GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A Phase IIa, open-label, non-randomized, controlled, mono-center study to evaluate the efficacy, immunogenicity and safety of a fractional (Fx) booster dose of GlaxoSmithKline Biologicals' malaria candidate vaccine RTS,S/AS01$_E$ when given to healthy adults previously receiving various primary dose schedules in a sporozoite challenge model
eTrack study number and Abbreviated Title	209003 (MALARIA-102 BST 092)
Scope:	All data pertaining to the above study
Date of Statistical Analysis Plan	Final: 20 December 2018
Co-ordinating author:	PPD (Statistician)
Reviewed by:	PPD (Clinical Research and Development Lead) PPD (Clinical Research and Development Lead/Epidemiologist) PPD (Lead statistician) PPD (Lead statistical analyst) PPD (Scientific writer) Public disclosure
Approved by:	PPD (Clinical Research and Development Lead/Epidemiologist) delegating to PPD PPD (Clinical Research and Development Lead) PPD (Lead statistician) PPD (Statistician) PPD (Lead Scientific writer) delegating to PPD (Scientific writer) PPD (Lead statistical analyst)

APP 9000058193 Statistical Analysis Plan Template (Effective date: 14 April 2017))

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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
Anti-CS	Antibody to the *Plasmodium falciparum* circumsporozoite (CS) repeat domain
Anti-HBs	Antibody to the hepatitis B surface antigen
$AS01_B$	GSK's proprietary Adjuvant System containing MPL, QS-21 and liposome (50 µg MPL and 50 µg QS-21)
$AS01_E$	GSK's proprietary Adjuvant System containing MPL, QS-21 and liposome (25 µg MPL and 25 µg QS-21)
AST	Aspartate aminotransferase
CI	Confidence Interval
CRF	Case Report Form
C-term	CS terminal portion of the protein
CTRS	Clinical Trial Registry Summary
eCRF	electronic Case Report Form
ES	Exposed Set
EU/ml	ELISA unit per milliliter
GMC	Geometric mean concentration
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface Antigen
ICH	Internal Conference on Harmonization
IgG	Immunoglobulin G
ITTS	Intent-To-Treat Set
IU/ml	International units per milliliter
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
mIU/ml	Milli International units per milliliter
NP	Not protected
P	Protected
PCR	Polymerase chain reaction
pIMD	potential Immune Mediated Disease
PPS	Per-Protocol Set
SAE	Serious adverse event

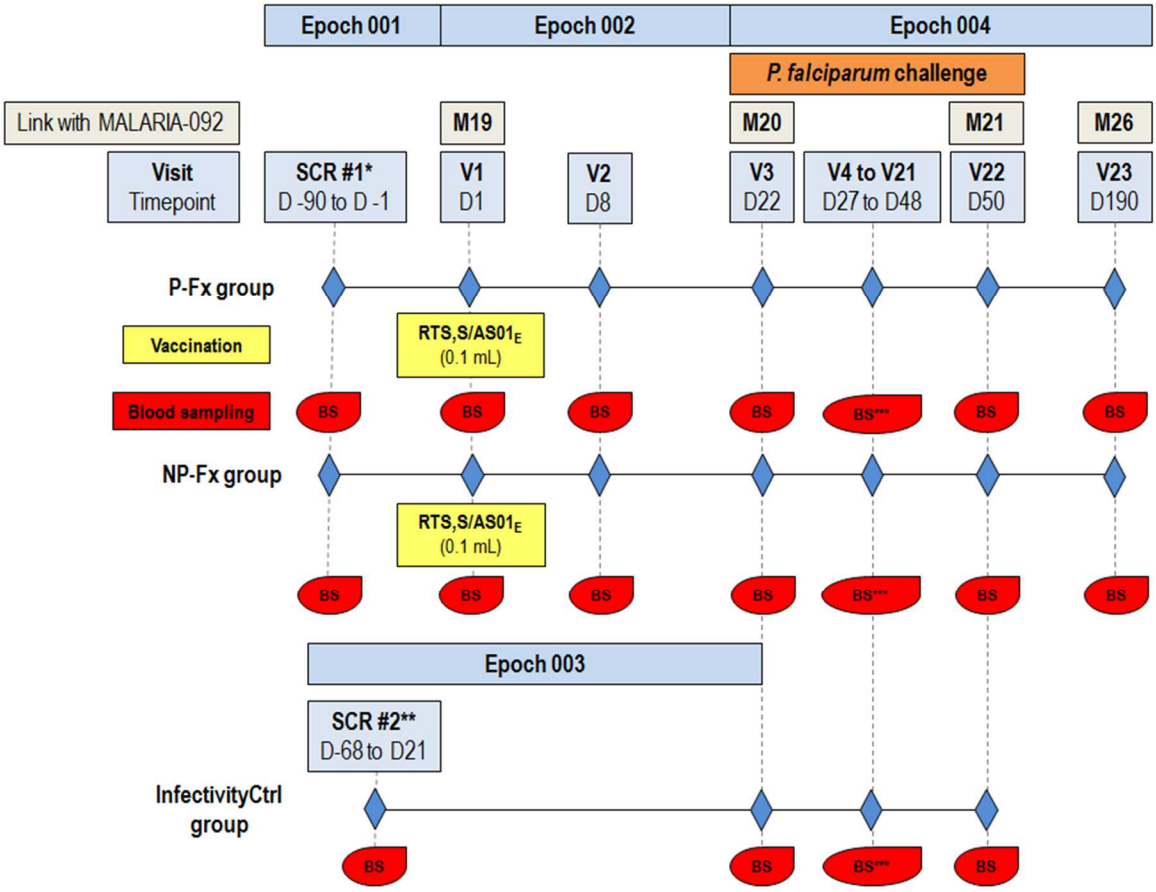
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
TFL	Tables Figures and Listings
TOC	Table of Content
UL	Upper Limit of the confidence interval
ULN	Upper Limit of normal range
VE	Vaccine Efficacy
WBC	White blood cells

