is $e^{\delta_{assay}}$

The analysis is made using `rjags` which use shape parameters for the $Beta$ distribution. The conversion between precision and shape parameters is as follow:

$$\mu = \frac{shape_1}{(shape_1 + shape_2)}$$

$$\phi = shape_1 + shape_2$$

And

$$shape_1 = \mu * \phi$$

$$shape_2 = (1 - \mu)\phi$$

Non informative priors are given for the parameters $(\alpha, \beta_{day}, \beta_{assay}, \gamma, \delta_{day}, \delta_{assay})$ as $\sim Normal(0, 0.001)$

The Marginal correlation between the probability of infection between assays by day and between days by assay will be estimated using Pearson correlation coefficient.

The model is fit with 10000 simulations of the posterior in 4 independent chains. Library `ggmcmc` is used to check the convergence of the model.

ANNEX 3

SHELL TABLES

[S]Table 1 Summary of enrollment status (Screened population)

	Total
Informed consent Signed	xxx
Eligible	xxx (xx.x%)
Undergo Baseline visit	xxx (xx.x%)
Undergo Final visit	xxx (xx.x%)
Enrolled Population	xxx (xx.x%)
Full analysis population	xxx (xx.x%)
Per Protocol population	xxx (xx.x%)

* Denominator of percentage is the number of subject screened

[S]Table 2 Summary of eligibility criteria (Enrolled population)

	Total
Informed consent signed	xxx
Subjects who met all eligibility criteria	xx (xx.x%)
Subjects who did not satisfy at least one eligibility criterion	xx (xx.x%)
Subject who did not met at least one inclusion criterion	xx (xx.x%)
Provision of signed or thumb printed and dated informed consent form.	xx (xx.x%)
Stated willingness to comply with all study procedures and availability for the duration of the study.	xx (xx.x%)
Male or female aged between 18 years and 55 years inclusive.	xx (xx.x%)
Resident within the study area.	xx (xx.x%)
In good general health as evidenced by medical history and clinical examination before entering the study.	xx (xx.x%)
Ability to take oral Coartem and low dose primaquine anti-malarials upon conclusion of day 2 (2nd direct skin feed) and be willing to adhere to the medication regimen.	xx (xx.x%)
For females, she must be of non-childbearing potential or use appropriate measures to prevent pregnancy for 30 days after receiving Coartem and primaquine. Non-childbearing potential means she is surgically sterilized or at least one year post-menopausal. Appropriate measures to prevent pregnancy include abstinence or adequate contraceptive precautions (i.e., intrauterine contraceptive device; oral contraceptives; diaphragm or condom in combination with contraceptive jelly, cream, or foam; Norplant or Depo-Provera).	xx (xx.x%)
For males, he must be willing to ensure that he does not get his partner(s) pregnant for at least 3 months after treatment with primaquine. Appropriate measures to prevent pregnancy include abstinence or adequate contraceptive precautions in either the participant or the partner.	xx (xx.x%)
Positive for P. falciparum gametocytes as measured by PCR with cT value < 31.	
Subjects that met at least one exclusion criteria	xx (xx.x%)
Presence of any signs or symptoms of malaria.	xx (xx.x%)
Presence of contraindications to administration of Coartem and primaquine as indicated in the respective drug package inserts.	xx (xx.x%)
History of severe allergic reactions to mosquito bites (other than pruritus and local swelling).	xx (xx.x%)
Pregnant (i.e., a positive pregnancy test).	xx (xx.x%)
Current or recent (within the preceding 2 weeks) use of antimalarial treatment.	xx (xx.x%)
Current participation in a malaria vaccine study.	xx (xx.x%)
Any other findings that the investigator feels would increase the risk of having an adverse outcome from participation in the trial.	xx (xx.x%)

* Denominator of percentage is the number of subject screened

[S]Table 3 Summary of protocol deviations

	Total
Protocol deviations	xxx
Major protocol deviations	xx (xx.x%)
Minor protocol deviations	xx (xx.x%)

[S]Table 4 Summary of baseline characteristics (Full analysis population)

Characteristic	Total (N =)
Age (years)	
Mean	xxx.x
SD	xxx.x
Minimum	xxx.x
1st Quartile	xxx.x
Median	xxx.x
3th Quartile	xxx.x
Maximum	xxx.x
Gender	
Male	xx (xx.x%)
Female	xx (xx.x%)
Ever had malaria?	
Yes	xx (xx.x%)
No	xx (xx.x%)
Unknown	xx (xx.x%)
Time since last episode of malaria	
N/A	xx (xx.x%)
<1Week	xx (xx.x%)
≥1-<2 Weeks	xx (xx.x%)
≥2-<4 Weeks	xx (xx.x%)
≥4Weeks	xx (xx.x%)
Was last episode of malaria confirmed by an RDT or any other laboratory test?	
N/A	xx (xx.x%)
Yes	xx (xx.x%)
No	xx (xx.x%)
Mode of treatment for last episode of malaria	
N/A	xx (xx.x%)
In patient	xx (xx.x%)

Outpatient	xx (xx.x%)
Malaria treatment taken for last episode of malaria	
N/A	xx (xx.x%)
None	xx (xx.x%)
ACT	xx (xx.x%)
SP	xx (xx.x%)
AQ	xx (xx.x%)
Quinine	xx (xx.x%)
Other	xx (xx.x%)
Time since last malaria medication taken	
N/A	xx (xx.x%)
Current	xx (xx.x%)
<1Week	xx (xx.x%)
≥1-<2 Weeks	xx (xx.x%)
≥2-<4 Weeks	xx (xx.x%)
≥ 4 Weeks	xx (xx.x%)

N: Number of subjects enrolled

[S]Table 5 Summary of entomology results (Optical microscopy) (Full analysis population)

Outcome	Baseline-DSFA	Baseline-DMFA	Final-DSFA	Final-DMFA
Oocyst prevalence				
N	xx	xx	xx	xx
Mean	xx	xx	xx	xx
SD	x.xx	x.xx	x.xx	x.xx
ICC	x.xxx	x.xxx	x.xxx	x.xxx
Min	x.xx	x.xx	x.xx	x.xx
Median	x.xx	x.xx	x.xx	x.xx
Max	x.xx	x.xx	x.xx	x.xx
Oocyst density				
N	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x
Min	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x
Max	xx.x	xx.x	xx.x	xx.x
Sporozoite prevalence				
N	xx	xx	xx	xx
Mean	x.xx	x.xx	x.xx	x.xx
ICC	x.xxx	x.xxx	x.xxx	x.xxx
SD	x.xx	x.xx	x.xx	x.xx
Min	x.xx	x.xx	x.xx	x.xx
Median	x.xx	x.xx	x.xx	x.xx
Max	x.xx	x.xx	x.xx	x.xx

N: Number of subjects with available data, SD: Standard deviation; ICC Intra class correlation
Min: Minimum value, Max: Maximum value

[S]Table 6 Oocyst prevalence (Optical microscopy) stratified by gametocytemia before feeding (Full analysis population)

	Detectable gametocytemia by qPCR before assay				No detectable gametocytemia by qPCR before feeding			
Outcome	Baseline-DSFA	Baseline-DMFA	Final-DSFA	Final-DMFA	Baseline-DSFA	Baseline-DMFA	Final-DSFA	Final-DMFA
Oocyst prevalence								
N	xx	xx	xx	xx	xx	xx	xx	xx
Mean	xx	xx	xx	xx	xx	xx	xx	xx
SD	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
ICC	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
Min	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
Median	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
Max	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx

N: Number of subjects with available data, SD: Standard deviation; ICC Intra class correlation
Min: Minimum value, Max: Maximum value

[S]Table 7 Paired comparisons in prevalence of Oocyst positivity DSFA Final - Baseline (Optical microscopy) (Full analysis population)

	DSFA Baseline		DSFA Final		Difference in proportions				
Subject	Positive	Negative	Positive	Negative	Point Estimate	LCI	UCI	Weight	Percentage of Weight (%)
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx

Difference in proportion: DSFA Final - DSFA Baseline.

LCI Lower limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology.

UCI Upper limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology

Weight: Inverse of the variance estimated using the Agresti-Caffo methodology

Percentage of Weight: Percentage of the total weight

[S]Table 8 Paired comparisons in prevalence of Oocyst positivity DMFA Final - Baseline (Optical microscopy) (Full analysis population)

	DMFA Baseline		DMFA Final		Difference in proportions				
Subject	Positive	Negative	Positive	Negative	Point Estimate	LCI	UCI	Weight	Percentage of Weight (%)
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx

Difference in proportion: DMFA Final - DMFA Baseline.

LCI Lower limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology.

UCI Upper limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology

Weight: Inverse of the variance estimated using the Agresti-Caffo methodology

Percentage of Weight: Percentage of the total weight

[S]Table 9 Paired comparisons in prevalence of Oocyst positivity Baseline visit (DSFA – DMFA) (Optical microscopy) (Full analysis population)

	DMFA Baseline		DSFA Baseline		Difference in proportions				
Subject	Positive	Negative	Positive	Negative	Point Estimate	LCI	UCI	Weight	Percentage of Weight (%)
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx

Difference in proportion: DSFA Baseline - DMFA Baseline.

LCI Lower limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology.

