GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A Phase IIa, open-label, controlled, mono-center study to evaluate the efficacy, immunogenicity and safety of GSK Biologicals' candidate malaria vaccines RTS,S/AS01$_E$ and RTS,S/AS01$_B$ administered as various dose schedules according to a 0, 1, 7-month or a 0, 7-month schedule in healthy malaria-naïve subjects aged 18-55 years.
eTrack study number and Abbreviated Title	205081 (MALARIA-092)
Scope:	All data pertaining to the above study.
Date of Statistical Analysis Plan	Amendment 1 Final: 05-DEC-2018
Co-ordinating author:	PPD / PPD (Statistician)
Reviewed by:	PPD (Clinical Research and Development Lead) PPD (Lead Scientific writer) PPD (Scientific writer) PPD (Regulatory Affair) PPD (SERM physician) PPD (SERM Scientist) PPD (CLS Manager) PPD (Lead statistical analyst) PPD (Lead statistician) PPD (Public disclosure)
Approved by:	PPD (Clinical Research and Development Lead) PPD (Lead Scientific writer) PPD (Lead statistical analyst) PPD (Lead statistician)

APP 9000058193 Statistical Analysis Plan Template (Effective date: 14April 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
ATP	According-To-Protocol
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CLS	Clinical laboratory sciences
CRF	Case Report Form
C-term	CS terminal portion of the protein
CTRS	Clinical Trial Registry Summary
eCRF	electronic Case Report Form
EPT	Endpoint titer
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
IU/ml	International units per milliliter
ITTS	Intent-To-Treat Set
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

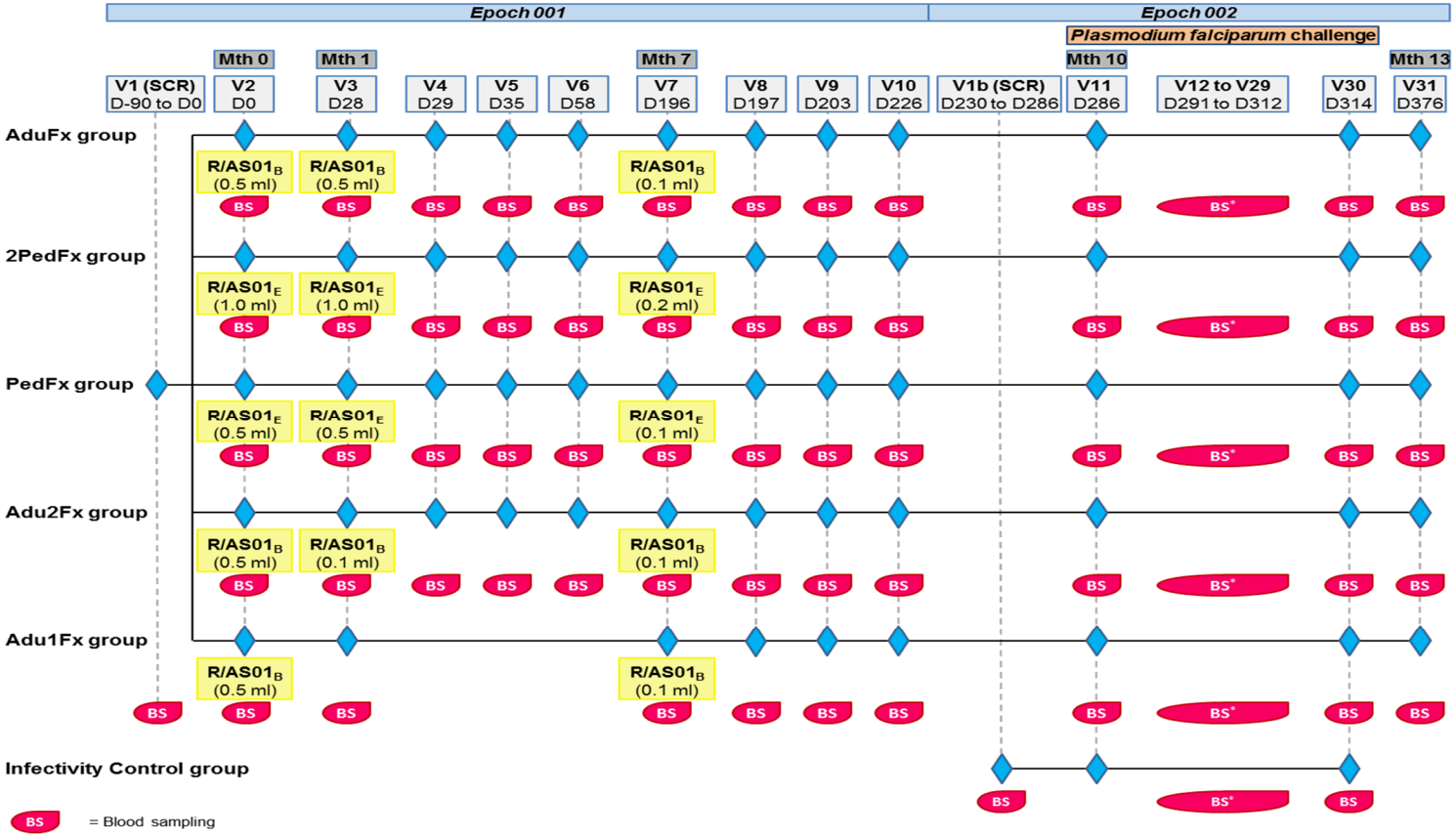
PCR	Polymerase chain reaction
PD	Protocol Deviation
pIMD	potential Immune Mediated Disease
PPS	Per-Protocol Set
SAE	Serious adverse event
SAS	Statistical Analysis System
SAP	Statistical Analysis Plan
SD	Standard Deviation
SERM	Safety Evaluation and Risk Management
SHS	Study Headline Summary
TFL	Tables 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
24-MAY-2018	Final version	Administrative Change – 19-JUN-2017
05-DEC-2018	Amendment 1: Addition of one analysis set and update in the standard computation rules	Administrative Change – 19-JUN-2017

2. STUDY DESIGN

Figure 1 Study design



D: Day; Mth: month; R: RTS,S; SCR: Screening; V: visit. * Blood sample for estimation of subjects with parasitemia (PCR testing) will be collected on the day of subject entry into the hotel phase (Day 295 [Visit 16]); blood sample for biochemistry and hematology parameters will be collected the day of first parasitemia and blood sample for assessment of parasitemia (blood smear) will be collected daily for 14 days (from Day 291 [Visit 12] to Day 304 [Visit 25]) and then every two days for nine days (Day 306 [Visit 26], Day 308 [Visit 27], Day 310 [Visit 28], Day 312 [Visit 29], and Day 314 [Visit 30]).

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 investigational vaccine groups: AduFx, 2PedFx, PedFx, and Adu2Fx

Interval	Optimal length of interval [1]	Allowed interval[2]
Visit 1 (Screening) → Visit 2 (1st vaccination)	0 to 90 days	-
Visit 2 → Visit 3 (2nd vaccination)	28 days	± 7 days
Visit 3 → Visit 5	7 days	± 1 day
Visit 3 → Visit 6	30 days	± 7 days
Visit 3 → Visit 7 (3rd vaccination)	168 days	± 14 days
Visit 7 → Visit 9	7 days	± 1 day
Visit 7 → Visit 10	30 days	± 7 days
Visit 7 → Visit 11 (Challenge)	90 days	+ 14 days
Visit 11 → Visit 30	28 days	± 7 days
Visit 30 → Visit 31	62 days	± 14 days

[1] Whenever possible the investigator should arrange study visits within this interval.
[2] Subjects may not be eligible for inclusion in the according-to-protocol (ATP) cohort for analysis of immunogenicity and efficacy if they make the study visit outside this interval.

Table 2 Intervals between study visits for the investigational vaccine group: Adu1Fx

Interval	Optimal length of interval [1]	Allowed interval[2]
Visit 1 (Screening) → Visit 2 (1st vaccination)	0 to 90 days	-
Visit 2 → Visit 7 (2nd vaccination)	196 days	± 14 days
Visit 7 → Visit 9	7 days	± 1 day
Visit 7 → Visit 10	30 days	± 7 days
Visit 7 → Visit 11 (Challenge)	90 days	+ 14 days
Visit 11 → Visit 30	28 days	± 7 days
Visit 30 → Visit 31	62 days	± 14 days

[1] Whenever possible the investigator should arrange study visits within this interval.
[2] Subjects may not be eligible for inclusion in the ATP cohort for analysis of immunogenicity and efficacy if they make the study visit outside this interval.

Table 3 Intervals between study visits for the infectivity control group

Interval	Optimal length of interval [1]	Allowed interval[2]
Visit 1b (Screening) → Visit 11 (Challenge)	0 to 56 days	-
Visit 11 → Visit 30	28 days	± 7 days

[1] Whenever possible the investigator should arrange study visits within this interval.
[2] Subjects may not be eligible for inclusion in the ATP cohort 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	AduFx	RTS,S/AS01$_B$ full dose administered at Month 0, Month 1 and RTS,S/AS01$_B$ 1/5th dose administered at Month 7
2	2PedFx	RTS,S/AS01$_E$ double dose administered at Month 0, Month 1 and double dose RTS,S/AS01$_E$ 1/5th dose administered at Month 7
3	PedFx	RTS,S/AS01$_E$ full dose administered at Month 0, Month 1 and RTS,S/AS01$_E$ 1/5th dose administered at Month 7
4	Adu2Fx	RTS,S/AS01$_B$ full dose at Month 0 and RTS,S/AS01$_B$ 1/5th dose administered at Month 1, Month 7
4	Adu1Fx	RTS,S/AS01$_B$ full dose at Month 0 and RTS,S/AS01$_B$ 1/5th dose administered at Month 7
5	Control	Subjects will not receive any immunization 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 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 and were part of one of the vaccinated groups

3. OBJECTIVES

3.1. Primary objective

3.1.1. Efficacy

- To assess the vaccine efficacy against the occurrence of *P. falciparum* parasitemia (defined by a positive blood slide) for each vaccination schedule (AduFx, 2PedFx, PedFx, Adu2Fx, and Adu1Fx) versus the infectivity controls.

Refer to Section 4.1 for the definition of the primary endpoint.

3.2. Secondary objectives

3.2.1. Efficacy

- To assess the time to onset of *P. falciparum* parasitemia (defined by a positive blood slide) for each vaccination schedule (AduFx, 2PedFx, PedFx, Adu2Fx, and Adu1Fx) versus the infectivity controls.
- To assess the occurrence of *P. falciparum* parasitemia (defined by a positive blood slide) after vaccine administration for alternative vaccination schedules (2PedFx, PedFx, Adu2Fx, and Adu1Fx) versus the immunization schedule of reference (AduFx).
- To assess the time to onset of *P. falciparum* parasitemia (defined by a positive blood slide) after vaccine administration for alternative vaccination schedules (2PedFx, PedFx, Adu2Fx, and Adu1Fx) versus the immunization schedule of reference (AduFx).

3.2.2. Immunogenicity

For each vaccination schedule:

- To evaluate anti-CS repeat region antibody response at specified timepoints.
- To evaluate anti-HBs immunoglobulin G (IgG) antibody response at specified timepoints.

3.2.3. Safety

For each vaccination schedule:

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

Refer to Section 4.2 for the definition of the secondary endpoints.

3.3. Tertiary objectives

3.3.1. Immunogenicity

For each vaccination schedule:

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

Refer to Section 4.3 for the definition of the tertiary endpoints.

4. ENDPOINTS

4.1. Primary endpoint

4.1.1. Efficacy

- Occurrence of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge, comparing RTS,S/AS01$_B$ administered as full doses at Month 0 and Month 1 and 1/5th dose at Month 7 (AduFx group) versus infectivity controls.
- Occurrence of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge, comparing RTS,S/AS01$_E$ administered as double dose at Month 0 and Month 1 and double 1/5th dose at Month 7 (2PedFx group) versus infectivity controls.
- Occurrence of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge, comparing RTS,S/AS01$_E$ administered as full doses at Month 0 and Month 1 and 1/5th dose at Month 7 (PedFx group) versus infectivity controls.
- Occurrence of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge, comparing RTS,S/AS01$_B$ administered as one full dose at Month 0 and 1/5th doses at Month 1 and Month 7 (Adu2Fx group) versus infectivity controls.
- Occurrence of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge, comparing RTS,S/AS01$_B$ administered as one full dose at Month 0 and 1/5th doses at Month 7 (Adu1Fx group) versus infectivity controls.

4.2. Secondary endpoints

4.2.1. Efficacy

- Occurrence of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge, comparing RTS,S/AS01$_E$ administered as double dose at Month 0 and Month 1 and double 1/5th dose at Month 7 (2PedFx group) versus immunization schedule of reference (AduFx group).
- Occurrence of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge, comparing RTS,S/AS01$_E$ administered as full doses at Month 0 and Month 1 and 1/5th dose at Month 7 (PedFx) versus immunization schedule of reference (AduFx group).
- Occurrence of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge, comparing RTS,S/AS01$_B$ administered as one full dose at Month 0 and 1/5th full dose at Month 1 and Month 7 (Adu2Fx) versus immunization schedule of reference (AduFx group).
- Occurrence of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge, comparing RTS,S/AS01$_B$ administered as one full dose at Month 0 and 1/5th full doses at Month 7 (Adu1Fx) versus immunization schedule of reference (AduFx group).
- Time to onset of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge in each vaccination schedule versus immunization schedule of reference (AduFx group).
- Time to onset of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge in each vaccination schedule versus infectivity controls.

4.2.2. Immunogenicity

- For each vaccination schedule, the immune response to the CS antigen of the investigational vaccine:
  - Anti-CS repeat region antibody concentrations before vaccine administration (Day 0), one month post-Dose 2 (Day 58), six months post-Dose 2 (Day 196), one month post-Dose 3 (Day 226), on the day of challenge (Day 286), 28 days post-challenge (Day 314), and at study end (Day 376) for subjects from AduFx, 2PedFx, PedFx, and Adu2Fx groups and before vaccine administration (Day 0), before Dose 2 (Day 196), one month post-Dose 2 (Day 226), on the day of challenge (Day 286), 28 days post-challenge (Day 314), and at study end (Day 376) for subjects from Adu1Fx group.