1. DOCUMENT HISTORY

Date	Description	Protocol Version
20 DEC 2018	Final	Final: 26 SEP 2018

2. STUDY DESIGN

Figure 1 Study design overview



SCR = screening; **V** = visit; **D** = day; **M** = month; **BS** = blood sampling
*Screening visit applicable for the groups from the MALARIA-092 study receiving the fractional booster dose
**Screening visit applicable for subjects in the infectivity control group
***Blood sample for biochemistry and hematology parameters will be collected the day of first parasitemia and blood sample for assessment of parasitemia (blood smear and PCR) will be collected daily for 14 days (from Day 27 [Visit 4] to Day 40 [Visit 17]) and then every two days for nine days (Day 42 [Visit 18], Day 44 [Visit 19], Day 46 [Visit 20], Day 48 [Visit 21] and Day 50 [Visit 22]). Exceptionally this can occur within 1 or 3 days if the subject cannot make the visit or for schedule conflicts.

The following table gives the intervals between study visits at defined visits to apply, as described in the protocol:

Table 1 Intervals between study visits for the P-Fx and NP-Fx groups

Interval	Optimal length of interval*	Allowed interval**
Screening #1 → Visit 1	1 to 90 days	-
Visit 1 → Visit 2	7 days	6-8 days
Visit 1 → Visit 3 (challenge)	21 days	21-28 days
Visit 3 → Visit 22	28 days	21-35 days
Visit 22 → Visit 23	140 days	126-154 days

*Whenever possible the investigator should arrange study visits within this interval.
**Subjects may not be eligible for inclusion in the Per-Protocol Set (PPS) for analysis of immunogenicity and efficacy if they make the study visit outside this interval.

Table 2 Intervals between study visits for the infectivity control group

Interval	Optimal length of interval*	Allowed interval**
Screening #2 → Visit 3 (challenge)	1 to 90 days	-
Visit 3 → Visit 22	28 days	21-35 days

*Whenever possible the investigator should arrange study visits within this interval.
**Subjects may not be eligible for inclusion in the PPS for analysis of immunogenicity and efficacy if they make the study visit outside this interval.

The following group names will be used for the statistical analyses:

Group order in tables	Group label in tables	Group definition for footnote
1	P-Fx	Pooled subjects from the MALARIA-092 study vaccinated with RTS,S/AS01 (different doses/formulations) and protected following the first challenge who received a Fx booster dose of RTS,S/AS01E
2	NP-Fx	Pooled subjects from the MALARIA-092 study vaccinated with RTS,S/AS01 (different doses/formulations) and not protected following the first challenge who received a Fx booster dose of RTS,S/AS01E
3	Control	Subjects who did not received any vaccination but will undergo sporozoite challenge

Two defined pooled groups:

Group order in tables	Group label in tables	Group definition for footnote
1	P	All subjects who have not been infected by *P. falciparum* parasitemia (defined by a positive blood slide) during the challenge in MALARIA-102 study and were part of one of the vaccinated groups
2	NP	All subjects who have been infected by *P. falciparum* parasitemia (defined by a positive blood slide) during the challenge in MALARIA-102 study and were part of one of the vaccinated groups

3. OBJECTIVES/ENDPOINTS

3.1. OBJECTIVES

3.1.1. Primary objective

- To assess vaccine efficacy against the occurrence of *P. falciparum* parasitemia (defined by a positive blood slide):
  - In subjects who were protected following challenge in the MALARIA-092 study and who receive a Fx booster dose versus infectivity controls.
  - In subjects who were not protected following challenge in the MALARIA-092 study and who receive a Fx booster dose versus infectivity controls.

3.1.2. Secondary objectives

Efficacy

- To assess the time-to-onset of *P. falciparum* parasitemia (defined by a positive blood slide):
  - In subjects who were protected following challenge in the MALARIA-092 study and who receive a Fx booster dose versus the infectivity controls.
  - In subjects who were not protected following challenge in the MALARIA-092 study and who receive a Fx booster dose versus the infectivity controls.

Immunogenicity

- To evaluate anti-circumsporozoite protein (CS) repeat region antibody response at specified timepoints.
- To evaluate anti-hepatitis B antigen (HBs) Igtot antibody response at specified timepoints.