UCI Upper limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology

Weight: Inverse of the variance estimated using the Agresti-Caffo methodology

Percentage of Weight: Percentage of the total weight

[S]Table 10 Paired comparisons in prevalence of Oocyst positivity Final visit (DSFA – DMFA) (Optical microscopy) (Full analysis population)

	DMFA Final		DSFA Final		Difference in proportions				
Subject	Positive	Negative	Positive	Negative	Point Estimate	LCI	UCI	Weight	Percentage of Weight (%)
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx

Difference in proportion: DSFA Final - DMFA Final.

LCI Lower limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology.

UCI Upper limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology

Weight: Inverse of the variance estimated using the Agresti-Caffo methodology

Percentage of Weight: Percentage of the total weight

[S]Table 11 Summary of combined estimations for Oocyst prevalence (Optical microscopy) (Full analysis population)

Comparison	n	Combined Estimate	LCI	UCI	p-value	Q Test	Q Test p-value	I2 (%)	CV
DMFA Final vs Baseline	xx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
DSFA Final vs Baseline	xx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
Baseline DSFA - DMFA	xx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
Final DSFA - DMFA	xx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	xx.x	x.xx

n: Number of observations included in the meta-analysis
LCI: Lower limit of the 95% Confidence interval
UCI: Upper limit of the 95% Confidence interval
p-value: For the test that the combined difference is equal to zero
Q: Heterogeneity Q test
I2: I square test.
CV: Coefficient of variation

[S]Table 12 Paired comparisons in prevalence of Sporozoite positivity DSFA Final - Baseline (Optical microscopy) (Full analysis population)

	DSFA Baseline		DSFA Final		Difference in proportions				
Subject	Positive	Negative	Positive	Negative	Point Estimate	LCI	UCI	Weight	Percentage of Weight (%)
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx

Difference in proportion: DSFA Final - DSFA Baseline.

LCI Lower limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology.

UCI Upper limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology

Weight: Inverse of the variance estimated using the Agresti-Caffo methodology

Percentage of Weight: Percentage of the total weight

[S]Table 13 Paired comparisons in prevalence of Sporozoite positivity DMFA Final - Baseline (Optical microscopy) (Full analysis population)

	DMFA Baseline		DMFA Final		Difference in proportions				
Subject	Positive	Negative	Positive	Negative	Point Estimate	LCI	UCI	Weight	Percentage of Weight (%)
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx

Difference in proportion: DMFA Final - DMFA Baseline.

LCI Lower limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology.

UCI Upper limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology

Weight: Inverse of the variance estimated using the Agresti-Caffo methodology

Percentage of Weight: Percentage of the total weight

[S]Table 14 Paired comparisons in prevalence of Sporozoite positivity Baseline visit (DSFA – DMFA) (Optical microscopy) (Full analysis population)

	DMFA Baseline		DSFA Baseline		Difference in proportions				
Subject	Positive	Negative	Positive	Negative	Point Estimate	LCI	UCI	Weight	Percentage of Weight (%)
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx

Difference in proportion: DSFA Baseline - DMFA Baseline.

LCI Lower limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology.

UCI Upper limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology

Weight: Inverse of the variance estimated using the Agresti-Caffo methodology

Percentage of Weight: Percentage of the total weight

[S]Table 15 Paired comparisons in prevalence of Sporozoite positivity Final visit (DSFA – DMFA) (Optical microscopy) (Full analysis population)

	DMFA Final		DSFA Final		Difference in proportions				
Subject	Positive	Negative	Positive	Negative	Point Estimate	LCI	UCI	Weight	Percentage of Weight (%)
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx

Difference in proportion: DSFA Final - DMFA Final.

LCI Lower limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology.

UCI Upper limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology

Weight: Inverse of the variance estimated using the Agresti-Caffo methodology

Percentage of Weight: Percentage of the total weight

[S]Table 16 Summary of combined estimations for Sporozoite prevalence (Optical microscopy) (Full analysis population)

Comparison	n	Combined Estimate	LCI	UCI	p-value	Q Test	Q Test p-value	I2 (%)	CV
DMFA Final vs Baseline	xx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
DSFA Final vs Baseline	xx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
Baseline DSFA - DMFA	xx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
Final DSFA - DMFA	xx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	xx.x	x.xx

n: Number of observations included in the meta-analysis

LCI: Lower limit of the 95% Confidence interval

UCI: Upper limit of the 95% Confidence interval

p-value: For the test that the combined difference is equal to zero

Q: Heterogeneity Q test

I2: I square test.

CV: Coefficient of variation

[S]Table 17 Model for the Oocyst density (Optical microscopy) (Full analysis population)

Outcome(*)	Relative risk	LCI	UCI	p-value
Oocyte density				
Final/Baseline in DSFA assay	x.xx	x.xx	x.xx	x.xxx
Final/Baseline in DMFA assay	x.xx	x.xx	x.xx	x.xxx
DMFA/DSFA in baseline visit	x.xx	x.xx	x.xx	x.xxx
DMFA/DSFA in final visit	x.xx	x.xx	x.xx	x.xxx

UCI: Upper limit of the 95% Confidence interval

p-value by likelihood ratio test

(*) Each row is a separate model with random effects for subject

[S]Table 18 Summary of entomology results (PCR) (Full analysis population)

Outcome	Baseline-DSFA	Baseline-DMFA	Final-DSFA	Final-DMFA
Oocyst prevalence				
N	xx	xx	xx	xx
Mean	xx	xx	xx	xx
SD	x.xx	x.xx	x.xx	x.xx
ICC	x.xxx	x.xxx	x.xxx	x.xxx
Min	x.xx	x.xx	x.xx	x.xx
Median	x.xx	x.xx	x.xx	x.xx
Max	x.xx	x.xx	x.xx	x.xx
Oocyst density				
N	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x
Min	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x
Max	xx.x	xx.x	xx.x	xx.x
Sporozoite prevalence				
N	xx	xx	xx	xx
Mean	x.xx	x.xx	x.xx	x.xx
ICC	x.xxx	x.xxx	x.xxx	x.xxx
SD	x.xx	x.xx	x.xx	x.xx
Min	x.xx	x.xx	x.xx	x.xx
Median	x.xx	x.xx	x.xx	x.xx
Max	x.xx	x.xx	x.xx	x.xx
Sporozoite density				
N	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x
Min	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x
Max	xx.x	xx.x	xx.x	xx.x

N: Number of subjects with available data, SD: Standard deviation; ICC Intra class correlation
Min: Minimum value, Max: Maximum value

[S]Table 19 Paired comparisons in prevalence of Oocyst positivity DSFA Final - Baseline (PCR) (Full analysis population)

	DSFA Baseline		DSFA Final		Difference in proportions				
Subject	Positive	Negative	Positive	Negative	Point Estimate	LCI	UCI	Weight	Percentage of Weight (%)
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx

Difference in proportion: DSFA Final - DSFA Baseline.

LCI Lower limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology.

UCI Upper limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology

Weight: Inverse of the variance estimated using the Agresti-Caffo methodology

Percentage of Weight: Percentage of the total weight

[S]Table 20 Paired comparisons in prevalence of Oocyst positivity DMFA Final - Baseline (PCR) (Full analysis population)

	DMFA Baseline		DMFA Final		Difference in proportions				
Subject	Positive	Negative	Positive	Negative	Point Estimate	LCI	UCI	Weight	Percentage of Weight (%)
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx

Difference in proportion: DMFA Final - DMFA Baseline.

LCI Lower limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology.

UCI Upper limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology

Weight: Inverse of the variance estimated using the Agresti-Caffo methodology

Percentage of Weight: Percentage of the total weight

[S]Table 21 Paired comparisons in prevalence of Oocyst positivity Baseline visit (DSFA – DMFA) (PCR) (Full analysis population)

	DMFA Baseline		DSFA Baseline		Difference in proportions				
Subject	Positive	Negative	Positive	Negative	Point Estimate	LCI	UCI	Weight	Percentage of Weight (%)
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx

Difference in proportion: DSFA Baseline - DMFA Baseline.

LCI Lower limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology.

UCI Upper limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology

Weight: Inverse of the variance estimated using the Agresti-Caffo methodology

Percentage of Weight: Percentage of the total weight

[S]Table 22 Paired comparisons in prevalence of Oocyst positivity Final visit (DSFA – DMFA) (PCR) (Full analysis population)

	DMFA Final		DSFA Final		Difference in proportions				
Subject	Positive	Negative	Positive	Negative	Point Estimate	LCI	UCI	Weight	Percentage of Weight (%)
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx

Difference in proportion: DSFA Final - DMFA Final.

LCI Lower limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology.

UCI Upper limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology

Weight: Inverse of the variance estimated using the Agresti-Caffo methodology

Percentage of Weight: Percentage of the total weight

[S]Table 23 Summary of combined estimates for Oocyst density prevalence (PCR) (Full analysis population)

Comparison	n	Combined Estimate	LCI	UCI	p-value	Q Test	Q Test p-value	I2 (%)	CV
DMFA Final vs Baseline	xx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
DSFA Final vs Baseline	xx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
Baseline DSFA - DMFA	xx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
Final DSFA - DMFA	xx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	xx.x	x.xx

n: Number of observations included in the meta-analysis

LCI: Lower limit of the 95% Confidence interval

UCI: Upper limit of the 95% Confidence interval

p-value: For the test that the combined difference is equal to zero

Q: Heterogeineity Q test

I2: I square test.