- For each vaccination schedule, the immune response to the hepatitis B antigen of the investigational vaccine:
  - Anti-HBs IgG antibody concentrations before vaccine administration (Day 0), one month post-Dose 2 (Day 58), six months post-Dose 2 (Day 196), one month post-Dose 3 (Day 226), on the day of challenge (Day 286), 28 days post-challenge (Day 314), and at study end (Day 376) for subjects from AduFx, 2PedFx, PedFx, and Adu2Fx groups and before vaccine administration (Day 0), before Dose 2 (Day 196), one month post-Dose 2 (Day 226), on the day of challenge (Day 286), 28 days post-challenge (Day 314), and at study end (Day 376) for subjects from Adu1Fx group.

4.2.3. Safety

- Safety and reactogenicity of the investigational vaccine for each vaccination schedule:
  - Occurrence of solicited local and general AEs within seven days (day of vaccination and six subsequent days) after each vaccination.
  - Occurrence of unsolicited AEs within 30 days (day of vaccination and 29 subsequent days) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
  - Occurrence of AEs within 30 days (day of challenge and 29 subsequent days) after challenge, according to the MedDRA classification.
  - Occurrence of SAEs (all, fatal, related to investigational vaccine) within 30 days (day of vaccination and 29 subsequent days) after each vaccination, according to the MedDRA classification.
  - Occurrence of SAEs (all, fatal, related to investigational vaccine) during the whole study period (from Dose 1 [Day 0] up to study conclusion [Day 376]), according to the MedDRA classification.
  - Occurrence of AEs and SAEs leading to withdrawal from further vaccination from Dose 1 (Day 0) up to study conclusion (Day 376), according to the MedDRA classification, for each vaccinated subject.
  - Occurrence of pIMDs from Dose 1 (Day 0) up to study conclusion (Day 376), according to the MedDRA classification, for each vaccinated subject.
  - Occurrence of meningitis from Dose 1 (Day 0) up to study conclusion (Day 376), according to the MedDRA classification, for each vaccinated subject.
  - Occurrence of abnormal laboratory values at screening, Day 35, Day 58, Day 203, Day 226, the day of first parasitemia, and Day 314 for each vaccinated subject and at screening, the day of first parasitemia and Day 314 for the infectivity control subjects.

- Safety after sporozoite challenge in the infectivity control group.
  - Occurrence of AEs within 30 days (day of challenge and 29 subsequent days) after challenge, according to the MedDRA classification.
  - Occurrence of SAEs (all, fatal, related) from day of challenge (Day 286) to the end of the challenge phase (Day 314), according to the MedDRA classification.

4.3. Tertiary endpoints

4.3.1. Immunogenicity

- For each vaccination schedule, the immune response to the CS antigen of the investigational vaccine:
  - Anti-CS repeat region IgG avidity index before vaccine administration (Day 0), one month post-Dose 2 (Day 58), six months post-Dose 2 (Day 196), one month post-Dose 3 (Day 226), on the day of challenge (Day 286), 28 days post-challenge (Day 314), and at study end (Day 376) for subjects from AduFx, 2PedFx, PedFx, and Adu2Fx groups and before vaccine administration (Day 0), before Dose 2 (Day 196), one month post-Dose 2 (Day 226), on the day of challenge (Day 286), 28 days post-challenge (Day 314), and at study end (Day 376) for subjects from Adu1Fx group.
  - Anti-full length CS protein IgG concentrations and anti-C-term IgG concentrations before vaccine administration (Day 0), one month post-Dose 2 (Day 58), six months post-Dose 2 (Day 196), one month post-Dose 3 (Day 226), on the day of challenge (Day 286), 28 days post-challenge (Day 314), and at study end (Day 376) for subjects from AduFx, 2PedFx, PedFx, and Adu2Fx groups and before vaccine administration (Day 0), before Dose 2 (Day 196), one month post-Dose 2 (Day 226), on the day of challenge (Day 286), 28 days post-challenge (Day 314), and at study end (Day 376) for subjects from Adu1Fx group.
  - Anti-full length CS protein and anti-C-term IgG avidity before vaccine administration (Day 0), one month post-Dose 2 (Day 58), six months post-Dose 2 (Day 196), one month post-Dose 3 (Day 226), on the day of challenge (Day 286), 28 days post-challenge (Day 314), and at study end (Day 376) for subjects from AduFx, 2PedFx, PedFx, and Adu2Fx groups and before vaccine administration (Day 0), before Dose 2 (Day 196), one month post-Dose 2 (Day 226), on the day of challenge (Day 286), 28 days post-challenge (Day 314), and at study end (Day 376) for subjects from Adu1Fx group.

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

5. ANALYSIS SETS

5.1. Definition

Note that in order to align to ICH and CDISC terminology the According To Protocol (ATP) cohort has been renamed the Per-Protocol Set (PPS).

5.1.1. Enrolled Set

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

5.1.2. Intent-to-treat set (ITTS)

The Intent-To-Treat Set (ITTS) will include all subjects who received at least one dose of study vaccine. The ITTS analysis will be performed per treatment actually administered. All challenged infectivity controls will also be included and will be presented as a separate study group.

5.1.3. Solicited Safety Set

The solicited Safety Set will include all subjects who received at least one dose of study vaccine and had solicited safety data.

5.1.4. Per-Protocol Set for analysis of immunogenicity and efficacy (PPS for analysis of immunogenicity and efficacy)

The PPS for analysis of immunogenicity and efficacy will include all subjects included in the ITTS who fulfilled all eligibility criteria and received all vaccinations according to protocol procedures within the protocol specified intervals, 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 vaccination.

5.1.5. Adapted Per-Protocol Set for analysis of efficacy (Adapted PPS for analysis of efficacy)

The Adapted PPS for analysis of efficacy will include all subjects included in the ITTS who fulfilled all eligibility criteria and received all vaccinations according to protocol procedures within the protocol specified intervals and underwent *P. falciparum* challenge.

5.2. 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.

5.2.1. Elimination from ITTS

Code 1030 (Study vaccine not administered at all) for all subjects except those from the infectivity control group and code 900 (invalid informed consent or fraud data) will be used for identifying subjects eliminated from ITTS.

5.2.2. Elimination from the Solicited Safety Set

Code 1030 (study vaccine not administered at all), code 900 (invalid informed consent or fraud data) and code 1160 (no post-vaccination solicited safety data) will be used for identifying subjects eliminated from the solicited safety set.

5.2.3. Elimination from the PPS for analysis of immunogenicity and efficacy

5.2.3.1. Excluded subjects

A subject will be excluded from the PPS analysis of immunogenicity and efficacy analysis under the following conditions

Code	Condition under which the code is used
900	Invalid informed consent or fraud data
1030	Study vaccine not administered at all
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.
1070	Vaccination not according to protocol • Incomplete vaccination course before treatment withdrawal or subject study conclusion. • Administration not according to protocol for reason specified by the investigator, other than side, site and route. • Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number). • Study vaccine RTS,S/AS01 not prepared as per protocol

Code	Condition under which the code is used
1080	Good Manufacturing Practice No-Go: Vaccine temperature deviation
1090	Expired vaccine administered
2010	Protocol violation (inclusion/exclusion criteria) • Eligibility criteria not met with an impact on immunogenicity data
2040	Administration of any medication forbidden by the protocol which may influence the efficacy endpoints • 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). • Immunoglobulins and/or any blood products administered during the study period. • Drugs known to have anti-*Plasmodium* properties, used during the challenge period before identification of parasitemia.
2050	Underlying medical condition forbidden by the protocol which may influence the efficacy endpoints
2080	Subjects did not comply with vaccination schedule (See Table 1, Table 2, Table 3)
2090	Subjects did not comply with blood sampling schedule (See Table 1, Table 2, Table 3)
2100	Serological results not available for anti-CS at all post-vaccination visits
2120	Obvious incoherence or abnormality or error in immunogenicity (antibody) data
3000	Subject did not undergo challenge

5.2.4. Elimination from the Adapted PPS for analysis of efficacy

5.2.4.1. Excluded subjects

A subject will be excluded from the Adapted PPS analysis of efficacy analysis under the following conditions:

Code	Condition under which the code is used
900	Invalid informed consent or fraud data
1030	Study vaccine not administered at all
1070	Vaccination not according to protocol • Incomplete vaccination course before treatment withdrawal or subject study conclusion. • Administration not according to protocol for reason specified by the investigator, other than side, site and route. • Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number). • Study vaccine RTS,S/AS01 not prepared as per protocol
3000	Subject did not undergo challenge

5.3. Important protocol deviations not leading to elimination from per-protocol analysis set

Important protocol deviations not leading to elimination from PPS are defined in MALARIA-092 (205081) Protocol Deviation Management Plan.

PPD

(MALARIA-092 (205081) Protocol Deviation Management Plan)

6. STATISTICAL ANALYSES

Note that standard data derivation rules and statistical methods are described in Annex 1 and will not be repeated below.

6.1. Demography

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

A study flow table (consort) will be generated to present the number of subjects screened, randomized, receiving doses and included in the PPS for analyses.

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

Demographic characteristics (age at first vaccination in years for the vaccinated groups and at the time of the screening for the 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.

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 will be tabulated.
- The number of withdrawn subjects will be tabulated according to the reason for withdrawal.

6.2. Exposure

6.2.1. Analysis of exposure planned in the protocol

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

6.3. Efficacy analysis

6.3.1. 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.

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 vaccine groups (AduFx, 2PedFx, PedFx, Adu2Fx, and Adu1Fx) 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 vaccine groups (AduFx, 2PedFx, PedFx, Adu2Fx, and Adu1Fx) and the infectivity control group, using the log-rank statistic.

The same methodology will be applied for the evaluation of the vaccinated groups versus the immunization schedule of reference (AduFx group).

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

6.3.2. Additional considerations

6.3.2.1. Case definition

The primary case definition of *P. falciparum* infection is an asexual blood stage *P. falciparum* parasite density > 0 detected by blood slide reading.

6.3.2.2. 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 protocol visit D314 (28 days post challenge), drop-out date, start date of antimalarial treatment or date meeting an endpoint, whichever occurs first. Time at risk will be calculated as: censor date – date challenge + 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 (visit D314 - 28 days post challenge).

6.4. Immunogenicity analysis

6.4.1. 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 study group, at each timepoint that a blood sample result is available:

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 in each group (AduFx, 2PedFx, PedFx, Adu2Fx, and Adu1Fx). Anti-CS antibody concentrations will be summarized by GMC. Anti-CS antibody concentrations will be displayed using reverse cumulative curves. Similar analysis will be performed for the anti-full length CS protein (proportion of subjects with anti-CS antibody titres ≥ 200 1/DIL) and anti-C-term antibodies (proportion of subjects with anti-CS antibody concentrations ≥100 EPT).

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 in each group (AduFx, 2PedFx, PedFx, Adu2Fx, and Adu1Fx). Anti-HBs antibody concentrations will be summarized by GMC. Anti-HBs antibody concentrations will be displayed using reverse cumulative curves.

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.

6.4.2. 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.

A 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?).

6.5. Analysis of safety

6.5.1. Analysis of safety planned in the protocol

The analysis of safety will be performed on the ITTS.

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 30-day follow-up period after each vaccine dose and overall will be tabulated with exact 95% CI. The percentage of doses followed by at least one local AE (solicited and unsolicited), by at least one general AE (solicited and unsolicited) and by any AE during the 7-day or 30-day follow-up period will be tabulated with exact 95% CI. The 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 (Day 0-6) after each vaccine dose and overall will be tabulated for each group. Similarly, the percentage of doses followed by each individual solicited local and general AE will be tabulated, for the overall and for each vaccination course, with exact 95% CI.

For fever (fever is defined as temperature ≥ 37.5°C/99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C/100.4°F for rectal route), the number and percentage of subjects reporting fever by half degree (°C) cumulative increments during the first seven days (Day 0-6) after each vaccine dose and overall 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 (Day 0-6) overall doses will be tabulated.

The percentage of subjects reporting unsolicited AEs within 30 days (Day 0-29) after each vaccine dose (overall doses) and percentage of subjects reporting AEs after the sporozoite challenge 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 reporting SAEs (all, fatal, related) occurring within 30 days (day of vaccination and 29 subsequent days) after each dose of study vaccine, classified by the MedDRA preferred term level will be tabulated with exact 95% CI.

The percentage of subjects reporting SAEs (all, fatal, related) occurring from Dose 1 (Day 0) until last study visit (Day 376), classified by the MedDRA preferred term level will be tabulated with exact 95% CI.

The percentage of subjects reporting SAEs (all, fatal, related) occurring from day of challenge (Day 286) to the end of the challenge phase (Day 314), according to the MedDRA classification 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 further vaccination from Dose 1 (Day 0) until last study visit (Day 376), classified by MedDRA preferred term level, will be tabulated with exact 95% CI.

The percentage of vaccinated subjects reporting AEs of specific interest (meningitis and pIMDs) from Dose 1 (Day 0) until last study visit (Day 376), classified by MedDRA preferred term level, will be tabulated with exact 95% CI.

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 Table 4

Table 4 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)].

The percentage of subjects using concomitant medication (any medication, any antipyretic and any prophylactic medication, respectively) during the 7-day follow-up period (Day 0-6) after vaccination will be summarized by group after each dose and overall. The percentage of subjects using concomitant medication during the entire sporozoite challenge (D286-314) will be summarized by group.

6.5.2. Additional considerations

A summary of subjects with all combined solicited (regardless of their duration) and unsolicited adverse events will be provided. Solicited adverse events 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

The following analysis will be performed if at least 5 subjects have used concomitant vaccination during the 7-day follow-up period (Day 0-6) after study vaccination during the full study period.

The percentage of subjects using any concomitant vaccination during the 7-day follow-up period (Day 0-6) after study vaccination will be summarized by group after each dose and overall. The percentage of subjects using concomitant vaccination during the entire sporozoite challenge will be summarized by group.

Note that the study will be converted in CDISC. Accordingly protocol Day 0-Day N will be replaced by Day 1-Day N+1 for the statistical analysis.