Safety

- To assess the reactogenicity (solicited adverse events [AEs]) and safety (unsolicited AEs, AEs of specific interest and serious adverse events [SAEs]).

3.1.3. Tertiary objectives

Efficacy

- To assess vaccine efficacy against the occurrence of *P. falciparum* parasitemia (defined by a positive blood slide):
  - In subjects who were protected versus subjects who were not protected following challenge in the MALARIA-092 study and who receive a Fx booster dose.

- To assess the time-to-onset of *P. falciparum* parasitemia (defined by a positive blood slide):
  - In subjects who were protected versus subjects who were not protected following challenge in the MALARIA-092 study and who receive a Fx booster dose.
- To assess the occurrence of *P. falciparum* parasitemia, defined by a positive PCR.
- To assess the time-to-onset of *P. falciparum* parasitemia, defined by a positive PCR.

Immunogenicity

- To evaluate the anti-CS repeat region IgG avidity index at specified timepoints.
- To evaluate the anti-full length CS protein IgG concentrations and anti-C terminal portion of the protein (C-term) IgG concentrations at specified timepoints.
- To evaluate the anti-full length CS protein and anti-C-term IgG avidity at specified timepoints.

Note: other immuno-assays evaluating the immune response targeting the CS and HBsAg might be performed.

3.2. ENDPOINTS

3.2.1. Primary endpoint

- Occurrence of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge (in all study groups versus infectivity controls).

3.2.2. Secondary endpoints

Efficacy

- Time-to-onset of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge.

Immunogenicity

- Anti-CS repeat region antibody concentrations at screening, Day 1, prior to challenge (Day 22), 28 days post-challenge (Day 50) and at study end (Day 190).
- Anti-HBs Igtot antibody concentrations at screening, Day 1, prior to challenge (Day 22), 28 days post-challenge (Day 50) and at study end (Day 190).

Safety

- Occurrence of solicited local and general AEs within 7 days after vaccination (day of vaccination and 6 subsequent days) in the booster vaccination groups.

- Occurrence of unsolicited AEs up to 21 days after vaccination (day of vaccination and 20 subsequent days), according to the Medical Dictionary for Regulatory Activities (MedDRA) classification, in the booster vaccination groups.
- Occurrence of AEs up to 29 days after challenge (day of challenge and 28 subsequent days), according to the MedDRA classification, in all study groups.
- Occurrence of AEs of specific interest (potential immune-mediated diseases [pIMDs] and meningitis) from Day 1 up to study conclusion (Day 190), according to the MedDRA classification, in all study groups.
- Occurrence of SAEs (all, fatal, related to investigational vaccine) during the whole study period (from screening up to study conclusion [Day 190]), according to the MedDRA classification, in all study groups.
- Occurrence of abnormal laboratory values at screening, Day 1, Day 8, Day 22, the day of first parasitemia and 28 days post-challenge (Day 50) for the booster vaccination groups; and at screening, Day 22, the day of first parasitemia and 28 days post-challenge (Day 50) for the infectivity control subjects.

3.2.3. Tertiary endpoints

Efficacy

- Occurrence of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge (between study groups).
- Time-to-onset of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge (between study groups).
- Occurrence of *P. falciparum* parasitemia (defined by a positive PCR) following sporozoite challenge (between study groups).
- Time-to-onset of *P. falciparum* parasitemia (defined by a positive PCR) following sporozoite challenge (between study groups).

Immunogenicity

- Anti-CS repeat region IgG avidity index at Day 1, prior to challenge (Day 22), 28 days post-challenge (Day 50) and at study end (Day 190).
- Anti-full length CS protein IgG concentrations and anti-C-term IgG concentrations at Day 1, prior to challenge (Day 22), 28 days post-challenge (Day 50) and at study end (Day 190).
- Anti-full length CS protein and anti-C-term IgG avidity at Day 1, prior to challenge (Day 22), 28 days post-challenge (Day 50) and at study end (Day 190).

4. ANALYSIS SETS

4.1. Definition

4.1.1. Enrolled Set

The Enrolled Set will include all screened subjects who provide informed consent and provide any demographic and/or other baseline screening measurements, regardless of the subject's randomization and vaccination status in the trial, and receive a subject ID (for infectivity control subjects).

4.1.2. Intent-to-treat set

The Intent-To-Treat Set (ITTS) will include all subjects from the P-Fx and NP-Fx groups who received the Fx dose of study vaccine. All challenged infectivity controls will also be included and will be presented as a separate study group.

4.1.3. Solicited Safety Set

The solicited Safety Set will include all subjects who received the dose of study vaccine and had any solicited safety data.

4.1.4. Per-protocol set for analysis of immunogenicity and efficacy

The Per-Protocol Set (PPS) for analysis of immunogenicity and efficacy will include all subjects included in the ITTS who fulfilled all eligibility criteria and received the Fx dose according to protocol procedures, did not use any medication, vaccine or blood products forbidden by the protocol, did not report any underlying medical condition influencing the efficacy response, had available data concerning immunogenicity endpoint measures, and underwent *P. falciparum* challenge. This will include subjects for whom assay results are available for antibodies against at least one study vaccine antigen after Day 1.