CV: Coefficient of variation

[S]Table 24 Paired comparisons in prevalence of Sporozoite positivity DSFA Final - Baseline (PCR) (Full analysis population)

	DSFA Baseline		DSFA Final		Difference in proportions				
Subject	Positive	Negative	Positive	Negative	Point Estimate	LCI	UCI	Weight	Percentage of Weight (%)
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx

Difference in proportion: DSFA Final - DSFA Baseline.

LCI Lower limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology.

UCI Upper limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology

Weight: Inverse of the variance estimated using the Agresti-Caffo methodology

Percentage of Weight: Percentage of the total weight

[S]Table 25 Paired comparisons in prevalence of Sporozoite positivity DMFA Final - Baseline (PCR) (Full analysis population)

	DMFA Baseline		DMFA Final		Difference in proportions				
Subject	Positive	Negative	Positive	Negative	Point Estimate	LCI	UCI	Weight	Percentage of Weight (%)
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx

Difference in proportion: DMFA Final - DMFA Baseline.

LCI Lower limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology.

UCI Upper limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology

Weight: Inverse of the variance estimated using the Agresti-Caffo methodology

Percentage of Weight: Percentage of the total weight

[S]Table 26 Paired comparisons in prevalence of Sporozoite positivity Baseline visit (DSFA – DMFA) (PCR) (Full analysis population)

	DMFA Baseline		DSFA Baseline		Difference in proportions				
Subject	Positive	Negative	Positive	Negative	Point Estimate	LCI	UCI	Weight	Percentage of Weight (%)
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx

Difference in proportion: DSFA Baseline - DMFA Baseline.

LCI Lower limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology.

UCI Upper limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology

Weight: Inverse of the variance estimated using the Agresti-Caffo methodology

Percentage of Weight: Percentage of the total weight

[S]Table 27 Paired comparisons in prevalence of Sporozoite positivity Final visit (DSFA – DMFA) (PCR) (Full analysis population)

	DMFA Final		DSFA Final		Difference in proportions				
Subject	Positive	Negative	Positive	Negative	Point Estimate	LCI	UCI	Weight	Percentage of Weight (%)
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
xx	xx	xx	xx	xx	x.xxx	x.xxx	x.xxx	xx.x	x.xx

Difference in proportion: DSFA Final - DMFA Final.

LCI Lower limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology.

UCI Upper limit of the 95% Confidence interval estimated using the Agresti-Caffo methodology

Weight: Inverse of the variance estimated using the Agresti-Caffo methodology

Percentage of Weight: Percentage of the total weight

[S]Table 28 Summary of combined estimates for Sporozoite density prevalence (PCR) (Full analysis population)

Comparison	n	Combined Estimate	LCI	UCI	p-value	Q Test	Q Test p-value	I2 (%)	CV
DMFA Final vs Baseline	xx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
DSFA Final vs Baseline	xx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
Baseline DSFA - DMFA	xx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	xx.x	x.xx
Final DSFA - DMFA	xx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	xx.x	x.xx

n: Number of observations included in the meta-analysis

LCI: Lower limit of the 95% Confidence interval

UCI: Upper limit of the 95% Confidence interval

p-value: For the test that the combined difference is equal to zero

Q: Heterogeneity Q test

I2: I square test.

CV: Coefficient of variation

[S]Table 29 Models for the Oocyte and Sporozoite density (PCR) (Full analysis population)

Outcome(*)	Relative risk	LCI	UCI	p-value
Oocyte density				
Final/Baseline in DSFA assay	x.xx	x.xx	x.xx	x.xxx
Final/Baseline in DMFA assay	x.xx	x.xx	x.xx	x.xxx
DMFA/DSFA in baseline visit	x.xx	x.xx	x.xx	x.xxx
DMFA/DSFA in final visit	x.xx	x.xx	x.xx	x.xxx
Sporozoite density				
Final/Baseline in DSFA assay	x.xx	x.xx	x.xx	x.xxx
Final/Baseline in DMFA assay	x.xx	x.xx	x.xx	x.xxx
DMFA/DSFA in baseline visit	x.xx	x.xx	x.xx	x.xxx
DMFA/DSFA in final visit	x.xx	x.xx	x.xx	x.xxx

LCI: Lower limit of the 95% Confidence interval
UCI: Upper limit of the 95% Confidence interval
p-value by likelihood ratio test
(*) Each row is a separate model

[S]Table 30 Summary of gametocytemia persistence by qPCR (Full analysis population)

	n	N	%	LCI	UCI
Gametocytemia at Baseline visit	xx	xx	xx.x	xx.x	xx.x
Gametocytemia at Baseline and final visit	xx	xx	xx.x	xx.x	xx.x

n: Number of participants positive
N: Number of participants evaluated
%: Percentage
LCI: 95% Lower confidence interval
UCI: 95% Upper confidence interval

[S]Table 31 Bayesian analysis for the parasitological results in mosquitoes (Optical microscopy) (Full analysis population)

Outcome	Effective Sample	Mean	SD	Median	95% CI	
					Low	High
Oocyst Prevalence						
Probability of infection (Baseline visit, DSFA)	xxxxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
Odds ratio for the probability of infection DMFA vs DSFA	xxxxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
Odds ratio for the probability of infection Final vs Baseline visit	xxxxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
Odds ratio for the probability of infection by being gametocyte positive	xxxxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
Dispersion parameter (Baseline visit, DSFA)	xxxxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
Relative change in dispersion DMFA vs DSFA	xxxxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
Relative change in dispersion Final vs Baseline visit	xxxxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
Marginal correlation between Final and Baseline visit for DSFA	xxxxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
Marginal correlation between Final and Baseline visit for DMFA	xxxxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
Marginal correlation between DSFA and DMFA at baseline visit	xxxxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
Marginal correlation between DSFA and DMFA at final visit	xxxxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx

SD: standard deviation

CI: Credible intervals

[S]Table 32 Overall safety profile (Full analysis population)

Outcome	Total (N =)
Number of solicited adverse events	xxx
Number of subjects with any solicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of unsolicited adverse events	xxx
Number of subjects with any unsolicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of related adverse events	xxx
Number of subjects with any related adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of severe adverse events	xxx
number of subjects with any severe adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of adverse events of grade ≥ 2 (moderate or severe)	xxx
Number of subjects with any adverse event of grade ≥ 2 (moderate or severe)	xx (xx.x%, CI: xx.x%, xx.x%)
Number of events leading to study withdrawal	xxx
Number of subjects with any adverse event leading to study withdrawal	xx (xx.x%, CI: xx.x%, xx.x%)
Total number of serious adverse events	xxx
Subject with any serious adverse event	xx (xx.x%, CI: xx.x%, xx.x%)

N: Total number of subjects
CI: 95% Confidence intervals

[S]Table 33 Summary of solicited adverse events (Full analysis population)

Outcome	Total (N =)
Number of solicited adverse events	xxx
Number of subjects with any solicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any mild solicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any moderate solicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any severe solicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of pruritus	xxx
Number of subjects with any pruritus	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any mild pruritus	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any moderate pruritus	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any severe pruritus	xx (xx.x%, CI: xx.x%, xx.x%)
Number of erythema	xxx
Number of subjects with any erythema	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any mild erythema	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any moderate erythema	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any severe erythema	xx (xx.x%, CI: xx.x%, xx.x%)

N: Total number of subjects
CI: 95% Confidence intervals

[S]Table 34 Summary of solicited adverse events starting the date of baseline visit (Full analysis population)

Outcome	Total (N =)
Number of solicited adverse events	xxx
Number of subjects with any solicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any mild solicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any moderate solicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any severe solicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of pruritus	xxx
Number of subjects with any pruritus	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any mild pruritus	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any moderate pruritus	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any severe pruritus	xx (xx.x%, CI: xx.x%, xx.x%)
Number of erythema	xxx
Number of subjects with any erythema	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any mild erythema	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any moderate erythema	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any severe erythema	xx (xx.x%, CI: xx.x%, xx.x%)

N: Total number of subjects
CI: 95% Confidence intervals

[S]Table 35 Summary of solicited adverse events starting the date of final visit (Full analysis population)

Outcome	Total (N =)
Number of solicited adverse events	xxx
Number of subjects with any solicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any mild solicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any moderate solicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any severe solicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of pruritus	xxx
Number of subjects with any pruritus	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any mild pruritus	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any moderate pruritus	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any severe pruritus	xx (xx.x%, CI: xx.x%, xx.x%)
Number of erythema	xxx
Number of subjects with any erythema	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any mild erythema	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any moderate erythema	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any severe erythema	xx (xx.x%, CI: xx.x%, xx.x%)

N: Total number of subjects
CI: 95% Confidence intervals
>> By overall, during first feeding and during the second feeding

[S]Table 36 Summary of unsolicited adverse events (Full analysis population)

Outcome	Total (N =)
Number of unsolicited adverse events	xxx
Number of subjects with any unsolicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any mild unsolicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any moderate unsolicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any severe unsolicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of unsolicited related adverse events	xxx
Number of subjects with any unsolicited related adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any mild unsolicited related adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any moderate unsolicited related adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any severe unsolicited related adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of unsolicited unrelated adverse events	xxx
Number of subjects with any unsolicited unrelated adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any mild unsolicited related adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any moderate unsolicited unrelated adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any severe unsolicited unrelated adverse event	xx (xx.x%, CI: xx.x%, xx.x%)