7. ANALYSIS INTERPRETATION

All the analyses performed during this study will be descriptive.

8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

The analyses will be performed stepwise:

- An interim analysis to allow an internal decision for the choice of the booster dose in study Malaria-102 will be performed as soon as the results of the challenge phase will be available on data as clean as possible. This analysis will be descriptive and performed on the Adapted PPS for analysis of efficacy.
- When all the remaining data up to Day 376 will be available, the main analysis will be performed. An integrated study report will be written.

8.2. Statistical considerations for interim analyses

A descriptive analysis to evaluate VE against infection of *P. falciparum* will be performed on the Adapted PPS for analysis of efficacy at the time of the interim analysis. 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.

9. CHANGES FROM PLANNED ANALYSES

The Total vaccinated cohort (TVC) defined in the protocol has been replaced by the Intent-To-Treat Set (ITTS) to include both subjects vaccinated and subjects from the infectivity control group in the same cohort.

An interim analysis has been added to allow an internal decision for the choice of the booster dose in study Malaria-102. This analysis will be descriptive and performed on data as cleaned as possible.

To allow an interim analysis as close as possible to the main analysis, an Adapted PPS for analysis of efficacy has been created.

An analysis of concomitant vaccination has been added to assess any effect on immune response or safety.

A Solicited Safety Set has been added in the analysis set section to fit with the new statistical rules and layouts applicable from the 12th of November.

10. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

The TFL TOC provides the list of tables/listings and figures needed for the study report. It also identifies the tables eligible for each analyses and their role (synopsis, in-text, post-text, SHS, CTRS, Annex). Note that all TFL aimed to be included as post-text are noted as post-text even if these are tabulations of individual data such as listings of SAEs. The post-text material contains all source material for the study report and accordingly a post-text table may be redundant with an in-text table.

11. ANNEX 1 STANDARD DATA DERIVATION RULE AND STATISTICAL METHODS

11.1. Statistical Method References

The exact two-sided 95% CIs for a proportion within a group will be the Clopper-Pearson exact CI [Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. *Biometrika*. 1934;26:404-413].

11.2. Standard data derivation

11.2.1. Date derivation

- SAS date derived from a character date: In case day is missing, 15 is used. In case day & month are missing, 30 June is used.
- Onset day for an event (AE, medication, vaccination): The onset day is the number of days between the last study vaccination & the onset/start date of the event. This is 1 for an event starting on the same day as a vaccination. See SAS date derived in case the start date of the event is incomplete.
- Duration: Duration of an event is expressed in days. It is the number of days between the start & the stop dates + 1. Therefore duration is 1 day for an event starting & ending on the same day.

11.2.2. Dose number

- The study dose number is defined in reference to the number of study visits at which vaccination occurred. More specifically dose 1 refers to all vaccines administered at the first vaccination visit while dose 2 corresponds to all vaccinations administered at the second vaccination visit even if this is the first time a product is administered to the subject.
- Relative dose: the relative dose for an event (AE, medication, vaccination) is the most recent study dose given before an event. In case the event takes place on the day a study dose is given, the related dose will be that of the study dose, even if the event actually took place before vaccination. For instance, if an AE begins on the day of the study vaccination but prior to administration of the vaccine, it will be assigned to this dose. In case a study dose is not administered (eg dose 2) and an event occurs after the subsequent study dose (eg 3rd study dose), the relative dose of the event will be study dose associated to the subsequent study dose (eg dose 3).
- The number of doses for a product is the number of times the product was administered to a subject.
- The incidence per dose is the number of vaccination visits at which an event was reported among all vaccination visits.

11.2.3. Demography

- Age: Age at the reference activity, computed as the number of years between the date of birth and the reference activity. Note that due to incomplete date, the derived age may be incorrect by 1 year when month is missing from the birthdate. This may lead to an apparent inconsistency between the derived age and the eligibility criteria/the age category used for randomization.
- Conversion of weight to kg

  The following conversion rule is used:

  – Weight in Kilogrammes= weight in Pounds / 2.2 + weight in Ounces / 35.2

  The result is rounded to 2 decimals.
- Conversion of height to cm

  The following conversion rule is used:

  – Height in Centimetres = Height in Feet * 30.48 + Height in Inches * 2.54

  The result is rounded to the unit (ie no decimal).
- Conversion of temperature to °C

  The following conversion rule is used:

  – Temperature in °Celsius = ((Temperature in °Fahrenheit -32) *5)/9

  The result is rounded to 1 decimal.

11.2.4. Immunogenicity

- For a given subject and given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.
- The Geometric Mean Concentrations (GMCs) calculations are performed by taking the anti-log of the mean of the log titre 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.
- The percentage of subjects seropositive/seroprotected and associated two-sided 95% Clopper-Pearson confidence intervals (CIs) will be computed by vaccine group for each available immunogenicity monitoring.
- A subject seropositive for anti-CS antibody will be a subject whose antibody concentration will be greater than or equal to the cut-off value (anti-CS ≥ 1.9 EU/ml).
- Seroprotection rate for anti-HBs antibody is defined as the percentage of subjects with antibody concentration greater than or equal to an established cut-off (anti-HBs ≥ 10 mIU/ml).

11.2.5. Safety

- Handling of missing data: subjects who missed reporting symptoms (unsolicited or concomitant medications) will be treated as subjects without symptoms (unsolicited or concomitant medications, respectively). In case of significant non-compliance of study procedures for reporting symptoms, the analysis plan will be reassessed to ensure more accurate reporting of study data by further analysis.
- For the analysis of solicited symptoms, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the ES will include only subjects/doses with documented safety data (i.e. symptom screen/sheet completed).
- For a given subject and the analysis of solicited symptoms within 7 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the ES will include only vaccinated subjects for doses with documented safety data (i.e., symptom screen completed). More specifically the following rules will be used:
  - Subjects who documented the absence of a solicited symptom after one dose will be considered not having that symptom after that dose.
  - Subjects who documented the presence of a solicited symptom and fully or partially recorded daily measurement over the solicited period will be included in the summaries at that dose and classified according to their maximum observed daily recording over the solicited period.
  - Subjects who documented the presence of a solicited symptom after one dose without having recorded any daily measurement will be assigned to the lowest intensity category at that dose (i.e., 37.5°C for fever or grade 1 for other symptoms).
  - Doses without symptom sheets documented will be excluded.
- For analysis of unsolicited AEs, such as SAEs or AEs by primary MedDRA term, and for the analysis of concomitant medications, all vaccinated subjects will be considered.
- For the analysis, temperatures will be coded as follows:

Grade	Temperature
0	< 37.5°C (< 99.5°F)
1	≥ 37.5°C (≥ 99.5°F) to ≤ 38.0°C (100.4°F)
2	> 38.0°C (> 100.4°F) to ≤ 39.0°C (102.1°F)
3	> 39.0°C (102.1°F)

- For the analysis, local injection site redness and swelling will be coded as follows:

Grade	Temperature
0	0 mm
1	> 0 to ≤ 50 mm
2	> 50 mm to ≤ 100 mm
3	> 100 mm

Note that for all tables described in this section, the way the percentage of subjects will be derived will depend on the event analysed (see table below for details). As a result, the N value will differ from one table to another.

Event	N used for deriving % per subject for Vaccination phase	N used for deriving % per dose for Vaccination phase
Concomitant vaccination	All subjects with study vaccine administered	All study visits with study vaccine administered
Solicited general symptom	All subjects with at least one solicited general symptom documented as either present or absent (i.e., symptom screen completed)	All study visits with study vaccine administered and with at least one solicited general symptom documented as either present or absent (i.e., symptom screen completed)
Solicited local symptom	All subjects with at least one solicited local symptom documented as either present or absent (i.e., symptom screen completed)	All study visits with study vaccine administered and with at least one solicited local symptom documented as either present or absent (i.e., symptom screen completed)
Unsolicited symptom	All subjects with study vaccine administered	All study visits with study vaccine administered
Concomitant medication	All subjects with study vaccine administered	All study visits with study vaccine administered

- Related dose: The related dose for an event (e.g., AE, medication, vaccination,…) is the study dose given before an event. In case the event takes place on a day a study dose is given, if the investigator has indicated the timing (before or after the vaccination) the related dose for this event is the most recent study dose given before this event. If the investigator has not indicated the timing, the related dose will be that of the study dose even if the event actually took place before.

Number of decimals displayed:

The following decimal description from the decision rules will be used for demography, efficacy, immunogenicity and safety/reactogenicity results.

Display Table	Parameters	Number of decimal digits
Demographic characteristics	Mean, median age	1
Demographic characteristics	SD (age)	1
Reactogenicity	Mean, Min, Q1, Median, Q3, Max for duration	1
All summaries	p-value	3

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.

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.

Serological summary statistics

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

GMT or 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 GMT or 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 GMT or GMC values of <0.1 appear in the same table as values of >=0.1 and <10, 3 decimals should be displayed for both.

12. ANNEX 2: TABLES, FIGURES AND LISTINGS

12.1. Demographics & baseline characteristics

Template #	Table Title	Output destination	Template name
Template 1	Summary of subject disposition from Enrolled Set to Randomized/Intent-To-Treat Set (Enrolled set)	Post-text	TCONSORT1PART1/Specific
Template 2	Summary of subject disposition from Intent-To-Treat Set to Per Protocol Set for analysis of immunogenicity and efficacy (Intent-to-treat set)	Post-text / in-text	TCONSORT1PART3
Template 3	Summary of visit attendance (Intent-to treat set)	Post-text	TMH1SOCPT
Template 3	Summary of visit attendance (Per protocol set for analysis of immunogenicity and efficacy for efficacy)	Post-text	TMH1SOCPT
Template 4	Summary of study completion with reasons for withdrawal (Intent-to-treat set)	Post-text / Web disclosure	TSL1WITHDRAWAL
Template 4	Summary of study completion with reasons for withdrawal (Per protocol set for analysis of immunogenicity and efficacy for efficacy)	Post-text	TSL1WITHDRAWAL
Template 5	Summary of important protocol deviations leading to elimination (Intent-to-treat set)	In-text / Post-text	TDV1PROTDEV
Template 6	Deviations from protocol for age and intervals between study visits (Intent-to-treat set)	Post-text	TDEVINT1INTVAL
Template 6	Deviations from protocol for age and intervals between study visits (Per protocol set for analysis of immunogenicity and efficacy for efficacy)	Post-text	TDEVINT1INTVAL
Template 10	Exposure to study vaccine (Intent-to-treat set)	In-text / Post-text	TEXOVW1EXPOBYBYVAC
Template 7	Summary of demographic characteristics and baseline characteristics (Intent-to-treat set)	In-text / Post-text	TSL1DEMOG
Template 7	Summary of demographic and baseline characteristics (Per protocol set for analysis of immunogenicity and efficacy for efficacy)	Post-text / in-text/Synopsis	TSL1DEMOG
Template 7	Summary of demographic and baseline characteristics by protection status (Per protocol set for analysis of immunogenicity and efficacy for efficacy)	Post-text	TSL1DEMOG
Template 8	Summary of demographic characteristics and baseline characteristics (Enrolled set)	Web posting	TSL1DEMOG
Template 9	Summary of previous Hepatitis B vaccination (Intent-to-treat set)	Post-text	Specific
Template 9	Summary of previous Hepatitis B vaccination (Per protocol set for analysis of immunogenicity and efficacy for efficacy)	Post-text	Specific
Template 32	Minimum and maximum visit dates (intent-to-treat)	Annex	TACTIV1DATE

12.2. Efficacy

Template #	Table / Figure Title	Output destination	Template name
Template 11	Parasitemia incidence defined by a positive blood slide and vaccine efficacy of each vaccination schedule versus Control group during challenge phase (Per protocol set for analysis of immunogenicity and efficacy)	Post-text / in-text / Web disclosure/Synopsis	Specific
Template 12	Time to onset of parasitemia in each vaccination schedule versus Control (by blood slide) (Per protocol set for analysis of immunogenicity and efficacy)	Post-text / Web disclosure	Specific
Template 12	Time to onset of parasitemia in each vaccination schedule versus AduFx (by blood slide) (Per protocol set for analysis of immunogenicity and efficacy)	Post-text/ Web disclosure	Specific
Template 13	Cumulative incidence of parasitemia onset defined by positive blood slide for all groups (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific
Template 11	Parasitemia incidence defined by a positive blood slide and vaccine efficacy of each vaccination schedule versus AduFx during challenge phase (Per protocol set for analysis of immunogenicity and efficacy)	Post-text/ Web disclosure	Specific

12.3. Immunogenicity

Template #	Table / Figure Title	Output destination	Template name
Anti-CS antibodies (repeat)			
Template 14	Number and percentage of subjects with anti-CS (repeat) equal or above 1.9 EU/mL and GMCs (Per protocol set for analysis of immunogenicity and efficacy)	Post-text / in-text / Web disclosure/Synopsis	TIS1GMT
Template 14	Number and percentage of subjects with anti-CS (repeat) equal or above 1.9 EU/mL and GMCs by protection status (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	TIS1GMT
Template 15	Reverse cumulative distribution curve for anti-CS antibodies (repeat) post-vaccination (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	FIS1REVCUM
Template 15	Reverse cumulative distribution curve for anti-CS antibodies (repeat) post-vaccination by protection status (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	FIS1REVCUM
Template 15	Reverse cumulative distribution curve for anti-CS antibodies (repeat) at the time of the challenge (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	FIS1REVCUM
Template 15	Reverse cumulative distribution curve for anti-CS antibodies (repeat) at the time of the challenge by protection status (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	FIS1REVCUM
Template 17	Box and whiskers plot of anti-CS antibodies (repeat) at post-vaccination and the day of the challenge (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific
Template 17	Box and whiskers plot of anti-CS antibodies (repeat) at post-vaccination and the day of the challenge by protection status (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific

Template #	Table / Figure Title	Output destination	Template name
Template 18	Evolution over time for anti-CS antibodies (repeat) by group (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific
Template 18	Evolution over time for anti-CS antibodies (repeat) per protection status (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific
Template 16	Comparison of the log-transformed means of the anti-CS (repeat) antibodies at post-vaccination and at the time of the challenge of each vaccination schedule versus AduFx groups (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	specific
Template 16	Comparison of the log-transformed means of the anti-CS (repeat) antibodies at post-vaccination and at the time of the challenge between Protected and Non-Protected groups (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	specific
Anti-CS antibodies (full length)			
Template 14	Number and percentage of subjects with anti-CS (full length) equal or above 200 1/DIL and GMTs (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	TIS1GMT
Template 14	Number and percentage of subjects with anti-CS (full length) equal or above 200 1/DIL and GMTs by protection status (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	TIS1GMT
Template 15	Reverse cumulative distribution curve for anti-CS antibodies (full length) at post-vaccination (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	FIS1REVCUM
Template 15	Reverse cumulative distribution curve for anti-CS antibodies (full length) at post-vaccination by protection status (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	FIS1REVCUM
Template 15	Reverse cumulative distribution curve for anti-CS antibodies (full length) at the time of the challenge (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	FIS1REVCUM
Template 15	Reverse cumulative distribution curve for anti-CS antibodies (full length) at the time of the challenge by protection status (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	FIS1REVCUM
Template 17	Box and whiskers plot of anti-CS antibodies (full length) at post-vaccination and the day of the challenge (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific
Template 17	Box and whiskers plot of anti-CS antibodies at post-vaccination and the day of the challenge (full length) by protection status (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific
Template 18	Evolution over time for anti-CS antibodies (full length) by group (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific
Template 18	Evolution over time for anti-CS antibodies (full length) per protection status (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific
Template 16	Comparison of the log-transformed means of the anti-CS (full length) antibodies at post-vaccination and at the time of the challenge of each vaccination schedule versus AduFx	Post-text	specific

Template #	Table / Figure Title	Output destination	Template name
	groups (Per protocol set for analysis of immunogenicity and efficacy)		
Template 16	Comparison of the log-transformed means of the anti-CS antibodies (full length) at post-vaccination and at the time of the challenge between Protected and Non-Protected groups (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	specific
Anti-CS antibodies (C-term)			
Template 14	Number and percentage of subjects with anti-CS (C-term) equal or above 100 EPT and GMTs (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	TIS1GMT
Template 14	Number and percentage of subjects with anti-CS (C-term) equal or above 100 EPT and GMTs by protection status (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	TIS1GMT
Template 15	Reverse cumulative distribution curve for anti-CS antibodies (C-term) at post-vaccination (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	FIS1REVCUM
Template 15	Reverse cumulative distribution curve for anti-CS antibodies (C-term) at post-vaccination by protection status (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	FIS1REVCUM
Template 15	Reverse cumulative distribution curve for anti-CS antibodies (C-term) at the time of the challenge (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	FIS1REVCUM
Template 15	Reverse cumulative distribution curve for anti-CS antibodies (C-term) at the time of the challenge by protection status (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	FIS1REVCUM
Template 17	Box and whiskers plot of anti-CS antibodies (C-term) at post-vaccination and the day of the challenge (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific
Template 17	Box and whiskers plot of anti-CS antibodies (C-term) at post-vaccination and the day of the challenge by protection status (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific
Template 18	Evolution over time for anti-CS antibodies (C-term) by group (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific
Template 18	Evolution over time for anti-CS antibodies (C-term) per protection status (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific
Template 16	Comparison of the log-transformed means of the anti-CS (C-term) antibodies at post-vaccination and at the time of the challenge of each vaccination schedule versus AduFx groups (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	specific
Template 16	Comparison of the log-transformed means of the anti-CS antibodies (C-term) at post-vaccination and at the time of the challenge between Protected and Non-Protected groups (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	specific

Template #	Table / Figure Title	Output destination	Template name
Anti-CS Avidity Index (repeat)			
Template 16	Comparison of the log-transformed means of the anti-CS avidity index (repeat) at post-vaccination and at the time of the challenge of each vaccination schedule versus AduFx groups (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific
Template 16	Comparison of the log-transformed means for anti-CS avidity index (repeat) at post-vaccination and at the time of the challenge on Protected and Non-Protected groups (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific
Template 17	Box and whiskers plot of anti-CS avidity index (repeat) at post-vaccination and at the time of the challenge (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific
Template 17	Box and whiskers plot of anti-CS avidity index (repeat) at post-vaccination and at the time of the challenge per protection status (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific
Anti-CS Avidity Index post dose (full length)			
Template 16	Comparison of the log-transformed means of the anti-CS avidity index (full length) at post-vaccination and at the time of the challenge of each vaccination schedule versus AduFx groups (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific
Template 16	Comparison of the log-transformed means for anti-CS avidity index (full length) at post-vaccination and at the time of the challenge on Protected and Non-Protected groups (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific
Template 17	Box and whiskers plot of anti-CS avidity index (full length) at post-vaccination and at the time of the challenge (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific
Template 17	Box and whiskers plot of anti-CS avidity index (full length) at post-vaccination and at the time of the challenge per protection status (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific
Anti-CS Avidity Index post dose (C-term)			
Template 16	Comparison of the log-transformed means of the anti-CS avidity index (C-term) at post-vaccination and at the time of the challenge of each vaccination schedule versus AduFx groups (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific
Template 16	Comparison of the log-transformed means for anti-CS avidity index (C-term) at post-vaccination and at the time of the challenge on Protected and Non-Protected groups (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific
Template 17	Box and whiskers plot of anti-CS avidity index (C-term) at post-vaccination and at the time of the challenge (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific
Template 17	Box and whiskers plot of anti-CS avidity index (C-term) at post-vaccination and at the time of the challenge per protection status (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	Specific

Template #	Table / Figure Title	Output destination	Template name
Anti-HBs antibodies			
Template 14	Number and percentage of subjects with anti-HBs equal or above 6.2 and 10 mIU/ml and GMCs (Per protocol set for analysis of immunogenicity and efficacy)	Post-text / in-text / Web disclosure	TIS1GMT
Template 14	Number and percentage of subjects with anti-HBs equal or above 6.2 and 10 mIU/ml and GMCs by protection status (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	TIS1GMT
Template 15	Reverse cumulative distribution curve for anti-HBs antibodies at post-vaccination (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	FIS1REVCUM
Template 15	Reverse cumulative distribution curve for anti-HBs antibodies at the time of the challenge (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	FIS1REVCUM
Template 15	Reverse cumulative distribution curve for anti-HBs antibodies at post-vaccination by protection status (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	FIS1REVCUM
Template 15	Reverse cumulative distribution curve for anti-HBs antibodies at the time of the challenge by protection status (Per protocol set for analysis of immunogenicity and efficacy)	Post-text	FIS1REVCUM

12.4. Reactogenicity and Safety

Template #	Table / Listing Title	Output destination	Template name
Template 19	Compliance in completing solicited adverse events information (Intent-to-treat set)	Post-text	TEX1COMPLIANCE
Template 20	Summary of adverse events (solicited and unsolicited) within 7 days following each vaccination and overall (Intent to treat set)	In-text / Post-text/Synopsis	TAC1LOCGEN
Template 20	Summary of grade 3 adverse events (solicited and unsolicited) within 7 days following each vaccination and overall (Intent to treat set)	Post-text	TAC1LOCGEN
Template 20	Summary of adverse events (solicited and unsolicited) with causal relationship to vaccination within 7 days following each vaccination and overall (Intent to treat set)	Post-text	TAC1LOCGEN
Template 20	Summary of grade 3 adverse events (solicited and unsolicited) with causal relationship to vaccination within 7 days following each vaccination and overall (Intent to treat set)	Post-text	TAC1LOCGEN
Template 20	Summary of adverse events (solicited and unsolicited) within 30 days following each vaccination and overall (Intent to treat set)	Post-text	TAC1LOCGEN
Template 20	Summary of grade 3 adverse events (solicited and unsolicited) within 30 days following each vaccination and overall (Intent to treat set)	Post-text	TAC1LOCGEN
Template 20	Summary of adverse events (solicited and unsolicited) with causal relationship to vaccination within 30 days following each vaccination and overall (Intent to treat set)	Post-text	TAC1LOCGEN
Template 20	Summary of grade 3 adverse events (solicited and unsolicited) with causal relationship to vaccination within 30 days following each vaccination and overall (Intent to treat set)	Post-text	TAC1LOCGEN

Template #	Table / Listing Title	Output destination	Template name
Template 21	Percentage of subject with solicited local symptoms within 7 days following each vaccination and overall (Intent to treat set)	Post-text / Web disclosure	TCEMAX1FREQSEV
Template 31	Bar graph of the daily prevalence of pain between day 1 and day 7 following each vaccination (Intent to treat set)	Post-text	CEMAX1BARGRAPH
Template 31	Bar graph of the daily prevalence of redness between day 1 and day 7 following each vaccination (Intent to treat set)	Post-text	CEMAX1BARGRAPH
Template 31	Bar graph of the daily prevalence of swelling between day 1 and day 7 following each vaccination (Intent to treat set)	Post-text	CEMAX1BARGRAPH
Template 21	Percentage of subject with solicited general symptoms within 7 days following each vaccination and overall (Intent to treat set)	Post-text / Web disclosure	TCEMAX1FREQSEV
Template 31	Bar graph of the daily prevalence of fatigue between day 1 and day 7 following each vaccination (Intent to treat set)	Post-text	CEMAX1BARGRAPH
Template 31	Bar graph of the daily prevalence of gastrointestinal between day 1 and day 7 following each vaccination (Intent to treat set)	Post-text	CEMAX1BARGRAPH
Template 31	Bar graph of the daily prevalence of headache between day 1 and day 7 following each vaccination (Intent to treat set)	Post-text	CEMAX1BARGRAPH
Template 22	Percentage of subjects with temperature by maximum value, within 7 days following each vaccination and overall (Intent to treat set)	Post-text	TCEMAX1TEMP
Template 31	Bar graph of the daily prevalence of temperature between day 1 and day 7 following each vaccination (Intent to treat set)	Post-text	CEMAX1BARGRAPH
Template 30	Summary of subjects taking a concomitant medication within 7-day following each vaccination and overall (Intent to treat set)	Post-text	specific
Template 30	Summary of subjects taking a concomitant medication during the challenge phase (Intent to treat set)	Post-text	specific
Template 23	Summary of subjects with at least one unsolicited adverse event classified by MedDRA Primary System Organ Class and Preferred Term within 30 days of any vaccination (Intention-to-treat set)	Post-text / Web disclosure	TAE1SOCPT
Template 25	Summary of subjects with unsolicited adverse events within 30 days of any vaccination by category (Intention-to-treat set)	Post-text	TAE1SOCPTSUMMARY
Template 23	Summary of subjects with at least one grade 3 unsolicited adverse evens classified by MedDRA Primary System Organ Class and Preferred Term within 30 days of any vaccination (Intention-to-treat set)	Post-text	TAE1SOCPT
Template 23	Summary of subjects with at least one related unsolicited adverse event classified by MedDRA Primary System Organ Class and Preferred Term within 30 days of any vaccination (Intention-to-treat set)	Post-text	TAE1SOCPT
Template 23	Summary of subjects with at least one grade 3 related unsolicited adverse event classified by MedDRA Primary System Organ Class and Preferred Term within 30 days of any vaccination (Intention-to-treat set)	Post-text	TAE1SOCPT
Template 23	Summary of subjects with at least one unsolicited adverse event classified by MedDRA Primary System Organ Class and Preferred Term within 30 days post- challenge (Intention-to-treat set)	Post-text/ Web disclosure	TAE1SOCPT

Template #	Table / Listing Title	Output destination	Template name
Template 23	Summary of subjects with at least one grade 3 unsolicited adverse event classified by MedDRA Primary System Organ Class and Preferred Term within 30 days post- challenge (Intention-to-treat set)	Post-text	TAE1SOCPT
Template 23	Summary of subjects with at least one related unsolicited adverse event classified by MedDRA Primary System Organ Class and Preferred Term within 30 days post- challenge (Intention-to-treat set)	Post-text	TAE1SOCPT
Template 23	Summary of subjects with at least one grade3 related unsolicited adverse event classified by MedDRA Primary System Organ Class and Preferred Term within 30 days post- challenge (Intention-to-treat set)	Post-text	TAE1SOCPT
Template 25	Summary of subjects with unsolicited adverse events within the 30 days post-challenge by category (Intention-to-treat set)	Post-text	TAE1SOCPTSUMMARY
Template 26	Listing of potential immune mediated disorders (pIMDs) reported as identified by predefined list of preferred terms and/or by investigator assessment (Intention-to-treat set)	Post-text / Web disclosure	TAE1PIMDLIST
Template 26	Listing of meningitis reported as identified by predefined list of preferred terms and/or by investigator assessment (Intention-to-treat set)	Post-text / Web disclosure	TAE1PIMDLIST