4.1.5. Adapted Per-Protocol Set for analysis of efficacy

The Adapted PPS (APPS) for analysis of efficacy will include all subjects included in the ITTS who fulfilled all eligibility criteria and received the Fx dose according to protocol procedures and underwent *P. falciparum* challenge.

4.2. Criteria for eliminating data from Analysis Sets

Elimination codes are used to identify subjects to be eliminated from analysis. Detail is provided below for each set.

4.2.1. Elimination from Intent-to-treat set (ITTS)

Code 1030 (Study vaccine not administered at all for P-Fx and NP-Fx groups), code 800 (fraudulent data), code 900 (invalid informed consent) and code 3000 (Subject who did not undergo challenge for control group) will be used for identifying subjects eliminated from ITTS.

4.2.2. Elimination from the Solicited Safety Set

Code 1030 (Study vaccine not administered at all for P-Fx and NP-Fx groups), code 800 (fraudulent data), code 900 (invalid informed consent) and code 1160 (no post-vaccination solicited safety data) will be used for identifying subjects eliminated from the solicited safety set.

4.2.3. Elimination from Per-protocol analysis Set for analysis of immunogenicity and efficacy (PPS) And from the Adaptive PPS for analysis of efficacy (APPS)

4.2.3.1. Excluded subjects

A subject will be excluded from the PPS and the APPS analysis under the following conditions

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
800	Fraudulent data	All	PPS, APPS
900	Invalid informed consent or fraudulent data	All	PPS, APPS
1030	Study vaccine not administered at all	All	PPS, APPS
1040	Administration of concomitant vaccine(s) forbidden in the protocol • Any investigational or non-registered vaccine other than the study vaccines used during the study period. • A vaccine not foreseen by the study protocol administered during the period starting seven days before each dose and ending seven days after each dose of vaccines administration.	All	PPS
1070	Vaccination not according to protocol • Administration not according to protocol for reason specified by the investigator, other than side, site and route.	All	PPS, APPS
1080	Good Manufacturing Practice No-Go: Vaccine temperature deviation	All	PPS
1090	Expired vaccine administered	All	PPS
2010	Protocol violation (inclusion/exclusion criteria) • Eligibility criteria not met with an impact on immunogenicity or efficacy data	All	PPS

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
2040	Administration of any medication forbidden by the protocol • Any investigational or non-registered product drug other than the study vaccines used during the study period. • Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days in total) during the study period. For corticosteroids, this will mean prednisone ≥ 20 mg/day (for adult subjects), or equivalent. Inhaled and topical steroids are allowed. • Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab). • A vaccine not foreseen by the study protocol administered during the period starting seven days before dose and ending seven days after the dose of vaccine administration. • Immunoglobulins and/or any blood products administered during • Drugs known to have anti-*Plasmodium* properties, used during the challenge period before identification of parasitemia	All	PPS
2050	Underlying medical condition forbidden by the protocol which may influence the efficacy endpoints	All	PPS
2080	Subjects did not comply with challenge schedule (see Tables 1	All	PPS
2090	Subjects did not comply with blood sample schedule (see Tables 1	All	PPS
2100	Serological results not available for all visits for anti-CS	All	PPS
2120	Obvious incoherence or abnormality or error in immunogenicity (antibody) data	All	PPS
3000	Subject did not undergo challenge	All	PPS, APPS

5. STATISTICAL ANALYSES

Note that standard data derivation rules and stat methods are described in "business rules document" and will not be repeated below.

5.1. Demography

5.1.1. Analysis of demographics/baseline characteristics planned in the protocol

A study flow table will be generated to present the number of subjects screened, randomized, receiving the Fx dose and included in the PPS for analyses of immunogenicity and efficacy.

The analysis of demographics will be performed on the ITTS and on the PPS for analysis of immunogenicity and efficacy.

Demographic characteristics (age at booster vaccination in years for the vaccinated groups and at the time of the screening for the infectivity control group, gender, and race) will be summarized by group and overall using descriptive statistics:

- Frequency tables will be generated for categorical variables such as race.
- Mean, median, standard deviation (SD) and range will be provided for continuous data such as age.

Previous study group (i.e., in the MALARIA-092 study) will be tabulated.

Withdrawal status will be summarized by group using descriptive statistics:

- The number of subjects enrolled into the study as well as the number of subjects excluded from PPS for analyses of immunogenicity and efficacy will be tabulated.
- The number of withdrawn subjects will be tabulated according to the reason for withdrawal.

5.2. Exposure

5.2.1. Analysis of exposure planned in the protocol

The number and percentage of subjects with vaccination will be summarized overall and by group for all study groups where a vaccination is part of the study procedure. The analysis of exposure will be performed on the ITTS.

5.3. Efficacy

5.3.1. Analysis of efficacy planned in the protocol

The analysis of efficacy will be performed on the PPS for analysis of immunogenicity and efficacy.

Efficacy will be assessed by comparison of *P. falciparum* parasitemia incidence and time-to-onset of *P. falciparum* parasitemia after sporozoite challenge. The analysis of the primary objective will be based on blood smears results; additional exploratory analyses will be performed based on PCR results (tertiary objectives).