N: Total number of subjects
CI: 95% Confidence intervals

[S]Table 37 Summary of unsolicited adverse events starting the date of baseline visit (Full analysis population)

Outcome	Total (N =)
Number of unsolicited adverse events	xxx
Number of subjects with any unsolicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any mild unsolicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any moderate unsolicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any severe unsolicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of unsolicited related adverse events	xxx
Number of subjects with any unsolicited related adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any mild unsolicited related adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any moderate unsolicited related adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any severe unsolicited related adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of unsolicited unrelated adverse events	xxx
Number of subjects with any unsolicited unrelated adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any mild unsolicited related adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any moderate unsolicited unrelated adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any severe unsolicited unrelated adverse event	xx (xx.x%, CI: xx.x%, xx.x%)

N: Total number of subjects
CI: 95% Confidence intervals

[S]Table 38 Summary of unsolicited adverse events (Full analysis population) Starting the date of final visit

Outcome	Total (N =)
Number of unsolicited adverse events	xxx
Number of subjects with any unsolicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any mild unsolicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any moderate unsolicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any severe unsolicited adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of unsolicited related adverse events	xxx
Number of subjects with any unsolicited related adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any mild unsolicited related adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any moderate unsolicited related adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any severe unsolicited related adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of unsolicited unrelated adverse events	xxx
Number of subjects with any unsolicited unrelated adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any mild unsolicited related adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any moderate unsolicited unrelated adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Number of subjects with any severe unsolicited unrelated adverse event	xx (xx.x%, CI: xx.x%, xx.x%)

N: Total number of subjects
CI: 95% Confidence intervals

[S]Table 39 Summary of serious adverse events (Full analysis population)

Outcome	Total (N =)
Total number of serious adverse events	xxx
Subject with any serious adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Total number of unrelated serious adverse events	xxx
Subject with any unrelated serious adverse event	xx (xx.x%, CI: xx.x%, xx.x%)
Total number of related serious adverse events	xxx
Subject with any serious adverse event	xx (xx.x%, CI: xx.x%, xx.x%)

N: Total number of subjects
CI: 95% Confidence intervals

[S]Table 40 Summary of adverse events by system and preferred term (Full analysis population)

	Total (N =)
All systems	xx (xx.x%, CI: xx.x%, xx.x%)
System Organ Class 1	xx (xx.x%, CI: xx.x%, xx.x%)
Prefered Term 1	xx (xx.x%, CI: xx.x%, xx.x%)
Prefered Term 2	xx (xx.x%, CI: xx.x%, xx.x%)
Prefered Term 3	xx (xx.x%, CI: xx.x%, xx.x%)
…..	xx (xx.x%, CI: xx.x%, xx.x%)
System Organ Class 1	xx (xx.x%, CI: xx.x%, xx.x%)
Prefered Term 1	xx (xx.x%, CI: xx.x%, xx.x%)
Prefered Term 2	xx (xx.x%, CI: xx.x%, xx.x%)
Prefered Term 3	xx (xx.x%, CI: xx.x%, xx.x%)
…..	xx (xx.x%, CI: xx.x%, xx.x%)
….	

N: Total number of subjects
CI: 95% Confidence intervals

[S]Table 41 Summary of vital signs (Full analysis population)

Characteristic	Screening	Baseline	Final visit
Weight (Kg)			
N	xx	xx	xx
Mean	xxx.x	xxx.x	xxx.x
SD	xxx.x	xxx.x	xxx.x
Min	xxx.x	xxx.x	xxx.x
1st Quartile	xxx.x	xxx.x	xxx.x
Median	xxx.x	xxx.x	xxx.x
Max	xxx.x	xxx.x	xxx.x
Pulse (b/min)			
N	xx	xx	xx
Mean	xxx.x	xxx.x	xxx.x
SD	xxx.x	xxx.x	xxx.x
Min	xxx.x	xxx.x	xxx.x
Median	xxx.x	xxx.x	xxx.x
Max	xxx.x	xxx.x	xxx.x
Axillary Temperature (ºC)			
N	xx	xx	xx
Mean	xxx.x	xxx.x	xxx.x
SD	xxx.x	xxx.x	xxx.x
Min	xxx.x	xxx.x	xxx.x
Median	xxx.x	xxx.x	xxx.x
Max	xxx.x	xxx.x	xxx.x
Respiratory rate (b/min)			
N	xx	xx	xx
Mean	xxx.x	xxx.x	xxx.x
SD	xxx.x	xxx.x	xxx.x
Min	xxx.x	xxx.x	xxx.x

Median	xxx.x	xxx.x	xxx.x
Max	xxx.x	xxx.x	xxx.x
Weight			
N	xx	xx	xx
Mean	xxx.x	xxx.x	xxx.x
SD	xxx.x	xxx.x	xxx.x
Min	xxx.x	xxx.x	xxx.x
Median	xxx.x	xxx.x	xxx.x
Max	xxx.x	xxx.x	xxx.x
Blood Presure Sys (mmHg)			
N	xx	xx	xx
Mean	xxx.x	xxx.x	xxx.x
SD	xxx.x	xxx.x	xxx.x
Min	xxx.x	xxx.x	xxx.x
Median	xxx.x	xxx.x	xxx.x
Max	xxx.x	xxx.x	xxx.x
Blood Presure Dias (mmHg)			
N	xx	xx	xx
Mean	xxx.x	xxx.x	xxx.x
SD	xxx.x	xxx.x	xxx.x
Min	xxx.x	xxx.x	xxx.x
Median	xxx.x	xxx.x	xxx.x
Max	xxx.x	xxx.x	xxx.x

N: Total number of subjects, Min:Minimun, Max: Maxium

[S]Table 42 Summary of signs and symptoms (Full analysis population)

	Screening N = XXX	Baseline N = XXX	Final visit N = XXX
Headache	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
Chest pain	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
Vomiting	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
Nausea	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
Chills	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
Dizziness	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
Abdominal pain	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
Fatigue	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
Diarrhoea	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
Fever	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
Seizures	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
Jaundice	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
Spontaneous bleeding	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
Impaired consciousness	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
Prostration	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
Dark urine	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
Respiratory	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
Cardiovascular	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
Neurological	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
HEENT	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
Gastrointestinal	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
Urogenital	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
Musculoskeletal	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
Dermatological	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
Hematological/Lymphatic	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)	xx (xx.x%, CI xx.x%; xx.x%)
…..			

N: Total number of subjects

SHELL LISTINGS

[S]Listing 1 Elibility criteria not met

Subject ID	Criteria	Criteria Description
XXXX	INCLUSION	<Description of the inclusion criteria not met>
XXXX	EXCLUSION	<Description of the exclusion criteria met>
…..		

[S]Listing 2 Study populations

SubjectID	Enrolled	Full Analysis	Per Protocol DSFA final vs baseline	Per Protocol DMFA final vs baseline	Per Protocol DSFA vs DMFA baseline	Per Protocol DSFA vs DMFA baseline
XXXX	<YES>/<NO>	<YES>/<NO>	<YES>/<NO>	<YES>/<NO>	<YES>/<NO>	<YES>/<NO>
….						

[S]Listing 3 Visits and dates

SubjectID	Screening	Baseline	Final
xxxxxxx	<YYYY-MM-DD>	<YYYY-MM-DD>	<YYYY-MM-DD>
….			

[S]Listing 4 Protocol violations

SubjectID	Deviation	Description
xxxxx	<Mayor>/<Minor>	<Text>
…		

[S]Listing 5 Entomological results by Optical microscopy

Subject ID	Visit	Assay	Gut dissected	Positive Guts	Oocysts	Gland dissected	Positive Glands
XXXX	<BASELINE>/<FINAL>	<DSFA>/<DMFA>	XXX	XXX	XXX	XXX	XXX
....							

[S]Listing 6 Entomological results by PCR

SubjectID	Visit	Assay	MosquitoID	Dissection	CT
xxxxx	<Baseline>/<Final>	<DSFA>/<DMFA>	xxxx	<Gut>/<Gland>	xxxx
....					

[S]Listing 7 Gametocytemia (qPCR) CT

SubjectID	Screening	Baseline	Final
xxxxx	xx.x	xx.x	xx.x
....			

[S]Listing 8 Adverse events

Subject ID	AE Diagnosis	Prefered Term	System Organ Class	Start date	Intensity	Outcome	Duration (days)	Related	SAE
xxxx	<TEXT>			<yyyy-mmm-dd>	<INTENSITY>	<RECOVERED>	xxx	<Yes/No>	<Yes/No>
…									

[S]Listing 9 Vital signs

Subject	Characteristic	Screening	Baseline	Final visit
xxxx	Weight (Kg)			
	Pulse (b/min)			
	Axillary Temperature (ºC)			
	Respiratory rate (b/min)			
	Weight			
	Blood Presure Sys (mmHg)			
	Blood Presure Dias (mmHg)			
xxxx	Weight (Kg)			
	Pulse (b/min)			
	Axillary Temperature (ºC)			
	Respiratory rate (b/min)			
	Weight			
	Blood Presure Sys (mmHg)			
	Blood Presure Dias (mmHg)			
…..				