Template #	Table / Listing Title	Output destination	Template name
Template 23	Summary of subjects with at least one serious unsolicited adverse event classified by MedDRA Primary System Organ Class and Preferred Term within 30 days of any vaccination (Intention-to-treat set)	Post-text/ Web disclosure	TAE1SOCPT
Template 23	Summary of subjects with at least one serious fatal unsolicited adverse event classified by MedDRA Primary System Organ Class and Preferred Term within 30 days of any vaccination (Intention-to-treat set)	Post-text/ Web disclosure	TAE1SOCPT
Template 23	Summary of subjects with at least one serious related unsolicited adverse event classified by MedDRA Primary System Organ Class and Preferred Term within 30 days of any vaccination (Intention-to-treat set)	Post-text/ Web disclosure	TAE1SOCPT
Template 23	Summary of subjects with at least one serious unsolicited adverse event classified by MedDRA Primary System Organ Class and Preferred Term occurring from Dose 1 (Day 1) until the last study visit (Day 376) (Intention-to-treat set)	Post-text / Web disclosure	TAE1SOCPT
Template 24	Summary of occurrences and subjects with at least one serious unsolicited adverse event classified by MedDRA Primary System Organ Class and Preferred Term occurring from Dose 1 (Day 1) until the last study visit (Day 376) (Intention-to-treat set)	Web disclosure	TAC1SOCPT
Template 23	Summary of subjects with at least one serious fatal unsolicited adverse event classified by MedDRA Primary System Organ Class and Preferred Term occurring from Dose 1 (Day 1) until the last study visit (Day 376) (Intention-to-treat set)	Post-text / Web disclosure	TAE1SOCPT
Template 23	Summary of subjects with at least one serious related unsolicited adverse event classified by MedDRA Primary System Organ Class and Preferred Term occurring from Dose 1 (Day 1) until the last study visit (Day 376) (Intention-to-treat set)	Post-text/ Web disclosure	TAE1SOCPT
Template 23	Summary of subjects with at least one serious unsolicited adverse event classified by MedDRA Primary System Organ Class and Preferred Term occurring from day of challenge until the end of challenge phase (Day 314) (Intention-to-treat set)	Post-text / Web disclosure	TAE1SOCPT
Template 23	Summary of subjects with at least one serious fatal unsolicited adverse event classified by MedDRA Primary System Organ Class and Preferred Term occurring from day of challenge until the end of challenge phase (Day 314) (Intention-to-treat set)	Post-text/ Web disclosure	TAE1SOCPT
Template 23	Summary of subjects with at least one serious related unsolicited adverse event classified by MedDRA Primary System Organ Class and Preferred Term occurring from day of challenge until the end of challenge phase (Day 314) (Intention-to-treat set)	Post-text/ Web disclosure	TAE1SOCPT
Template 27	Listing of SAEs reported from study start to end of the study (Intention-to-treat population)	Post-text	TAE1SAELIST
Template 28	Listing of (S) AEs and solicited symptoms leading to study/treatment discontinuation (Intent to treat set)	Post-text / Web disclosure/	TAE1WITHDRAWAL

Template #	Table / Listing Title	Output destination	Template name
Template 24	Summary of occurrences and subjects with at least one solicited or unsolicited adverse event classified by MedDRA Primary System Organ Class and Preferred Term (excluding the SAEs) occurring within 30 days of any vaccination (Intention-to-treat set)	Web disclosure	TAC1SOCPT
Template 29	Summary of hematology and biochemistry results (Intention-to-treat population)	Post-text/ Web disclosure	TLB1RANGEVSBSL

12.5. Individual data listings:

Reason for non-eligibility (LIE1LIST)

Demography (LDM1DEMOG)

Reason for visit not done (LDS1NOVIS)

Immunogenicity (LIS1LIST)

Vaccine administration (LEC1EXPO)

Reason for vaccine not administered (LEC1NOADM)

Solicited local adverse events (LEC1LOC)

Solicited general adverse events (LEC1GEN)

Concomitant medications (LCM1LIST)

Pregnancy (Specific)

12.6. Template of tables, figures AND LISTINGS

12.6.1. Demographics and baseline characteristics

Template 1 Consort flow (Enrolled set)

	Total N=xx	
	n	%
NUMBER OF SUBJECTS WHO SIGNED INFORMED CONSENT		
NUMBER OF SUBJECTS WITHDRAWN PRIOR TO RANDOMIZATION		
Consent Withdrawal, Not Due To A Serious Adverse Event and/or An Adverse Event		
Eligibility Criteria Not Fulfilled		
Lost To Follow-Up		
Migrated / Moved From The Study Area		
Missing		
Other		
NUMBER OF SUBJECTS INCLUDED IN RANDOMIZED SET (=INTENT-TO-TREAT SET)		

N = Number of subjects who have signed ICF (screened)
% = n / Number of subjects with available results x 100
All Enrolled Set includes Screen Failures and non-Randomized subjects.
Withdrawal reason "Other" corresponds to Subject Enrollment target reached before Randomization

Template 2 Consort flow (Intent to treat set)

	<Group 1> N=XXX		<Group 2> N=XXX		Total N=XXX	
	N	%	N	%	N	%
Number of subjects eliminated from per protocol set	xxx	100	xxx	100	xxx	100
<Elimination reason 1 (code)>	xxxx		xxxx		xxxx	
<Elimination reason 2 (code)>	xxx		xxx		xxxx	
…						
Number of subjects included in PPS	XXXX	x.xx	XXX	X.XX	xxx	x.xx

Short group label = long group label
N = total number of subjects randomized
n/% = number / percentage of subjects in a given category

Template 3 Summary of visit attendance (Intent-to treat set)

	<Group 1> N=XXXX		<Group xxx> N=XXXX		Total N=XXXX	
	n	%	n	%	n	%
Visit 1 (Day 1)						
Attended	xxx	xx.x	xxx	xx.x	xxx	xx.x
Did not attend yet	xxx	xx.x	xxx	xx.x	xxx	xx.x
Withdrawal at visit or earlier	xxx	xx.x	xxx	xx.x	xxx	xx.x
Did not attend	xxx	xx.x	xxx	xx.x	xxx	xx.x
Visit 2 (Day xx)						
…						
Visit 3 (Day xx)						
…						
…						
Last study contact (Day 376)						
Completed	xxx	xx.x	xxx	xx.x	xxx	xx.x
Did not complete yet	xxx	xx.x	xxx	xx.x	xxx	xx.x
Withdrawal at visit or earlier	xxx	xx.x	xxx	xx.x	xxx	xx.x
Did not complete	xxx	xx.x	xxx	xx.x	xxx	xx.x

Template 4 Summary of disposition <analysis set name>

	<Group 1> N=XXXX		<Group 2> N=XXXX		Total N=XXXX	
	n	%	n	%	n	%
Completed the study	xxx	xx.x	xxx	xx.x	xxx	xx.x
Primary reason for withdrawal						
DEATH	xxx	xx.x	xxx	xx.x	xxx	xx.x
ADVERSE EVENT	xxx	xx.x	xxx	xx.x	xxx	xx.x
PROTOCOL DEVIATION	xxx	xx.x	xxx	xx.x	xxx	xx.x
WITHDRAWAL BY SUBJECT	xxx	xx.x	xxx	xx.x	xxx	xx.x
MIGRATED / MOVED FROM THE STUDY AREA	xxx	xx.x	xxx	xx.x	xxx	xx.x
LOST TO FOLLOW-UP	xxx	xx.x	xxx	xx.x	xxx	xx.x
STUDY TERMINATED BY SPONSOR	xxx	xx.x	xxx	xx.x	xxx	xx.x
OTHER	xxx	xx.x	xxx	xx.x	xxx	xx.x

Short group label = long group label
N = total number of subjects
n/% = number / percentage of subjects in a given category
Note: the list of reasons will be study specific

Template 5 Summary of important protocol deviations leading to elimination <analysis set name>

Category Sub-category	<Group 1> occ	 n	 %	<Group 2> occ	 n	 %	Total occ	 n	 %
At least one important protocol deviation	xxx	xxx	xx.x	xxx	xxx	xx.x	xxx	xxx	xx.x
<Category 1>	xxx	xxx	xx.x	xxx	xxx	xx.x	xxx	xxx	xx.x
<Sub-category 1>	xxx	xxx	xx.x	xxx	xxx	xx.x	xxx	xxx	xx.x
<Sub-category 2>	xxx	xxx	xx.x	xxx	xxx	xx.x	xxx	xxx	xx.x
…									
<Category 2>	xxx	xxx	xx.x	xxx	xxx	xx.x	xxx	xxx	xx.x
…									
…									

Short group label = long group label
Occ = number of occurrences = number of important protocol deviations
n/% = number / percentage of subjects in a given category
Note: Categories presented by occurrence frequency and within categories the sub-categories will be sorted by occurrence frequency. For a same frequency then sorted alphabetically

Template 6 Deviations from protocol for age and intervals between study visits <analysis set name>

Type of interval	Interval range			<Group 1> Value	<Group 1> %	<Group xxx> Value	<Group xxx> %
Age (years) at first vaccine administration	From <x> to <y> years	N		xxx		xxx	
		n		xxx		xxx	xx.x
		Below <x>	xx.x			xxx	xx.x
		Above <y>		xxx		xxx	xx.x
			xx.x				
Number of days between vaccination <x> and vaccination <y>	From <x> to <y> days	…		xxx			
			xx.x				
Number of days between vaccination <x> and visit <y>	From <x> to <y> days	…					
	From <x> to <y> days	…					
Number of days between vaccination <x> and blood sampling <y>							

Template 7 Summary of demographic characteristics <analysis set name>

	Value or n	<Each group> N=XXXX %
Age (years) at first vaccination/screening (for control)		
n	xxx	
Mean	xxx.x	
Standard Deviation	xxx.x	
Median	xxx.x	
Minimum	xxx	
Maximum	xxx	
…		
Sex		
Male	xxx	xx.x
Female	xxx	xx.x
Race		
American indian or alaska native	xxx	xx.x
Asian	xxx	xx.x
Black or african american	xxx	xx.x
Native hawaiian or other pacific islander	xxx	xx.x
White	xxx	xx.x
Other	xxx	xx.x

Short group label = long group label
n/% = number / percentage of subjects in a given category

Template 8 Summary of demography and baseline characteristics <Enrolled Set>

	Total N=XXXX	
	Value or n	%
Age (<days/weeks/months/years>) at first vaccination		
n	xxx	
Mean	xxx.x	
Standard Deviation	xxx.x	
Median	xxx.x	
Minimum	xxx	
Maximum	xxx	
Age group [EudraCT]		
Adults (18-64 years)	xxx	xx.x
Country		
USA	xxx	xx.x
…		
Sex		
Male	xxx	xx.x
Female	xxx	xx.x
Race		
American Indian Or Alaska Native	xxx	xx.x
Asian	xxx	xx.x
Black Or African American	xxx	xx.x
Native Hawaiian Or Other Pacific Islander	xxx	xx.x
White	xxx	xx.x
Other	xxx	xx.x

Template 9 Summary of previous Hepatitis B vaccination (Intent-to-treat set)

	Value or n	<Each group> N=XXXX %
Subjects **with** an history of Hepatitis B vaccination	xxxxx	xxxx
Subjects **without** an history of Hepatitis B vaccination	xxx	xxxxx

Short group label = long group label
n/% = number / percentage of subjects in a given category

Template 10 Exposure to study vaccine by visit (Intent-to-treat)

	Vaccine administered	**<Group 1> N=XXX**		**<Group 2> N=XXX**	
		n	**%**	**n**	**%**
Visit 2 (Day 1)	<Vaccine 1>	xxx	xx.x	xxx	xx.x
	<Vaccine 2>	xxx	xx.x	xxx	xx.x
	…				
Visit 3 (Day 28)					
…					

Short group label = long group label
n/% = number / percentage of subjects in a given category

12.6.2. Efficacy

Template 11 Parasitemia incidence defined by a positive blood slide and vaccine efficacy versus control of <each group> (Per protocol set for analysis of immunogenicity and efficacy)

		<Group 1> N=XXXX	<Group xxx> N=XXXX
Parasitemia	n	xx.x	xx.x
	%	xxxx	xxxx
	95% CI	(xx.x ; xx.x)	(xx.x ; xx.x)
	p-value (versus xxx)	xx.x	xx.x

Short group label = long group label
N = number of subjects included in each group (without missing values)
n/% = number / percentage of subjects reporting at least one event(s) in each group
LL, UL = 95% Lower and Upper confidence limits
P-value from Fisher's Exact test (computed versus control or AduFx group)

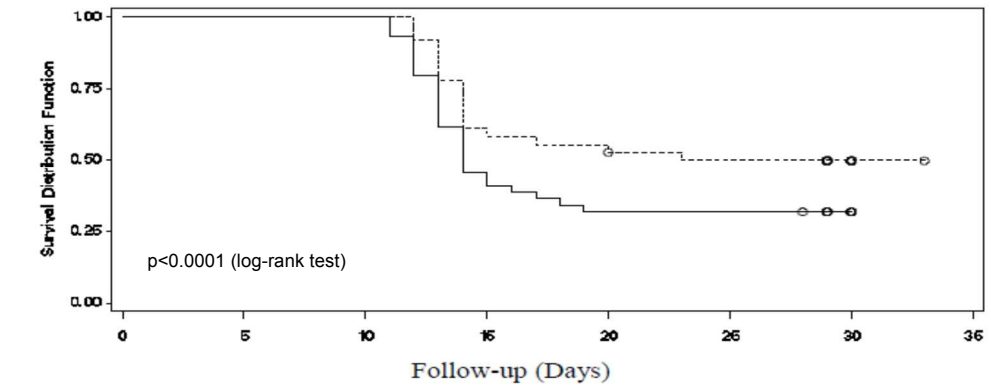
Template 12 **Time to onset of parasitemia by blood slide (Per protocol set for analysis of immunogenicity and efficacy)**

	Value or n	<Each group> N=XXXX %
Time to onset (days)		
n	xxx	
Mean	xxx.x	
Standard Deviation	xxx.x	
Median	xxx.x	
Minimum	xxx	
Maximum	xxx	
p-value (versus xx)	xxxx	

Short group label = long group label

Template 13 **Cumulative incidence of parasitemia onset defined by positive blood slide for all groups (Per protocol set for analysis of immunogenicity and efficacy)**

Figure 1 **Kaplan-Meier curve for time to onset of parasitemia following primary challenge: RTS,S/AS02A vs RTS,S/AS01B - pooled Cohorts 1 and 2**