Vaccine efficacy (VE) is defined as 100*(1-Relative Risk). Relative risk of infection and 95% CI will be calculated.

Fisher's Exact test will be used for the comparison of *P. falciparum* parasitemia incidence after challenge between each one of the study groups (P-Fx and NP-Fx) and the infectivity control group.

Kaplan-Meier analysis will be performed on time-to-onset of *P. falciparum* parasitemia, for comparisons between each one of the study groups (P-Fx and NP-Fx) and the infectivity control group, using the log-rank statistic.

The same methodology will be applied for the evaluation of the study groups (P-Fx vs. NP-Fx) versus each other. If there are sufficient evaluable subjects (at least a 1:2 ratio between vaccinated and control groups) to draw some conclusions, descriptive analyses based on initial group assignment versus control will be performed.

All statistical tests will be two-tailed at 5% significance level.

Risk periods

For the analyses of time-to-onset of parasitemia (Kaplan-Meier and log-rank), time-at-risk will start on first day of challenge. Time-at-risk will be censored on Visit 22 (Day 50; 28 days post-challenge), drop-out date, start date of anti-malarial treatment or date meeting an endpoint, whichever occurs first. Time-at-risk will be calculated as: censor date – challenge date + 1.

For the analysis of proportion affected (relative risk), all subjects included in the PPS for analysis of immunogenicity and efficacy will be considered at risk of infection and no censoring or elimination will be applied for subjects not completing the entire protocol defined post-challenge follow-up (Day 50; 28 days post challenge).

Case definition

The following will be used as case definition of *P. falciparum* infection:

Asexual blood stage *P. falciparum* parasite density > 0 detected by blood slide reading (or PCR for tertiary objectives).

5.4. Immunogenicity

5.4.1. Analysis of immunogenicity planned in the protocol

The analysis of immunogenicity will be performed on the PPS for analysis of immunogenicity and efficacy.

For each group, at each timepoint where a blood sample is collected:

- The percentage of subjects with seropositive levels of anti-CS (proportion of subjects with anti-CS antibody concentrations ≥ 1.9 EU/mL) with 95% CI will be determined at specified blood sampling timepoints. Anti-CS antibody concentrations will be summarized by GMC. Anti-CS antibody concentrations will be displayed using reverse cumulative curves (RCCs). Similar analysis will be performed for the anti-full length CS protein (proportion of subjects with anti-CS antibody titers ≥ 200 1/DIL) and anti-C-term antibodies (proportion of subjects with anti-CS antibody concentrations ≥ 100 Endpoint Titer).
- The percentage of subjects with seroprotection levels of anti-HBs (anti-HBs antibody concentrations ≥ 10 mIU/mL) with 95% CI will be determined at specified blood sampling timepoints. Anti-HBs antibody concentrations will be summarized by GMC. Anti-HBs antibody concentrations will be displayed using RCCs.

Anti-CS, anti-full length CS protein and anti-CS avidity index will be summarized by mean, SD, median and quartile and box and whiskers plots will be generated.

5.4.2. Additional considerations

In addition to the previous analyses, the immunogenicity analyses will be performed per protection status (P and NP) overall (pooled vaccine groups) and within each vaccine group.

Comparisons of the log-transformed means of anti-CS antibodies (repeated, full length, C-Term and avidity index). post vaccination and at the time of the challenge and for P vs NP (Student 2-Sample Test) will be performed.

Exploratory analyses using logistic regression models will be evaluated to describe the relationship between immune read outs and the probability of infection (P vs NP). Explanatory variables will include all or a part of available immune read outs at time of analysis (anti-CS, anti-full length CS protein, avidity index).

In a first step, immune responses will be plotted by group and protection status as well as cross-tabulated to understand potential correlation structures. Then, relevant models will be constructed to evaluate what are the independent predictors of protection, both pooled over the treatment groups (is/are there a generic driver(s)?) and by treatment schedule/including interactions (is protection mediated through different mechanisms between schedules?).

For the study groups and the pooled groups, we will also generated graphs to represent the evolution of the immunogenicity over the time.

5.5. Analysis of safety and reactogenicity

5.5.1. Analysis of safety and reactogenicity planned in the protocol

The analysis of safety will be performed on the ITTS.

For the P-Fx and NP-Fx groups:

- The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the 7-day or 21-day follow-up period after the booster Fx dose will be tabulated with exact 95% CI. Same computations will be done for grade 3 AEs, for any AEs considered related to vaccination and for any grade 3 AEs considered related to vaccination.
- The percentage of subjects reporting each individual solicited local AE (any grade and grade 3) and each individual solicited general AE (any grade, grade 3, any related, grade 3 related, resulting in medically attended visit) during the 7-day follow-up period (Days 1-7) after the booster Fx dose will be tabulated for each group, with exact 95% CI.
- For fever (defined as temperature ≥ 37.5°C/99.5°F for oral, axillary or tympanic route), the number and percentage of subjects reporting fever by half degree (°C) cumulative increments during the first seven days (Days 1-7) after the booster Fx dose will be tabulated. Similar tabulations will be performed for any fever with a causal relationship to vaccination and grade 3 (> 39.0°C) causally related fever. The maximum temperature reported over the 7-day follow-up period will be tabulated.
- The percentage of subjects reporting unsolicited AEs within 21 days (Days 1-21) after the booster Fx dose will be tabulated by group and by MedDRA preferred term with exact 95% CI. Similar tabulation will be done for grade 3 unsolicited AEs, for any causally related unsolicited AEs and for grade 3 causally related unsolicited AEs.
- The percentage of subjects using concomitant medication (any medication, any antipyretic and any prophylactic medication, respectively) during the 7-day follow-up period after vaccination will be summarized by group.