[S]Listing 10 Signs and symptoms

SubjectID	Visit	Sign/Symptom	Present	Comments
XXXXX	<Screening>/<Baseline>/<Final>	Headache	<YES>/<NO>	<Text>
		Chest pain	<YES>/<NO>	<Text>
		Vomiting	<YES>/<NO>	<Text>
		Nausea	<YES>/<NO>	<Text>
		Chills	<YES>/<NO>	<Text>
		Dizziness	<YES>/<NO>	<Text>
		Abdominal pain	<YES>/<NO>	<Text>
		Fatigue	<YES>/<NO>	<Text>
		Diarrhoea	<YES>/<NO>	<Text>
		Fever	<YES>/<NO>	<Text>
		Seizures	<YES>/<NO>	<Text>
		Jaundice	<YES>/<NO>	<Text>
		Spontaneous bleeding	<YES>/<NO>	<Text>
		Impaired consciousness	<YES>/<NO>	<Text>
		Prostration	<YES>/<NO>	<Text>
		Dark urine	<YES>/<NO>	<Text>
		Other (specify)	<YES>/<NO>	<Text>
…				

[S]Listing 11 Physical examination

SubjectID	Visit	System	Examination	If abnormal specify
XXXXX	<Screening>/<Baseline>/<Final>	Respiratory Cardiovascular Neurological HEENT Gastrointestinal Urogenital Musculoskeletal Dermatological Hematological/Lymphatic Other (specify)	<Normal>/<Abnormal>/<Not done>	<Text>

[S]Listing 12 Pregnancy test results

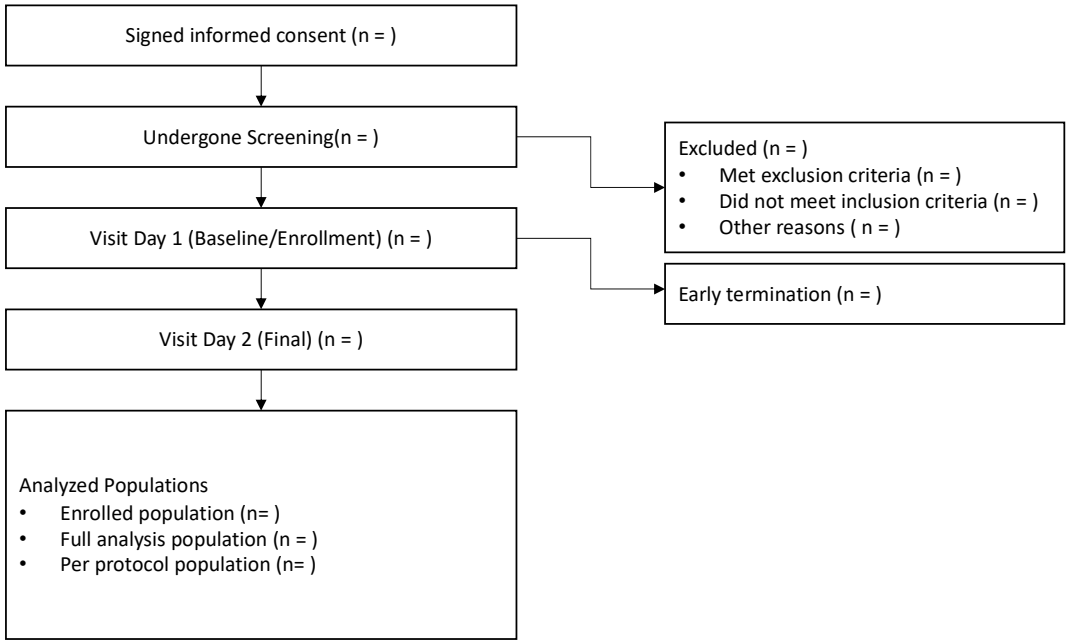
StudyID	Visit	Pregnancy test result
xxxxx	<Screening Visit>/<Final Visit>	<Positive>/<Negative>/<N/A>
….		

[S]Listing 13 Dispensed Coartem and Primaquine

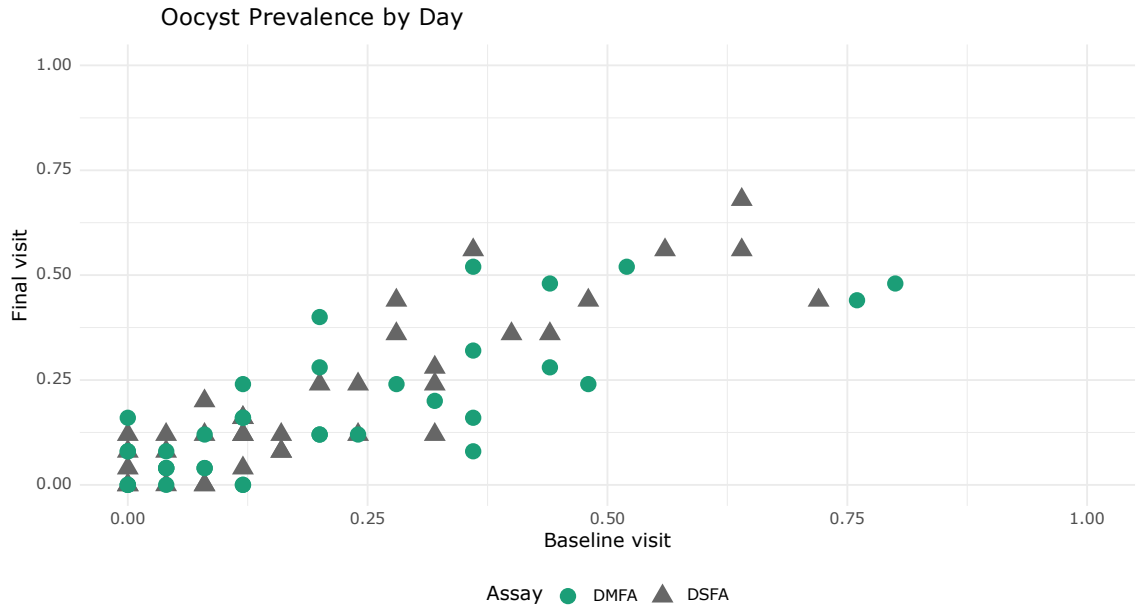
SubjectID	Coartem Dispensed	If not, reason	Primaquine Dispensed	If not reason
xxxxx	<Yes>/<No>	<Text>	<Yes>/<No>	<Text>
…				

SHELL FIGURES

[S]Figure 1 Consort diagram

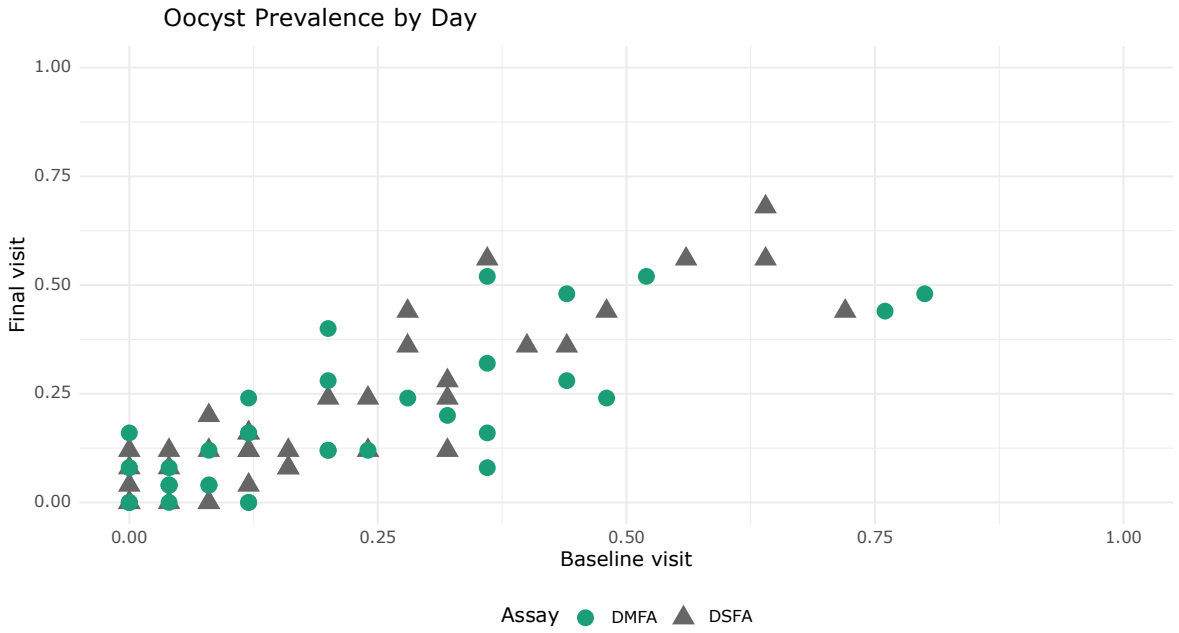


[S]Figure 2 Oocyst prevalence (optical microscopy) by day (Full analysis population)