---------- = RTS,S/AS02A; -------- = RTS,S/AS01B; ○ = censored

12.6.3. Immunogenicity

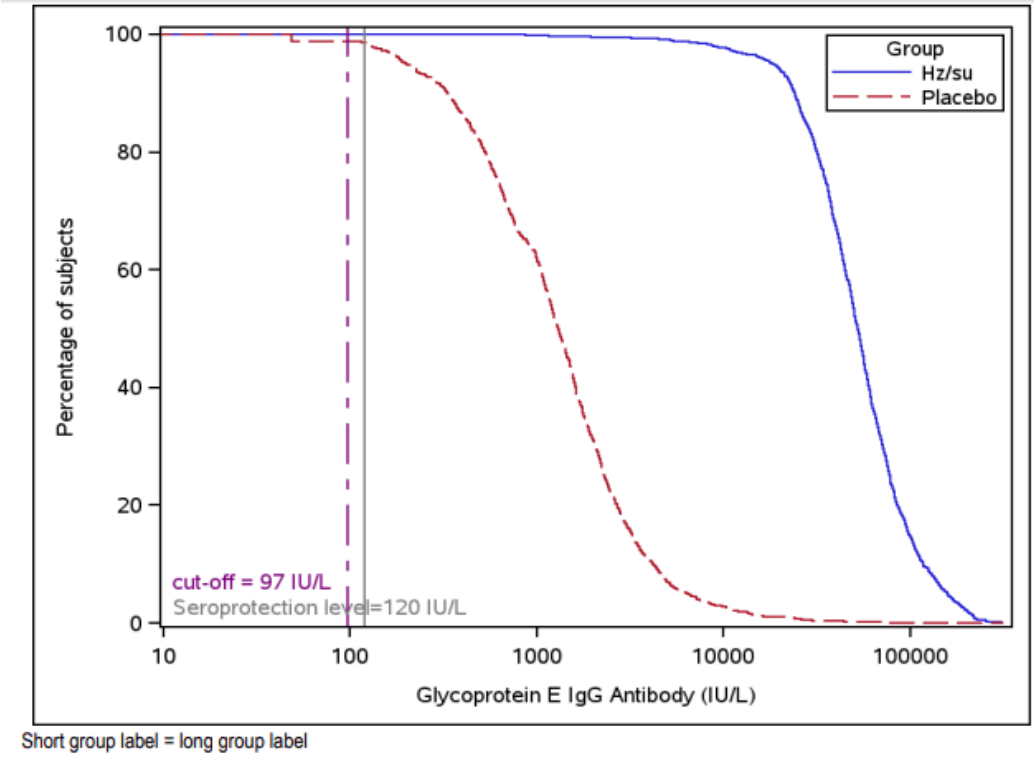
Template 14 Number and percentage of subjects with <assay description> equal or above <cut-off> and GMCs (Per protocol set for analysis of immunogenicity and efficacy)

Antibody	Time point	Cut-off		<Group 1>					<Group 2>					<Group 3>				
							95% CI					95% CI					95% CI	
				N	n	value	LL	UL	N	n	value	LL	UL	N	n	value	LL	UL
<Antibody 1>	<Time point 1>	<Cut-off 1>	%>=<cut-off 1> <unit>	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
			%>=<cut-off 2> <unit>	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
			%>=<cut-off 3> <unit>	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x	xxx	xxx	xx.x	xx.x	xx.x
			GM<T,C>	xxx		xx.x	xx.x	xx.x	xxx		xx.x	xx.x	xx.x	xxx		xx.x	xx.x	xx.x

GMC = geometric mean concentration
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit;

Template 15 Reverse cumulative distribution curve for <assay description> <timing> (Per protocol set for analysis of immunogenicity and efficacy)

Example:



All groups at one timepoint

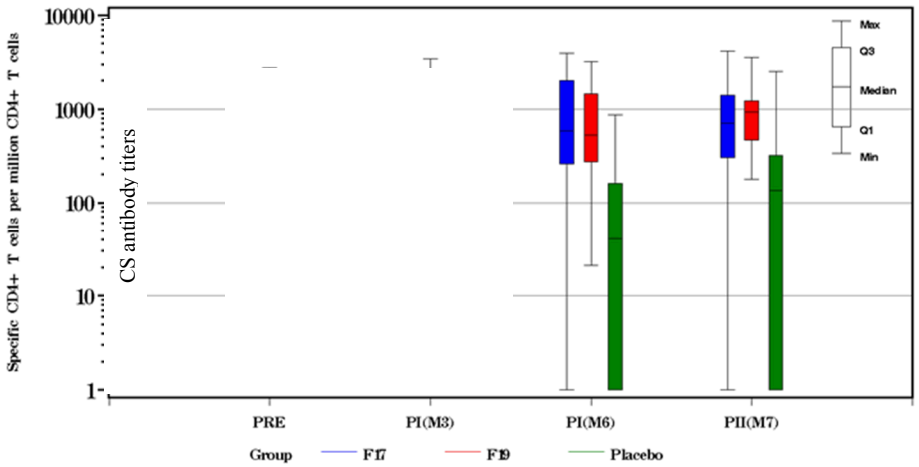
Template 16 Comparison of the log-transformed means of the <anti-CS> antibodies <repeat/full-length/C-term> at post-vaccination of <each vaccination schedule versus AduFx / Protected versus Non-protected> (Per protocol set for analysis of immunogenicity and efficacy)

	Value or n	<Each group> N=XXXX %
< timing >		
N	xxx	
Mean	xxx.x	
95% of the mean		
Standard Deviation	xxx.x	
Median		
Q1		
Q3		
Minimum		
Maximum		
p-value (versus xx)		
< timing >		
…		

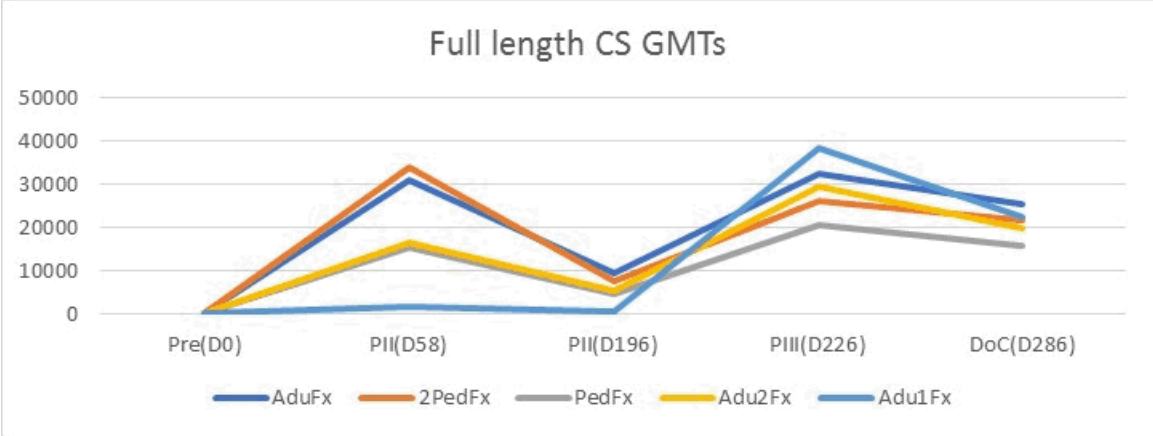
N = number of subjects with available results
Note: for Mean, also display the 95% CI
Timing: post-dose 2 or 2 and day of challenge (in the same table)

Template 17 Box and whiskers plot of <assay description> <timing> (Per protocol set for analysis of immunogenicity and efficacy)

Example:



Template 18 Evolution over time for <assay descrition (Per protocol set for analysis of immunogenicity and efficacy)



12.6.4. Reactogenicity and safety

Template 19 Compliance in completing solicited adverse events information (intent-to-treat)

		<Group 1>			<Group 2>		
		N	n	Compliance (%)	N	n	Compliance (%)
<Vaccination at visit 1>	General solicited adverse events	xxx	xxx	xx.x	xxx	xxx	xx.x
	Local solicited adverse events	xxx	xxx	xx.x	xxx	xxx	xx.x
<Vaccination at visit X>	General solicited adverse events	xxx	xxx	xx.x	xxx	xxx	xx.x
	Local solicited adverse events	xxx	xxx	xx.x	xxx	xxx	xx.x
…	…						
Per vaccination	General solicited adverse events	xxx	xxx	xx.x	xxx	xxx	xx.x
	Local solicited adverse events	xxx	xxx	xx.x	xxx	xxx	xx.x

Template 20 Incidence and nature of symptoms (solicited and unsolicited) within 7-day following each vaccination and overall (Intention-to-treat set)

		<Group 1>				<Group 2>			
				95% CI				95% CI	
		n	%	LL	UL	n	%	LL	UL
<Vaccination at visit 1>	N	xxx				xxx			
	Any symptom	xxx	xx.x	xx.x	xx.x	xxx	xx.x	xx.x	xx.x
	Local symptom	xxx	xx.x	xx.x	xx.x	xxx	xx.x	xx.x	xx.x
	General symptom	xxx	xx.x	xx.x	xx.x	xxx	xx.x	xx.x	xx.x
<Vaccination at visit 2>	…								
…									
Per subject									
Per vaccination									

For each dose and overall/subject:
N= number of subjects with at least one administered dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
For overall/dose:
N= number of administered doses
n/%= number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Template 21 Incidence of solicited <local/general> symptoms within 7-day following each vaccination and overall (Intention-to-treat set)

Symptom: Xxxxx

		<Group 1>				<Group 2>			
				95% CI				95% CI	
		n	%	LL	UL	n	%	LL	UL
<Vaccination at visit 1>	N	xxx				xxx			
	Any	xxx	xx.x	xx.x	xx.x	xxx	xx.x	xx.x	xx.x
	Related	xxx	xx.x	xx.x	xx.x	xxx	xx.x	xx.x	xx.x
	Grade 3	xxx	xx.x	xx.x	xx.x	xxx	xx.x	xx.x	xx.x
	Grade 3 related	xxx	xx.x	xx.x	xx.x	xxx	xx.x	xx.x	xx.x
	Medically attended visit								
<Vaccination at visit 2>	…								
…									
Per subject									
Per vaccination									

For each dose and overall/subject:
N= number of subjects with at least one administered dose
n/%= number/percentage of subjects reporting at least once the symptom
For Overall/dose:
N= number of administered doses
n/%= number/percentage of doses followed by at least one type of symptom
Total : n/%= number/percentage of subjects/doses with at least one local symptom whatever the number of injections.
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Template 22 **Incidence of temperature by maximum value, within 7 days following each vaccination and overall (Intention-to-treat set)**

		<Group 1>				<Group 2>			
				95% CI				95% CI	
		n	%	LL	UL	n	%	LL	UL
<Vaccination at visit 1>	N	xxx				xxx			
	≥37.5								
	……								
	<39.0	xxx	xx.x	xx.x	xx.x	xxx	xx.x	xx.x	xx.x
	related	xxx	xx.x	xx.x	xx.x	xxx	xx.x	xx.x	xx.x
	<39.0 related	xxx	xx.x	xx.x	xx.x	xxx	xx.x	xx.x	xx.x
<Vaccination at visit 2>	…								
…									
Per subject									
Per vaccination									

Template 23 **Summary of <subjects with/ vaccinations followed by> at least one <serious/related/related serious/fatal> unsolicited adverse events <medically attended visits>, <within 30 days of any vaccination/ within 30 days of post-challenge period / from study start to 30 days post-challenge> (Intention-to-treat set)**

	<Group 1> N=XXXX				<Group 2> N=XXXX			
Primary System Organ Class (CODE)			95% CI				95% CI	
Preferred Term (CODE)	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
Any <Ø, serious, related, related serious, fatal> unsolicited adverse event <Ø , - Medically Attended Visits>	xxx	xx.x	xx.x	xx.x	xxx	xx.x	xx.x	xx.x
<SOC 1 (code)>	xxx	xx.x	xx.x	xx.x	xxx	xx.x	xx.x	xx.x
<Preferred Term 1 (code)>	xxx	xx.x	xx.x	xx.x	xxx	xx.x	xx.x	xx.x
<Preferred Term 2 (code)>	xxx	xx.x	xx.x	xx.x	xxx	xx.x	xx.x	xx.x
…								
<SOC 2 (code)>	xxx	xx.x	xx.x	xx.x	xxx	xx.x	xx.x	xx.x
<Preferred Term 1 (code)>	xxx	xx.x	xx.x	xx.x	xxx	xx.x	xx.x	xx.x
<Preferred Term 2 (code)>	xxx	xx.x	xx.x	xx.x	xxx	xx.x	xx.x	xx.x
…								
…								

At least one symptom = At least one symptom experienced regardless of the System Organ Class
N = Number of subjects having received at least one dose
n/% = Number / percentage of subjects reporting at least once a specified symptom within 30 days after vaccination day 0 to day 29
95% CI = Exact 95% confidence interval

Template 24 **Summary of occurrences and subjects with at least one serious unsolicited adverse events from study start until last study visit (D314) (Intention-to-treat set)**

	<Group 1> N=XXXX			<Group xxx> N=XXXX		
Primary System Organ Class (CODE)						
Preferred Term (CODE)	**occ**	**n**	**%**	**occ**	**n**	**%**
Any <Ø, serious, related serious, fatal, related fatal> < Ø , solicited and> unsolicited adverse event	xxx	xxx	xx.x	xxx	xxx	xx.x
<SOC 1 (code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
<Preferred Term 1 (code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
<Preferred Term 2 (code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
…						
<SOC 2 (code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
<Preferred Term 1 (code)>	xxx	xxx	xx.x	xxx	xxx	xx.x
<Preferred Term 2 (code)>	xxx	xxx	xx.x	xxx	xxx	xx.x

Template 25 **Summary of subjects by unsolicited event category, <within 30 days of any vaccination/ within 30 days of post-challenge period / from study start to 30 days post-challenge> (Intention-to-treat set)**

	<Group 1> N=XXXX				<Group 2> N=XXXX			
			95% CI				95% CI	
	n	%	LL	UL	n	%	LL	UL
At least one unsolicited adverse event	xxx	xx.x	xx.x	xx.x	xxx	xx.x	xx.x	xx.x
At least one serious unsolicited adverse event	xxx	xx.x	xx.x	xx.x	xxx	xx.x	xx.x	xx.x
At least one related unsolicited adverse event	xxx	xx.x	xx.x	xx.x	xxx	xx.x	xx.x	xx.x
At least one serious related unsolicited adverse event	xxx	xx.x	xx.x	xx.x	xxx	xx.x	xx.x	xx.x

Template 26 **Listing of potential immune-mediated disorders (pIMDs) reported as identified by predefined list of preferred terms and/or by investigator assessment (Intent to treat set)**

Group	Subject number	Gender	Country	Race	Age at onset (Year)	Verbatim Preferred Term	Primary System Organ Class
xxxxx	xxxxx	xxxxx	xxxxxxx	xxxxxx	xx	xxxxx	xxxxx

Group	Subject number	Medical visit type	Vaccination	Day of onset	Duration	Intensity Causality	Outcome	SAE (Y/N)	pIMD Source
xxxxx	xxxxx	xxxxxxx	xxxxxx	xx	xx	xxxx xxx	xxxxx		xxxxxxx