For all subjects:

- The percentage of subjects reporting AEs during 29 days after the sporozoite challenge (Day 22-Day 50) will be tabulated by group and by MedDRA preferred term with exact 95% CI. Similar tabulation will be done for grade 3 unsolicited AEs, for any causally related unsolicited AEs and for grade 3 causally related unsolicited AEs post challenge.

- The percentage of subjects reporting AEs of specific interest (meningitis and pIMDs) from Day 1 until last study visit (Day 190) (for P-Fx and NP-Fx groups)/from the day of challenge until last study visit (Day 50) (for infectivity control group), classified by MedDRA preferred term level, will be tabulated with exact 95% CI.
- The percentage of subjects reporting SAEs (all, fatal, related) occurring from Day 1 until last study visit (Day 190) (for P-Fx and NP-Fx groups)/from the day of challenge until last study visit (Day 50) (for infectivity control group), classified by the MedDRA preferred term level will be tabulated with exact 95% CI.
- Subjects reporting pregnancies will be described.
- The percentage of subjects reporting an AE or SAE leading to withdrawal from study from Day 1 until last study visit (Day 190) (for P-Fx and NP-Fx groups)/from the day of challenge (for infectivity control group) until last study visit (Day 50), classified by MedDRA preferred term level, will be tabulated with exact 95% CI.
- The percentage of subjects using concomitant medication during the entire sporozoite challenge (Days 22-50) will be summarized by group.

Biochemistry (ALT, AST and creatinine) and hematological (hemoglobin, WBC and platelets) laboratory values will be presented by visit according to toxicity grading scales and tabulated by group. The normal ranges and toxicity grading for laboratory safety parameters used in this study are presented in the following table.

Table 3 Toxicity grading scales for blood testing

Adverse event	Intensity grade	Intensity*
Hemoglobin (males)	Normal range	≥12.5 g/dl
	1	< 12.5 but ≥ 11.0 g/dl
	2	< 11.0 but ≥ 10.0 g/dl
	3	< 10.0 g/dl
Hemoglobin (females)	Normal range	≥11.5 g/dl
	1	< 11.5 but ≥ 10.5 g/dl
	2	< 10.5 but ≥ 9.5 g/dl
	3	< 9.5 g/dl
Increase in leukocytes (WBC)	Normal range	≤10799 cells/mm^3
	1	10800 - 15000 cells/mm^3
	2	15001 - 20000 cells/mm^3
	3	> 20001 cells/mm^3
Decrease in leukocytes (WBC)	Normal range	≥3200 cells/mm^3
	1	2500 - 3199 cells/mm^3
	2	1500 - 2499 cells/mm^3
	3	< 1500 cells/mm^3
Decrease in platelets	Normal	≥140000 cells/mm^3
	1	125000 - 139000 cells/mm^3
	2	100000 - 124000 cells/mm^3
	3	< 100000 cells/mm^3
Alanine Aminotransferase	Normal range	Below ULN (60 U/l for males; 40 U/l for females)
	1	1.1 - 2.5 x ULN
	2	2.6 – 5 x ULN
	3	> 5 x ULN
Aspartate Aminotransferase	Normal range	Below ULN (40 U/l for males; 35 U/l for females)
	1	1.1 - 2.5 x ULN
	2	2.6 – 5 x ULN
	3	> 5 x ULN
Creatinine (males)	Normal range	≤1.39 mg/dl
	1	1.4 - 1.79 mg/dl
	2	1.8 - 2.0 mg/dl
	3	> 2.0 mg/dl
Creatinine (females)	Normal range	≤1.29 mg/dl
	1	1.3 – 1.69 mg/dl
	2	1.7 – 1.9 mg/dl
	3	>1.9 mg/dl

ULN: upper limit of normal range

* Grading scale adapted from [FDA guidance for industry toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials (September 2007)].

5.5.2. Additional considerations

A summary of subjects with all combined solicited (regardless of their duration) and unsolicited AEs will be provided. Solicited AEs will be coded by MedDRA as per the following codes:

Solicited symptom	Lower level term code	Corresponding Lower level term decode
FATIGUE	10016256	Fatigue
FEVER	10016558	Fever
GASTROINTESTINAL	10017944	Gastrointestinal disorder
HEADACHE	10019211	Headache
PAIN	10022086	Injection site pain
REDNESS	10022098	Redness at injection site
SWELLING	10053425	Swelling at injection site

6. ANALYSIS INTERPRETATION

All analyses performed during this study will be descriptive. The inferential analyses will not be considered confirmatory but rather used as an estimation of the probability that an effect is true

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

The analyses will be performed stepwise:

- An interim analysis will be performed as soon as the results of the challenge phase are available on data as clean as possible, including safety and immunogenicity results, if available. This analysis will be descriptive and performed on the Adapted PPS for analysis of efficacy and on ITTS for safety. Results will be used to make a decision on future field trials.
- When all the remaining data up to Day 190 will be available, the main analysis will be performed. An integrated clinical study report containing all data will be written and made available to the investigators.