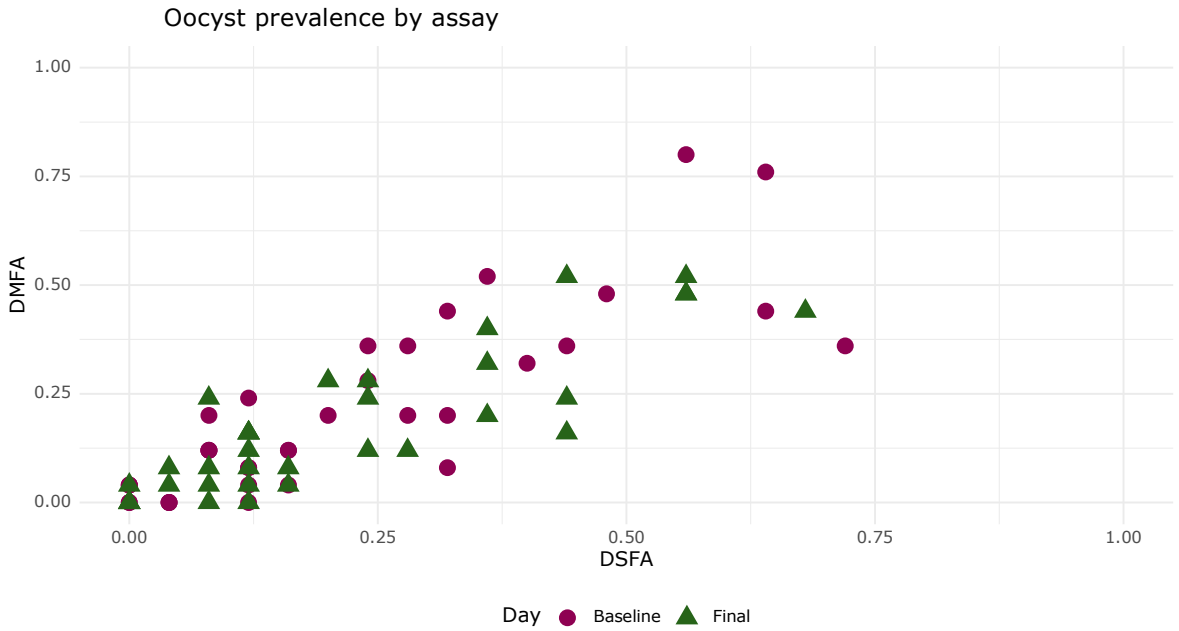


Note: For this type of graphs, the size of the dots will be based on the square root of the weight for the difference. Jitter will be add to make visible pairs with same values, specially the 0.0-0.0.

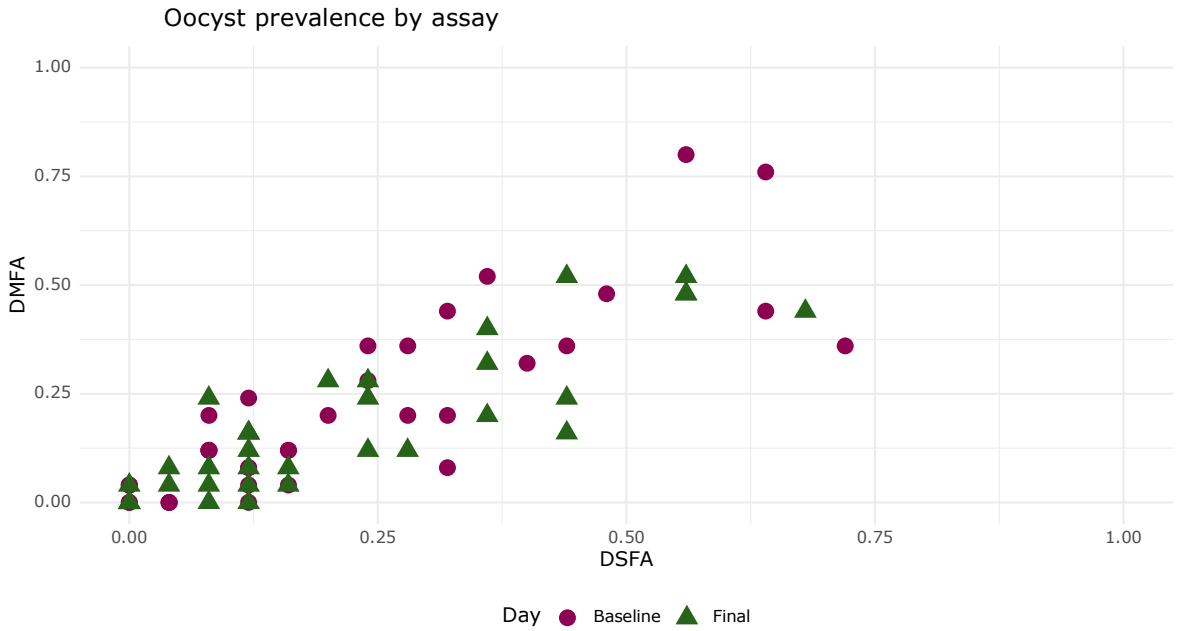
[S]Figure 3 Oocyst prevalence (optical microscopy) by day (Per protocol population)



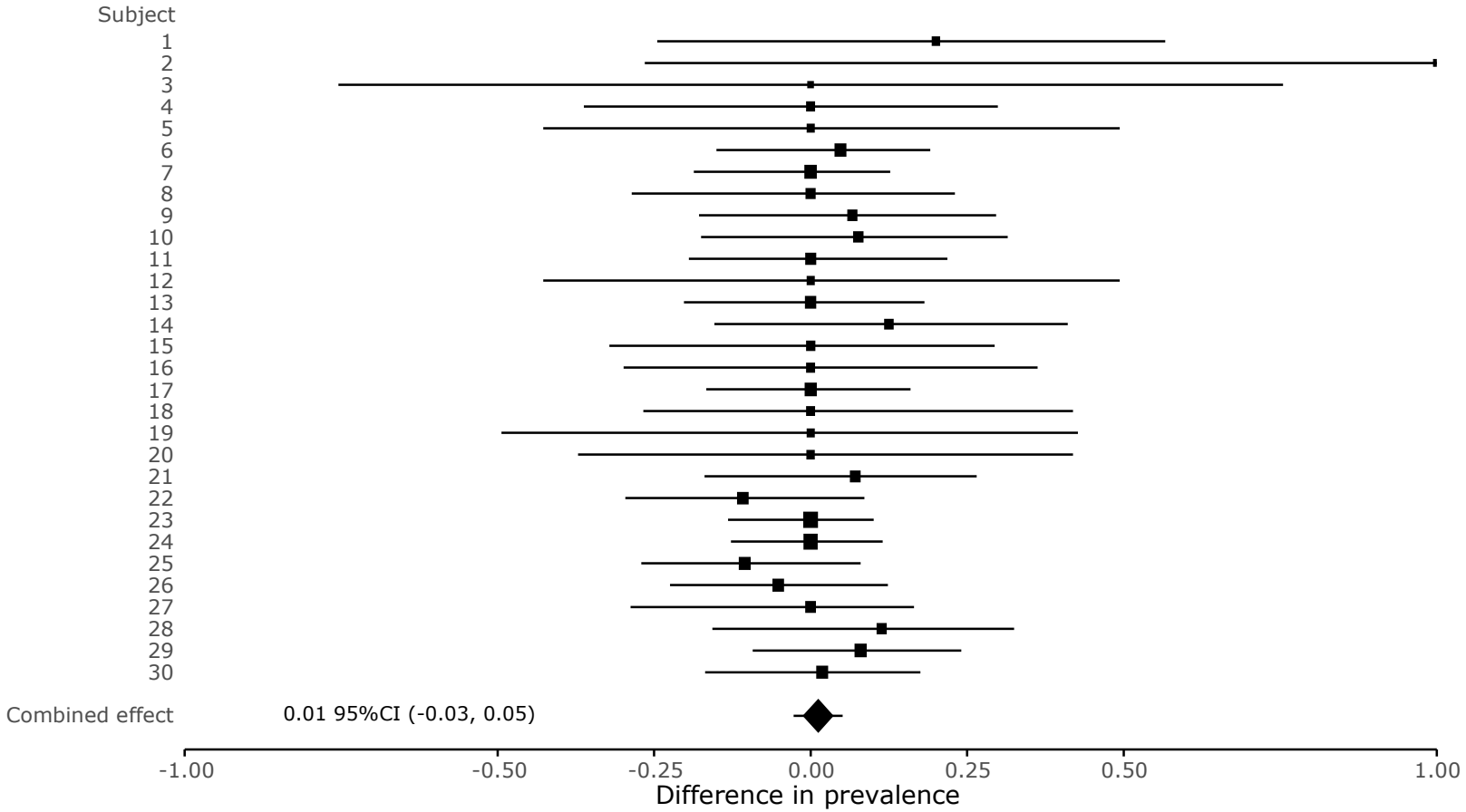
[S]Figure 4 Oocyst prevalence (Optical microscopy) by assay (Full analysis population)