Template 27 **Listing of SAEs reported from study start to 28 days post challenge (Intention-to-treat set)**

Group	Subject number	Gender	Country	Race	Age at onset (Year)	Verbatim Preferred Term	
xxxxx	xxxxx	xxxxx	xxxxxxx	xxxxxx	xx	xxxxx	xxxxx

Group	Subject number	Primary System Organ Class	Medical visit type	Vaccination	Day of onset	Duration	Intensity Causality		Outcome
xxxxx	xxxxx	xxxxx	xxxxxxx	xxxxxx	xx	xx	xxxx	xxx	xxxxx

Template 28 Listing of (S) AEs and solicited symptoms leading to study/treatment discontinuation (Intent to treat set)

Group	Subject number	Gender	Country	Race	AE Description	SAE (Y/N) Causality	Outcome	Vaccination and visit
xxxxx	xxxxx	xxxxx	xxxxxxx	xxxxxx	xxxxxx	x	xxxxx	xxxxx
						Vaccination: x at visit x		

Template 29 Summary of hematology and biochemistry results (Intention-to-treat set)

Timepoint	Value at timepoint	<Group 1>		<Group 2>	
		N	%	N	%
<Timepoint 1>	N	xxx		xxx	
	Grade 1	xxx	xx.x	xxx	xx.x
	Grade 2	xxx	xx.x	xxx	xx.x
	Grade 3	xxx	xx.x	xxx	xx.x
	Grade 4	xxx	xx.x	xxx	xx.x
	Unknown	xxx	xx.x	xxx	xx.x

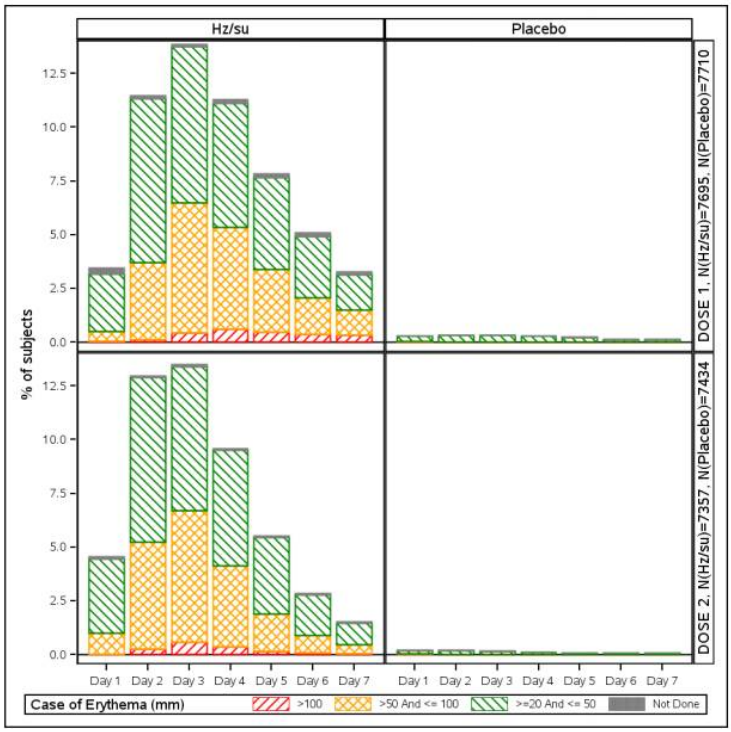
N = Number of subjects having received at least one dose
n/% = Number / percentage of subjects in each category

Template 30 Summary of subjects taking a concomitant medication with <7 days following each vaccination and overall / during challenge phase> (Intent to treat set)

		<Group 1>				<Group 2>			
				95% CI				95% CI	
		n	%	LL	UL	n	%	LL	UL
<Vaccination at visit 1>	N	xxx				xxx			
	Any	xxx	xx.x	xx.x	xx.x	xxx	xx.x	xx.x	xx.x
	Any antipyretic	xxx	xx.x	xx.x	xx.x	xxx	xx.x	xx.x	xx.x
<Vaccination at visit 2>	…								
…									
Per subject									
Per vaccination									

Template 31 Bar graph of the daily prevalence of <pain/redness/swelling> between day 1 and day 7 following each vaccination (Intent to treat set)

Example:



Template 32 Minimum and maximun dates (intent-to-treat set)

		<each group>	<each group>	Overall
Visit Description	**Parameter**	**Date**	**Date**	**Date**
< each informed consent>	Minimum	DDMMYYYY	DDMMYYYY	DDMMYYYY
	Maximum	DDMMYYYY	DDMMYYYY	DDMMYYYY
[Randomization]	Minimum	DDMMYYYY	DDMMYYYY	DDMMYYYY
	Maximum	DDMMYYYY	DDMMYYYY	DDMMYYYY
<each visit>	Minimum	DDMMYYYY	DDMMYYYY	DDMMYYYY
	Maximum	DDMMYYYY	DDMMYYYY	DDMMYYYY

Short group label = long group label

GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A Phase IIa, open-label, controlled, mono-center study to evaluate the efficacy, immunogenicity and safety of GSK Biologicals' candidate malaria vaccines RTS,S/AS01$_E$ and RTS,S/AS01$_B$ administered as various dose schedules according to a 0, 1, 7-month or a 0, 7-month schedule in healthy malaria-naïve subjects aged 18-55 years.
eTrack study number and Abbreviated Title	205081 (MALARIA-092)
Scope:	All data pertaining to the above study.
Date of Statistical Analysis Plan	Final: 24-MAY-2018
Co-ordinating author:	PPD (Statistician)
Reviewed by:	PPD (Clinical Research and Development Lead) PPD (Lead Scientific writer) PPD (Scientific writer) PPD (Regulatory Affair) PPD (SERM physician) PPD (SERM Scientist) PPD (CLS Manager) PPD (Lead statistical analyst) PPD (Lead statistician) PPD (Public disclosure)
Approved by:	PPD (Clinical Research and Development Lead) PPD (Lead Scientific writer) PPD (Lead statistical analyst) PPD (Lead statistician)

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

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LIST OF ABBREVIATIONS

AE	Adverse event
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)
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	According-To-Protocol
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CLS	Clinical laboratory sciences
CRF	Case Report Form
C-term	CS terminal portion of the protein
CTRS	Clinical Trial Registry Summary
eCRF	electronic Case Report Form
EPT	Endpoint titer
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
IU/ml	International units per milliliter
ITTS	Intent-To-Treat Set
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

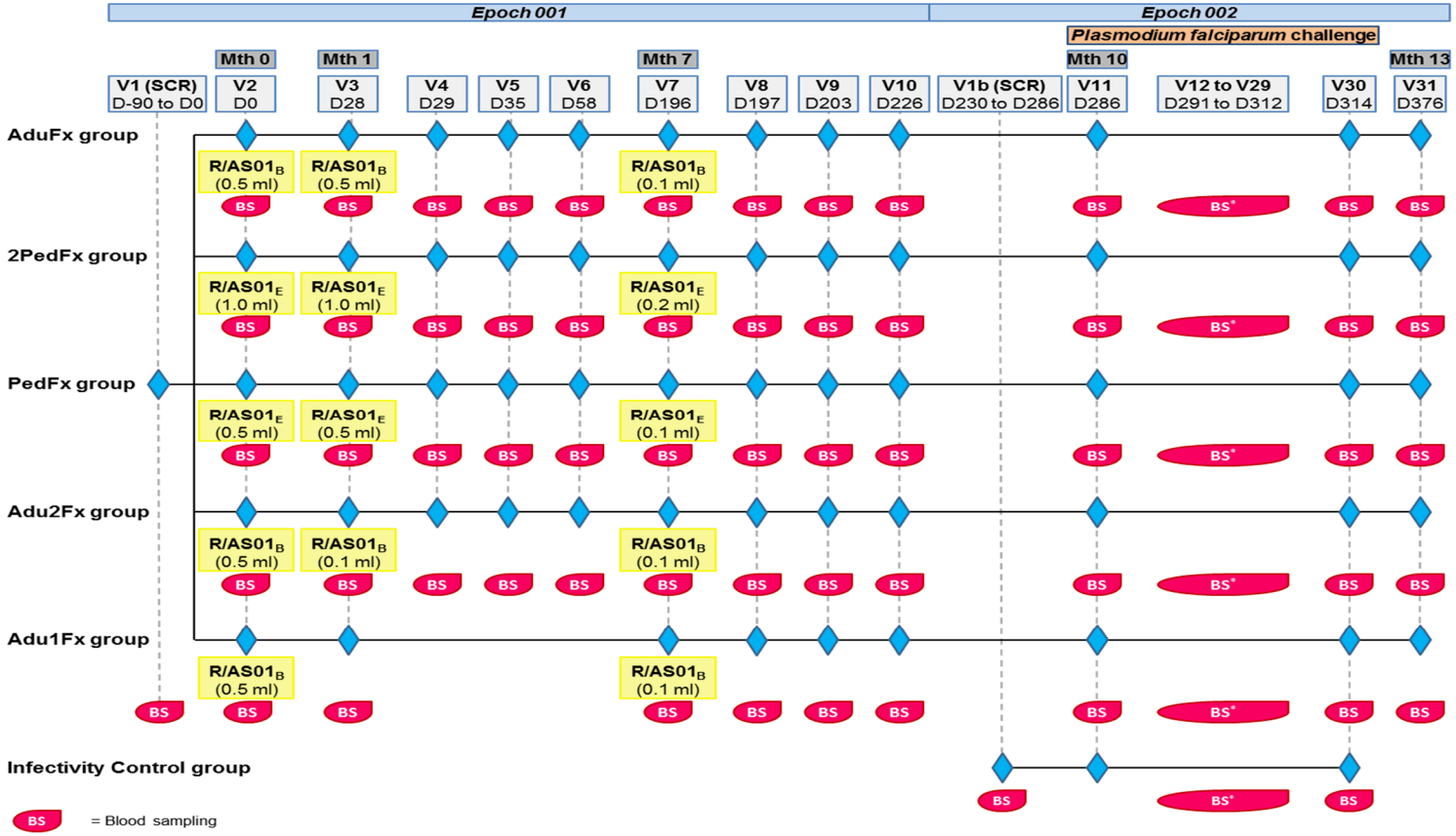
PCR	Polymerase chain reaction
PD	Protocol Deviation
pIMD	potential Immune Mediated Disease
PPS	Per-Protocol Set
SAE	Serious adverse event
SAS	Statistical Analysis System
SAP	Statistical Analysis Plan
SD	Standard Deviation
SERM	Safety Evaluation and Risk Management
SHS	Study Headline Summary
TFL	Tables 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
24-MAY-2018	Final version	Administrative Change – 19-JUN-2017

2. STUDY DESIGN

Figure 1 Study design



D: Day; Mth: month; R: RTS,S; SCR: Screening; V: visit. * Blood sample for estimation of subjects with parasitemia (PCR testing) will be collected on the day of subject entry into the hotel phase (Day 295 [Visit 16]); blood sample for biochemistry and hematology parameters will be collected the day of first parasitemia and blood sample for assessment of parasitemia (blood smear) will be collected daily for 14 days (from Day 291 [Visit 12] to Day 304 [Visit 25]) and then every two days for nine days (Day 306 [Visit 26], Day 308 [Visit 27], Day 310 [Visit 28], Day 312 [Visit 29], and Day 314 [Visit 30]).

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 investigational vaccine groups: AduFx, 2PedFx, PedFx, and Adu2Fx

Interval	Optimal length of interval [1]	Allowed interval[2]
Visit 1 (Screening) → Visit 2 (1st vaccination)	0 to 90 days	-
Visit 2 → Visit 3 (2nd vaccination)	28 days	± 7 days
Visit 3 → Visit 5	7 days	± 1 day
Visit 3 → Visit 6	30 days	± 7 days
Visit 3 → Visit 7 (3rd vaccination)	168 days	± 14 days
Visit 7 → Visit 9	7 days	± 1 day
Visit 7 → Visit 10	30 days	± 7 days
Visit 7 → Visit 11 (Challenge)	90 days	+ 14 days
Visit 11 → Visit 30	28 days	± 7 days
Visit 30 → Visit 31	62 days	± 14 days

[1] Whenever possible the investigator should arrange study visits within this interval.
[2] Subjects may not be eligible for inclusion in the according-to-protocol (ATP) cohort for analysis of immunogenicity and efficacy if they make the study visit outside this interval.

Table 2 Intervals between study visits for the investigational vaccine group: Adu1Fx

Interval	Optimal length of interval [1]	Allowed interval[2]
Visit 1 (Screening) → Visit 2 (1st vaccination)	0 to 90 days	-
Visit 2 → Visit 7 (2nd vaccination)	196 days	± 14 days
Visit 7 → Visit 9	7 days	± 1 day
Visit 7 → Visit 10	30 days	± 7 days
Visit 7 → Visit 11 (Challenge)	90 days	+ 14 days
Visit 11 → Visit 30	28 days	± 7 days
Visit 30 → Visit 31	62 days	± 14 days

[1] Whenever possible the investigator should arrange study visits within this interval.
[2] Subjects may not be eligible for inclusion in the ATP cohort for analysis of immunogenicity and efficacy if they make the study visit outside this interval.

Table 3 Intervals between study visits for the infectivity control group

Interval	Optimal length of interval [1]	Allowed interval[2]
Visit 1b (Screening) → Visit 11 (Challenge)	0 to 56 days	-
Visit 11 → Visit 30	28 days	± 7 days

[1] Whenever possible the investigator should arrange study visits within this interval.
[2] Subjects may not be eligible for inclusion in the ATP cohort 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	AduFx	RTS,S/AS01$_B$ full dose administered at Month 0, Month 1 and RTS,S/AS01$_B$ 1/5th dose administered at Month 7
2	2PedFx	RTS,S/AS01$_E$ double dose administered at Month 0, Month 1 and double dose RTS,S/AS01$_E$ 1/5th dose administered at Month 7
3	PedFx	RTS,S/AS01$_E$ full dose administered at Month 0, Month 1 and RTS,S/AS01$_E$ 1/5th dose administered at Month 7
4	Adu2Fx	RTS,S/AS01$_B$ full dose at Month 0 and RTS,S/AS01$_B$ 1/5th dose administered at Month 1, Month 7
4	Adu1Fx	RTS,S/AS01$_B$ full dose at Month 0 and RTS,S/AS01$_B$ 1/5th dose administered at Month 7
5	Control	Subjects will not receive any immunization 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 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 and were part of one of the vaccinated groups

3. OBJECTIVES

3.1. Primary objective

3.1.1. Efficacy

- To assess the vaccine efficacy against the occurrence of *P. falciparum* parasitemia (defined by a positive blood slide) for each vaccination schedule (AduFx, 2PedFx, PedFx, Adu2Fx, and Adu1Fx) versus the infectivity controls.