If the data for exploratory assessments become available at a later stage, (an) additional analysis/analyses will be performed and results will be reported in a publication, if applicable.

Description	Disclosure Purpose
Interim Efficacy analysis	Internal, publication/congress presentation
Final analysis	Web disclosure, Study report

7.2. Statistical considerations for interim analyses

A descriptive analysis to evaluate vaccine efficacy against infection of *P. falciparum* will be performed on the Adapted PPS for analysis of efficacy at the time of the interim analysis and will not be part of the CSR. Note that the main objective of the study linked to this endpoint will be analysed at the end of the study, on the PPS for analysis of immunogenicity and efficacy and can output different results. At the same time, we will perform some immunogenicity and safety/reactogenicity analyses, on data as clean as possible. All the analyses will be re-done during the final analysis which will be presented in the CSR.

8. CHANGES FROM PLANNED ANALYSES

Not applicable.

9. ANNEXES

9.1. Business rules for standard data derivations and statistical methods

This section contains GSK Vaccines' standard rules for data display and derivation for clinical and epidemiological studies.

9.1.1. Attributing events to vaccine doses

The dose relative to an event is the most recent study dose given to a subject prior to the start of a given event.

If an event starts on the same day as a study dose, the relative dose will be derived from the additional information provided in the CRF using the contents of the flag indicating if the event occurred before or after vaccination. If 'after vaccination' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'before vaccination' is selected, the relative dose for the event will be the dose prior to this one.

9.1.2. Handling of missing data

9.1.2.1. Dates

When partially completed dates (i.e. with missing day or month) are used in calculations, the following standard rules will be applied:

- A missing day will be replaced by 15
- A missing day and month will be replaced by June 30th.

The following exceptions apply:

- AE start dates with missing day:
  - If the event starts in the same month as the study dose, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the study dose given during that month. If 'before vaccination' is selected, the imputed date will be one day before the study dose given during that month.
- AE start dates with missing day and month:
  - If the event starts in the same year as the study dose, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the study dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the study dose given during that year.

All other cases of incomplete AE or concomitant medication/vaccination start date will follow the standard rules above.

9.1.2.2. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

9.1.2.3. Daily recording of solicited symptoms

For studies using paper diaries which have questions in the CRF indicating the presence or absence of solicited symptoms, the following rules are applicable.

Denominators for the summary of local (or general) solicited symptoms will be calculated using the number of subjects who respond "Yes" or "No" to the question concerning the occurrence of local (or general) symptoms.

When a specific symptom is marked as having not occurred following a specific vaccination (i.e. SDTM CE.CEOCCUR=N for the specified post-vaccination period for the symptom in question), all daily measurements will be imputed as Grade 0.

When a specific symptom is marked as having occurred following a specific vaccination (i.e. SDTM CE.CEOCCUR=Y for the specified post-vaccination period for the symptom in question), any missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the symptom summary tables.

When the occurrence of a specific symptom is not present (i.e. SDTM CE.CEOCCUR is neither Y nor N for the specified post-vaccination period for the symptom in question) but the group of symptoms (local or general) is marked as having occurred (i.e. SDTM CE.CEOCCUR=Y), all missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the symptom summary tables.

The following table shows how subjects contribute to each category for a specific solicited symptom over the Day X to Day Y post-vaccination period:

Solicited symptom category	Subjects included in the calculation of the numerator
Any	All subjects with at least one occurrence of the symptom at grade 1, grade 2, or grade 3 between Day X and Day Y or with the symptom marked as present and at least one missing daily recording between Day X and Day Y
At least grade 1	All subjects with at least one occurrence of the symptom at grade 1, grade 2, or grade 3 between Day X and Day Y
At least grade 2	All subjects with at least one occurrence of the symptom at grade 2 or grade 3 between Day X and Day Y
At least grade 3	All subjects with at least one occurrence of the symptom at grade 3 between Day X and Day Y

9.1.2.4. Unsolicited adverse events

Missing severity, relationship with study vaccine, and outcome of unsolicited AEs will not be replaced and will appear as 'UNKNOWN' in all statistical output.