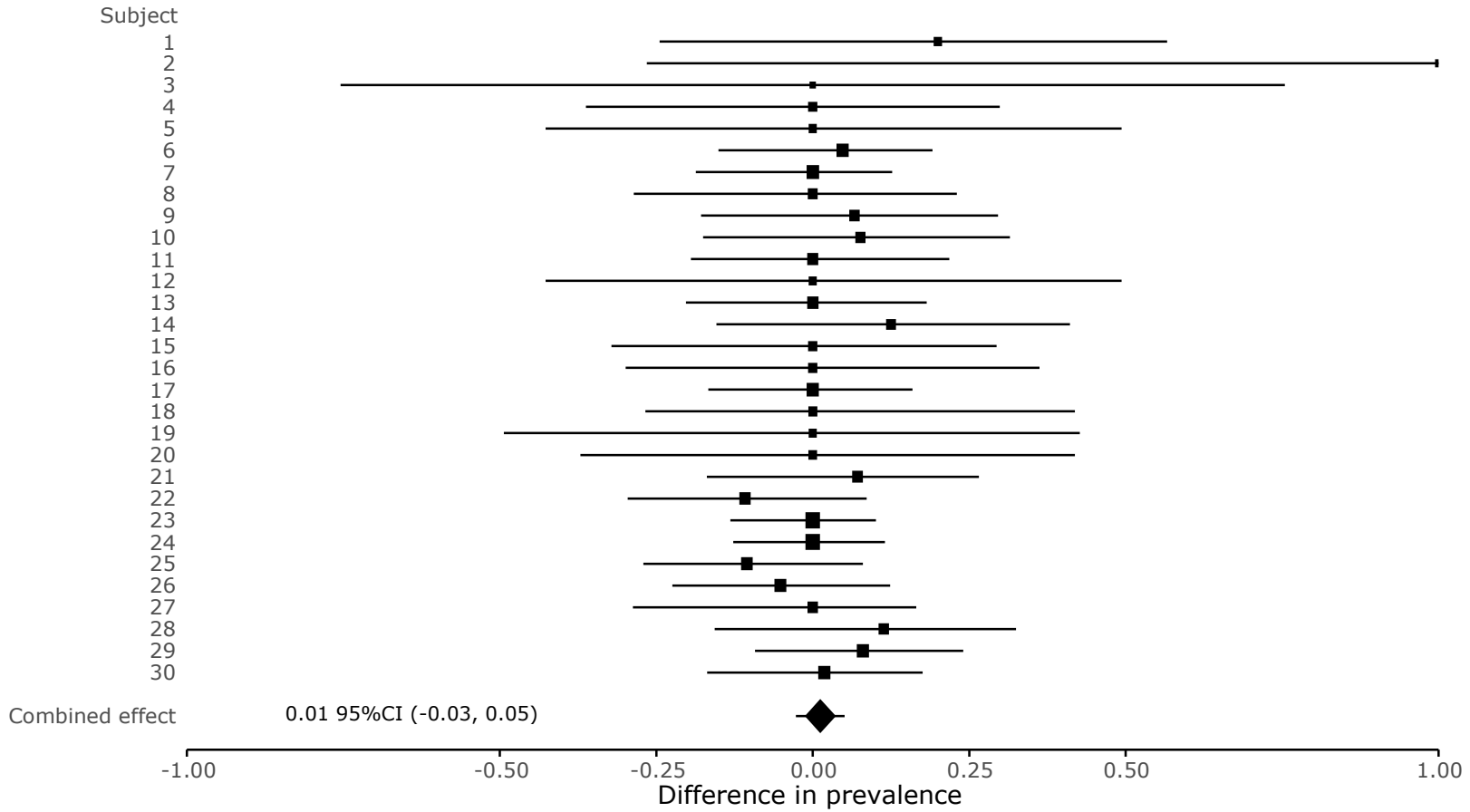
[S]Figure 5 Oocyst prevalence (Optical microscopy) by assay (Per protocol population)



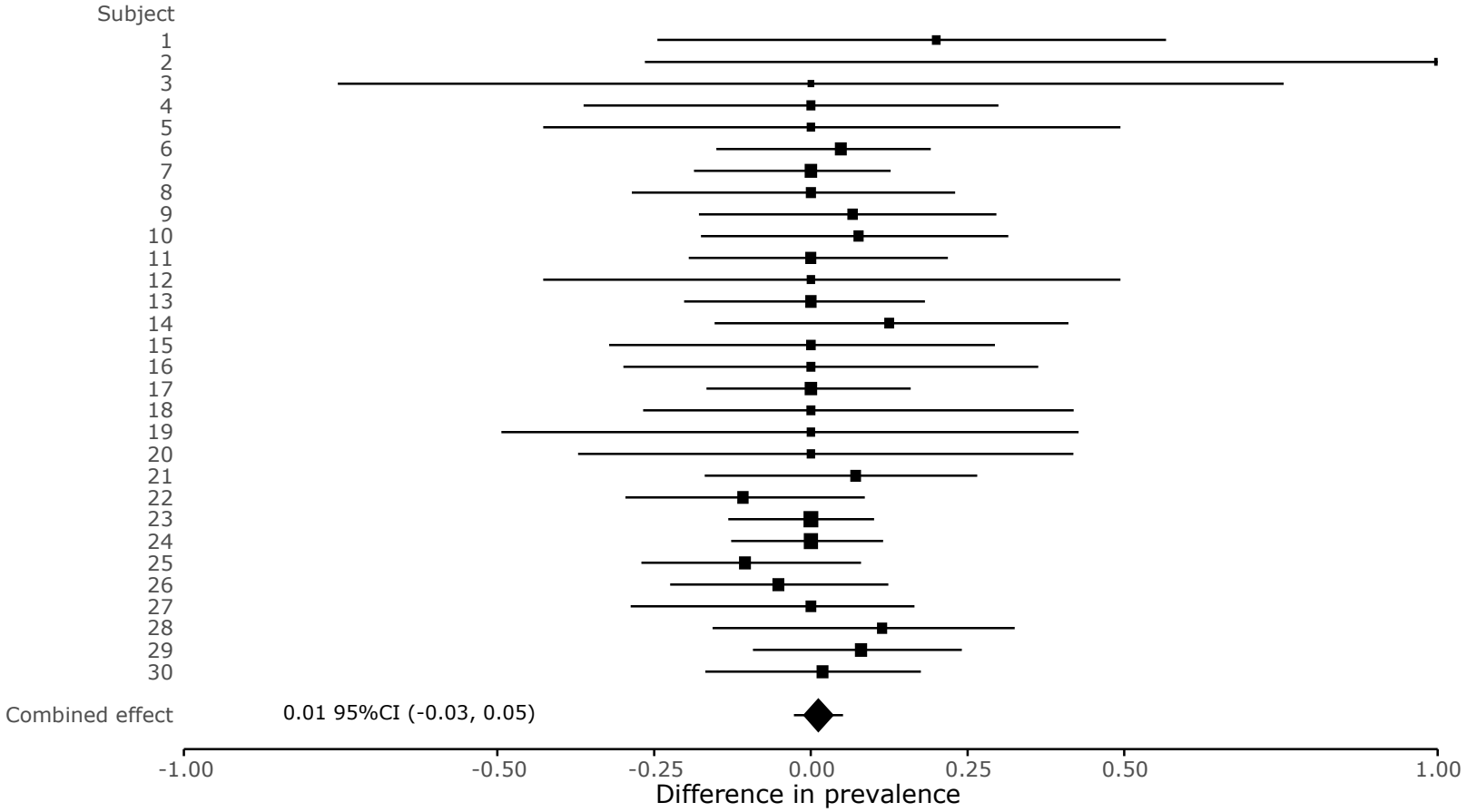
[S]Figure 6 Forest plot for the comparison oocyst prevalence DSFA Final - DSFA Baseline (Optical microscopy)



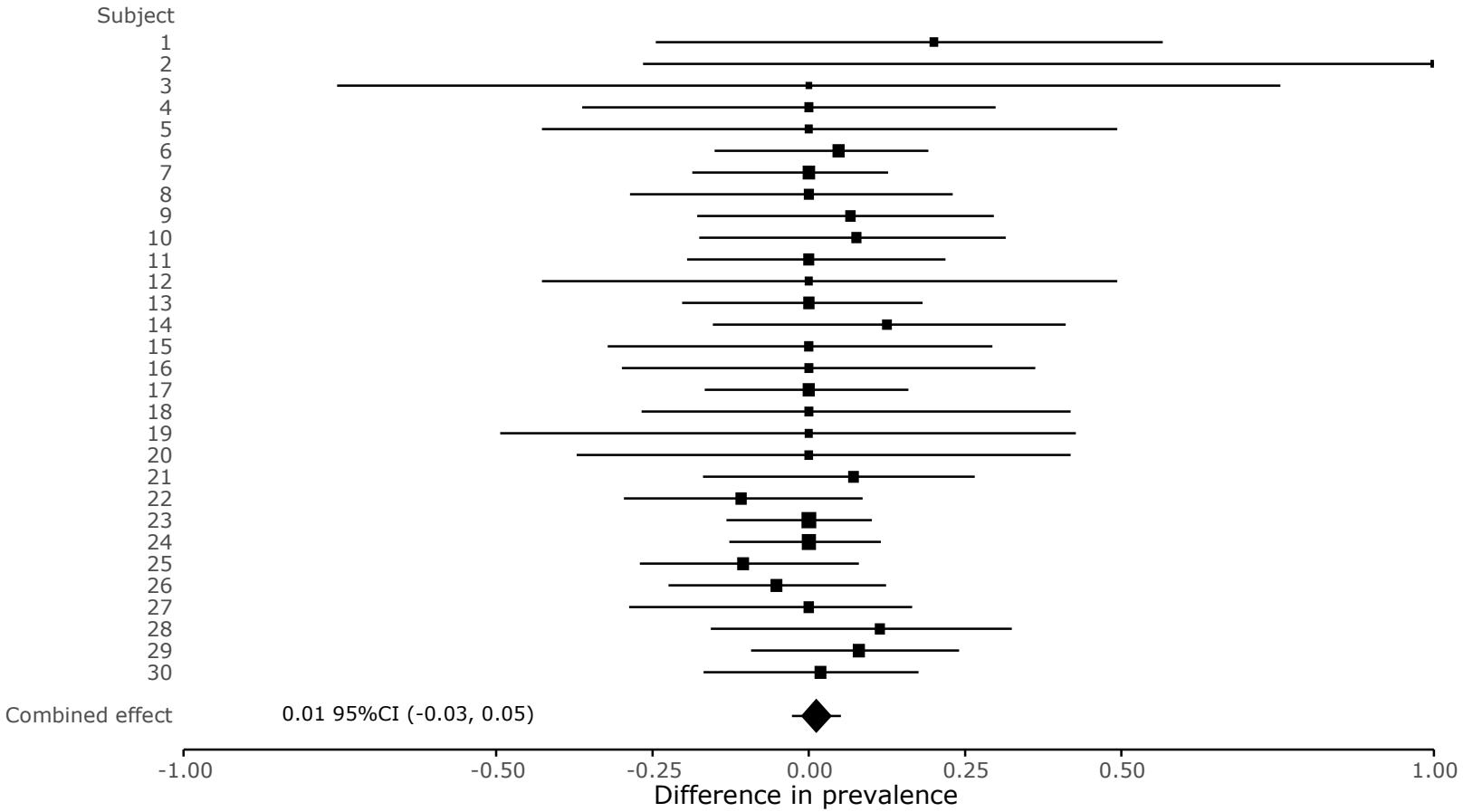
[S]Figure 7 Forest plot for the comparison oocyst prevalence DMFA Final - DMFA Baseline (Optical microscopy)