9.1.3. Data derivation

When age at vaccination is to be displayed in years, it will be calculated as the number of complete calendar years between the date of birth and the date of vaccination. For example:

DOB = PPD 1983, Date of vaccination = PPD -> Age = 34 years

DOB = 1983, Date of vaccination = -> Age = 35 years

9.1.3.1. Temperature

Temperatures will be presented in degrees Celsius (°C). Temperatures reported in degrees Fahrenheit (°F) will be converted as follows:

Temperature (Celsius) = ((Temperature (Fahrenheit) - 32) x 5)/9

9.1.3.2. Numerical serology results

Numerical serology results will be derived from the content of IS.ISORRES in the SDTM dataset. For assays with a specific cut-off, the following derivation rules apply:

IS.ISORRES	Derived value
"NEG", "-", or "(-)"	cut-off/2
"POS", "+", or "(+)"	cut-off
"< value" and value is <= assay cut-off	cut-off/2
"< value" and value is > assay cut-off	value
"> value" and value is < assay cut-off	cut-off/2
"> value" and value is >= assay cut-off	value
"value" and value is < cut-off	cut-off/2
"value" and value is >= cut-off	value
All other cases	missing

9.1.3.3. Geometric mean concentrations (GMCs)

Geometric Mean Concentration (GMC) calculations are performed by taking the inverse logarithm of the mean of the log concentration transformations. Antibody concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off of the assay for the purpose of GMC calculation. The cut-off value is defined by the laboratory before the analysis and is described in the protocol.

9.1.3.4. Onset day

The onset day for an event (e.g. AE, medication, vaccination) is the number of days between the study vaccination and the start date of the event. This is 1 for an event occurring on the same day as a vaccination (and reported as starting after vaccination).

9.1.3.5. Duration of events

The duration of an event with a start and end date will be the number of days between the start and end dates plus one day, i.e. an event that starts on 03MAR2018 and ends on 12MAR2018 has a duration of 10 days.

The duration of solicited events will be calculated as the sum of the individual days with the symptom reported at grade 1 or higher.

9.1.3.6. Counting rules for combining solicited and unsolicited adverse events

For output combining solicited and unsolicited AEs, all SAEs will be considered general events since the administration site flag is not included in the expedited adverse event CRF pages.

Multiple events with the same preferred term which start on the same day are counted as only one occurrence.

9.1.3.7. Counting rules for occurrences of solicited adverse events

When the occurrences of solicited AEs are summarized, each event recorded as having occurred during a specific period will be counted as only one occurrence regardless of the number of days on which it occurs.

9.1.4. Display of decimals

9.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

- no decimals when there are fewer than 50 subjects in each tabulated group
- one decimal when there are at least 50 subjects in at least one tabulated group

- Exceptions will be made for percentages that are not 0% or 100% but appear as 0% or 100% due to rounding. For these specific cases the number of decimals will be increased until the displayed value is no longer 0% or 100%. Examples are given in the following table.

n/N	Displayed percentage
10/45	22%
1/45	2%
10/55	18.2%
1/55	1.8%
1/300	0.3%
1/3000	0.03%
1/30000	0.003%
299/300	99.7%
2999/3000	99.97%
29999/30000	99.997%

- The display of additional decimals for values close to 0% or 100% will be applied only to point estimates and not confidence limits, which can be rounded and displayed as 0% or 100%.
- Values of exactly 0% or 100% will be presented with no decimals regardless of the number of subjects per tabulated group.

9.1.4.2. Differences in percentages

Differences in percentages and their corresponding confidence limits will be displayed with one more decimal than the maximum number used to display the individual percentages, for example the difference between two percentages displayed with one decimal will be displayed with two decimals.

9.1.4.3. Demographic/baseline characteristics statistics

The mean, median, and SD for continuous baseline characteristics (height, weight, body mass index (BMI), pre-vaccination body temperature) will be presented with one decimal.

The minimum and maximum values and quartile values (if required) will be presented with the same number of decimals as the observed values.

The maxima and minima of transformed height variables will be displayed with no decimals.

The maxima and minima of transformed weight variables will be displayed with no decimals with the exception of values are below 10kg where one decimal will be displayed.

The maximum and minima of transformed body temperatures will be displayed with one decimal.

9.1.4.4. Serological summary statistics

The number of decimals used when displaying geometric mean concentrations (GMC) and their confidence limits is shown in the following table:

GMC value	Number of decimals to display
<0.1	3
>=0.1 and <10	2
>=10 and <1000	1
>=1000	0

When multiple categories of GMC values are present in the same table, the number of decimals displayed should match that of the smallest category (i.e. the one with the higher number of decimals). For example, if GMC values of <0.1 appear in the same table as values of >=0.1 and <10, 3 decimals should be displayed for both.

GMC ratios and their confidence limits will be displayed with 2 decimals regardless of the actual values.

9.1.5. Statistical methodology

9.1.5.1. Exact confidence intervals around proportions

The exact CIs around within-group proportions are derived using the method of Clopper and Pearson [Clopper, 1934].

9.1.5.2. Standardized asymptotic confidence intervals around differences in proportions

The standardized asymptotic confidence intervals around differences in proportions are derived using the method of Mietinnen and Nurminen [Miettinen, 1985].

9.1.5.3. Adjusted GMC ratios

When between-group GMC ratios are computed and adjusted for two-level categorical co-variables, these co-variables should be included as dummy continuous variables in the SAS procedure.

9.2. TFL and/or TFL ToC

The TFL and/or the TFL ToC can be found in eTMF folder section 11.1.1.

10. REFERENCES

Clopper CJ, Pearson E. The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. *Biometrika.* 1934;26:404-13.

Miettinen, O. S. and Nurminen, M. Comparative analysis of two rates. Statistics in Medicine, 1985;4,213-226.