[S]Figure 8 Forest plot for the comparison oocyst prevalence Baseline visit DSFA - DMFA (Optical microscopy)



[S]Figure 9 Forest plot for the comparison oocyst prevalence Final visit DSFA - DMFA (Optical microscopy)



[S]Figure 10 Bayesian model diagnostics

(note: Graphs will be presented for the parameters alpha, beta_day, beta_assay, gamma, delta_day and delta_assay)

Figure 6 (A) Traceplots

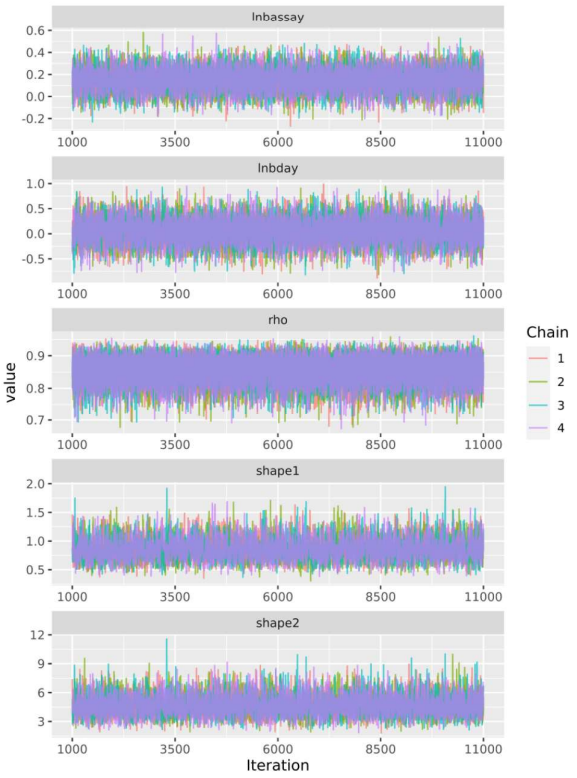


Figure 6 (B) Density plot of partial and full chains

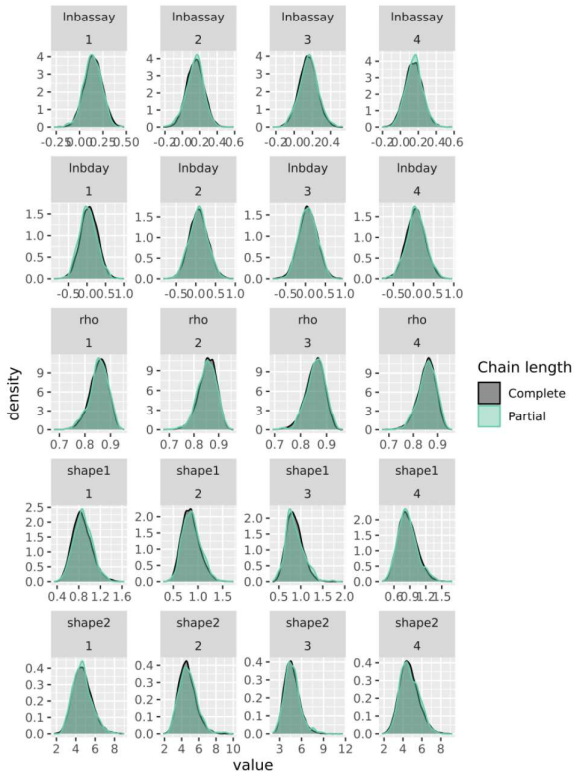


Figure 6 (C) Running mean by chain

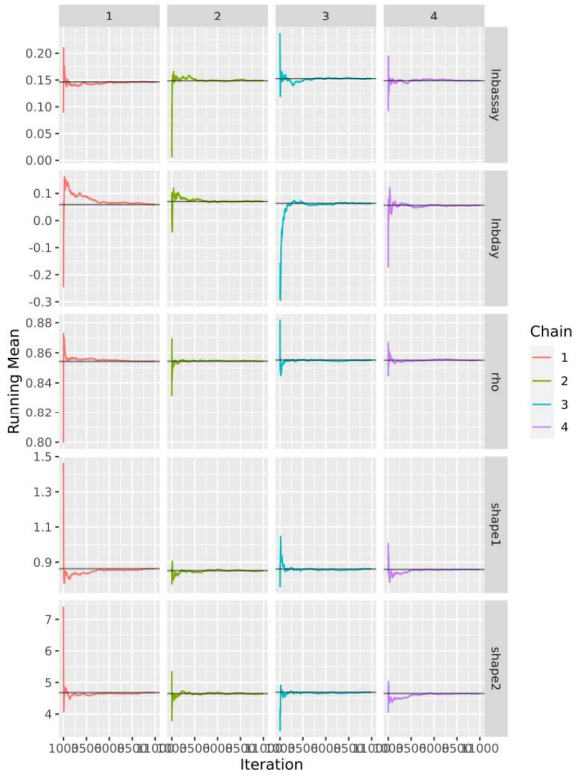


Figure 6 (D) Potential scale reduction factors

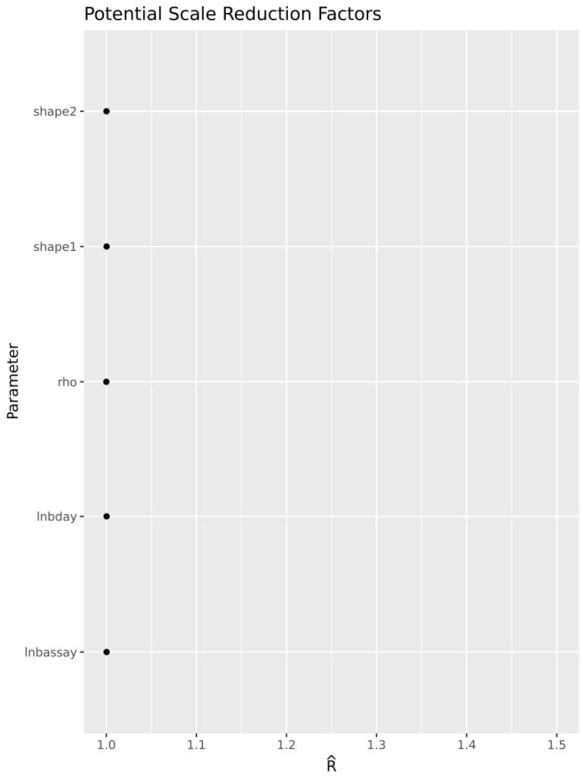


Figure 6 (E) Shrinkage of potential scale reduction factors

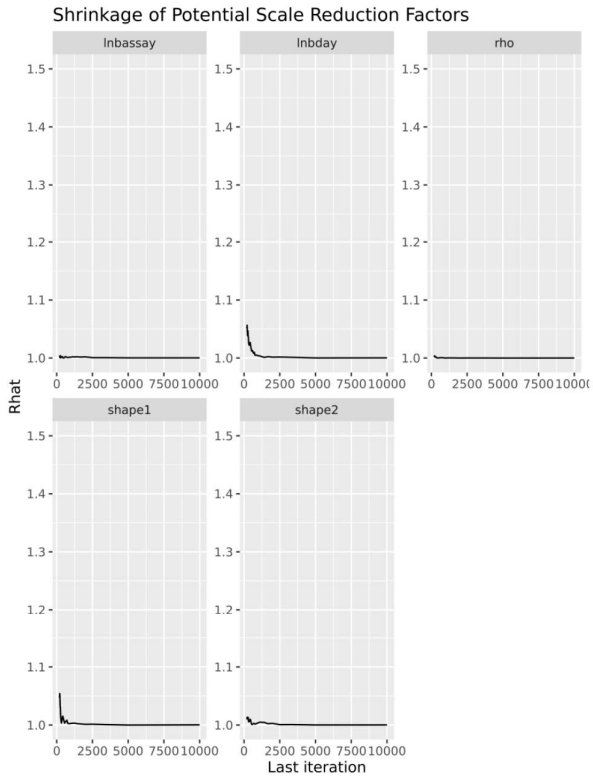


Figure 6 (F) Geweke Diagnosis