Refer to Section 4.1 for the definition of the primary endpoint.

3.2. Secondary objectives

3.2.1. Efficacy

- To assess the time to onset of *P. falciparum* parasitemia (defined by a positive blood slide) for each vaccination schedule (AduFx, 2PedFx, PedFx, Adu2Fx, and Adu1Fx) versus the infectivity controls.
- To assess the occurrence of *P. falciparum* parasitemia (defined by a positive blood slide) after vaccine administration for alternative vaccination schedules (2PedFx, PedFx, Adu2Fx, and Adu1Fx) versus the immunization schedule of reference (AduFx).
- To assess the time to onset of *P. falciparum* parasitemia (defined by a positive blood slide) after vaccine administration for alternative vaccination schedules (2PedFx, PedFx, Adu2Fx, and Adu1Fx) versus the immunization schedule of reference (AduFx).

3.2.2. Immunogenicity

For each vaccination schedule:

- To evaluate anti-CS repeat region antibody response at specified timepoints.
- To evaluate anti-HBs immunoglobulin G (IgG) antibody response at specified timepoints.

3.2.3. Safety

For each vaccination schedule:

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

Refer to Section 4.2 for the definition of the secondary endpoints.

3.3. Tertiary objectives

3.3.1. Immunogenicity

For each vaccination schedule:

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

Refer to Section 4.3 for the definition of the tertiary endpoints.

4. ENDPOINTS

4.1. Primary endpoint

4.1.1. Efficacy

- Occurrence of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge, comparing RTS,S/AS01$_B$ administered as full doses at Month 0 and Month 1 and 1/5th dose at Month 7 (AduFx group) versus infectivity controls.
- Occurrence of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge, comparing RTS,S/AS01$_E$ administered as double dose at Month 0 and Month 1 and double 1/5th dose at Month 7 (2PedFx group) versus infectivity controls.
- Occurrence of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge, comparing RTS,S/AS01$_E$ administered as full doses at Month 0 and Month 1 and 1/5th dose at Month 7 (PedFx group) versus infectivity controls.
- Occurrence of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge, comparing RTS,S/AS01$_B$ administered as one full dose at Month 0 and 1/5th doses at Month 1 and Month 7 (Adu2Fx group) versus infectivity controls.
- Occurrence of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge, comparing RTS,S/AS01$_B$ administered as one full dose at Month 0 and 1/5th doses at Month 7 (Adu1Fx group) versus infectivity controls.

4.2. Secondary endpoints

4.2.1. Efficacy

- Occurrence of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge, comparing RTS,S/AS01$_E$ administered as double dose at Month 0 and Month 1 and double 1/5th dose at Month 7 (2PedFx group) versus immunization schedule of reference (AduFx group).
- Occurrence of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge, comparing RTS,S/AS01$_E$ administered as full doses at Month 0 and Month 1 and 1/5th dose at Month 7 (PedFx) versus immunization schedule of reference (AduFx group).
- Occurrence of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge, comparing RTS,S/AS01$_B$ administered as one full dose at Month 0 and 1/5th full dose at Month 1 and Month 7 (Adu2Fx) versus immunization schedule of reference (AduFx group).
- Occurrence of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge, comparing RTS,S/AS01$_B$ administered as one full dose at Month 0 and 1/5th full doses at Month 7 (Adu1Fx) versus immunization schedule of reference (AduFx group).
- Time to onset of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge in each vaccination schedule versus immunization schedule of reference (AduFx group).
- Time to onset of *P. falciparum* parasitemia (defined by a positive blood slide) following sporozoite challenge in each vaccination schedule versus infectivity controls.

4.2.2. Immunogenicity

- For each vaccination schedule, the immune response to the CS antigen of the investigational vaccine:
  - Anti-CS repeat region antibody concentrations before vaccine administration (Day 0), one month post-Dose 2 (Day 58), six months post-Dose 2 (Day 196), one month post-Dose 3 (Day 226), on the day of challenge (Day 286), 28 days post-challenge (Day 314), and at study end (Day 376) for subjects from AduFx, 2PedFx, PedFx, and Adu2Fx groups and before vaccine administration (Day 0), before Dose 2 (Day 196), one month post-Dose 2 (Day 226), on the day of challenge (Day 286), 28 days post-challenge (Day 314), and at study end (Day 376) for subjects from Adu1Fx group.

- For each vaccination schedule, the immune response to the hepatitis B antigen of the investigational vaccine:
  - Anti-HBs IgG antibody concentrations before vaccine administration (Day 0), one month post-Dose 2 (Day 58), six months post-Dose 2 (Day 196), one month post-Dose 3 (Day 226), on the day of challenge (Day 286), 28 days post-challenge (Day 314), and at study end (Day 376) for subjects from AduFx, 2PedFx, PedFx, and Adu2Fx groups and before vaccine administration (Day 0), before Dose 2 (Day 196), one month post-Dose 2 (Day 226), on the day of challenge (Day 286), 28 days post-challenge (Day 314), and at study end (Day 376) for subjects from Adu1Fx group.

4.2.3. Safety

- Safety and reactogenicity of the investigational vaccine for each vaccination schedule:
  - Occurrence of solicited local and general AEs within seven days (day of vaccination and six subsequent days) after each vaccination.
  - Occurrence of unsolicited AEs within 30 days (day of vaccination and 29 subsequent days) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
  - Occurrence of AEs within 30 days (day of challenge and 29 subsequent days) after challenge, according to the MedDRA classification.
  - Occurrence of SAEs (all, fatal, related to investigational vaccine) within 30 days (day of vaccination and 29 subsequent days) after each vaccination, according to the MedDRA classification.
  - Occurrence of SAEs (all, fatal, related to investigational vaccine) during the whole study period (from Dose 1 [Day 0] up to study conclusion [Day 376]), according to the MedDRA classification.
  - Occurrence of AEs and SAEs leading to withdrawal from further vaccination from Dose 1 (Day 0) up to study conclusion (Day 376), according to the MedDRA classification, for each vaccinated subject.
  - Occurrence of pIMDs from Dose 1 (Day 0) up to study conclusion (Day 376), according to the MedDRA classification, for each vaccinated subject.
  - Occurrence of meningitis from Dose 1 (Day 0) up to study conclusion (Day 376), according to the MedDRA classification, for each vaccinated subject.
  - Occurrence of abnormal laboratory values at screening, Day 35, Day 58, Day 203, Day 226, the day of first parasitemia, and Day 314 for each vaccinated subject and at screening, the day of first parasitemia and Day 314 for the infectivity control subjects.

- Safety after sporozoite challenge in the infectivity control group.
  - Occurrence of AEs within 30 days (day of challenge and 29 subsequent days) after challenge, according to the MedDRA classification.
  - Occurrence of SAEs (all, fatal, related) from day of challenge (Day 286) to the end of the challenge phase (Day 314), according to the MedDRA classification.

4.3. Tertiary endpoints

4.3.1. Immunogenicity

- For each vaccination schedule, the immune response to the CS antigen of the investigational vaccine:
  - Anti-CS repeat region IgG avidity index before vaccine administration (Day 0), one month post-Dose 2 (Day 58), six months post-Dose 2 (Day 196), one month post-Dose 3 (Day 226), on the day of challenge (Day 286), 28 days post-challenge (Day 314), and at study end (Day 376) for subjects from AduFx, 2PedFx, PedFx, and Adu2Fx groups and before vaccine administration (Day 0), before Dose 2 (Day 196), one month post-Dose 2 (Day 226), on the day of challenge (Day 286), 28 days post-challenge (Day 314), and at study end (Day 376) for subjects from Adu1Fx group.
  - Anti-full length CS protein IgG concentrations and anti-C-term IgG concentrations before vaccine administration (Day 0), one month post-Dose 2 (Day 58), six months post-Dose 2 (Day 196), one month post-Dose 3 (Day 226), on the day of challenge (Day 286), 28 days post-challenge (Day 314), and at study end (Day 376) for subjects from AduFx, 2PedFx, PedFx, and Adu2Fx groups and before vaccine administration (Day 0), before Dose 2 (Day 196), one month post-Dose 2 (Day 226), on the day of challenge (Day 286), 28 days post-challenge (Day 314), and at study end (Day 376) for subjects from Adu1Fx group.
  - Anti-full length CS protein and anti-C-term IgG avidity before vaccine administration (Day 0), one month post-Dose 2 (Day 58), six months post-Dose 2 (Day 196), one month post-Dose 3 (Day 226), on the day of challenge (Day 286), 28 days post-challenge (Day 314), and at study end (Day 376) for subjects from AduFx, 2PedFx, PedFx, and Adu2Fx groups and before vaccine administration (Day 0), before Dose 2 (Day 196), one month post-Dose 2 (Day 226), on the day of challenge (Day 286), 28 days post-challenge (Day 314), and at study end (Day 376) for subjects from Adu1Fx group.

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

5. ANALYSIS SETS

5.1. Definition

Note that in order to align to ICH and CDISC terminology the According To Protocol (ATP) cohort has been renamed the Per-Protocol Set (PPS).

5.1.1. Enrolled Set

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

5.1.2. Intent-to-treat set (ITTS)

The Intent-To-Treat Set (ITTS) will include all subjects who received at least one dose of study vaccine. The ITTS analysis will be performed per treatment actually administered. All challenged infectivity controls will also be included and will be presented as a separate study group.

5.1.3. Per-Protocol Set for analysis of immunogenicity and efficacy (PPS for analysis of immunogenicity and efficacy)

The PPS for analysis of immunogenicity and efficacy will include all subjects included in the ITTS who fulfilled all eligibility criteria and received all vaccinations according to protocol procedures within the protocol specified intervals, 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 vaccination.

5.1.4. Adapted Per-Protocol Set for analysis of efficacy (Adapted PPS for analysis of efficacy)

The Adapted PPS for analysis of efficacy will include all subjects included in the ITTS who fulfilled all eligibility criteria and received all vaccinations according to protocol procedures within the protocol specified intervals and underwent *P. falciparum* challenge.

5.2. 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.

5.2.1. Elimination from ITTS

Code 1030 (Study vaccine not administered at all) for all subjects except those from the infectivity control group and code 900 (invalid informed consent or fraud data) will be used for identifying subjects eliminated from ITTS.

5.2.2. Elimination from the PPS for analysis of immunogenicity and efficacy

5.2.2.1. Excluded subjects

A subject will be excluded from the PPS analysis of immunogenicity and efficacy analysis under the following conditions

Code	Condition under which the code is used
900	Invalid informed consent or fraud data
1030	Study vaccine not administered at all
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.
1070	Vaccination not according to protocol • Incomplete vaccination course before treatment withdrawal or subject study conclusion. • Administration not according to protocol for reason specified by the investigator, other than side, site and route. • Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number). • Study vaccine RTS,S/AS01 not prepared as per protocol
1080	Good Manufacturing Practice No-Go: Vaccine temperature deviation
1090	Expired vaccine administered
2010	Protocol violation (inclusion/exclusion criteria) • Eligibility criteria not met with an impact on immunogenicity data

Code	Condition under which the code is used
2040	Administration of any medication forbidden by the protocol which may influence the efficacy endpoints • 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). • Immunoglobulins and/or any blood products administered during the study period. • Drugs known to have anti-*Plasmodium* properties, used during the challenge period before identification of parasitemia.
2050	Underlying medical condition forbidden by the protocol which may influence the efficacy endpoints
2080	Subjects did not comply with vaccination schedule (See Table 1, Table 2, Table 3)
2090	Subjects did not comply with blood sampling schedule (See Table 1, Table 2, Table 3)
2100	Serological results not available for anti-CS at all post-vaccination visits
2120	Obvious incoherence or abnormality or error in immunogenicity (antibody) data
3000	Subject did not undergo challenge

5.2.3. Elimination from the Adapted PPS for analysis of efficacy

5.2.3.1. Excluded subjects

A subject will be excluded from the Adapted PPS analysis of efficacy analysis under the following conditions:

Code	Condition under which the code is used
900	Invalid informed consent or fraud data
1030	Study vaccine not administered at all
1070	Vaccination not according to protocol • Incomplete vaccination course before treatment withdrawal or subject study conclusion. • Administration not according to protocol for reason specified by the investigator, other than side, site and route. • Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number). • Study vaccine RTS,S/AS01 not prepared as per protocol
3000	Subject did not undergo challenge

5.3. Important protocol deviations not leading to elimination from per-protocol analysis set

Important protocol deviations not leading to elimination from PPS are defined in MALARIA-092 (205081) Protocol Deviation Management Plan.

PPD

(MALARIA-092 (205081) Protocol Deviation Management Plan)

6. STATISTICAL ANALYSES

Note that standard data derivation rules and statistical methods are described in Annex 1 and will not be repeated below.

6.1. Demography

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

A study flow table (consort) will be generated to present the number of subjects screened, randomized, receiving doses and included in the PPS for analyses.

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

Demographic characteristics (age at first vaccination in years for the vaccinated groups and at the time of the screening for the 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.

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 will be tabulated.
- The number of withdrawn subjects will be tabulated according to the reason for withdrawal.

6.2. Exposure

6.2.1. Analysis of exposure planned in the protocol

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

6.3. Efficacy analysis

6.3.1. 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.

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 vaccine groups (AduFx, 2PedFx, PedFx, Adu2Fx, and Adu1Fx) 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 vaccine groups (AduFx, 2PedFx, PedFx, Adu2Fx, and Adu1Fx) and the infectivity control group, using the log-rank statistic.

The same methodology will be applied for the evaluation of the vaccinated groups versus the immunization schedule of reference (AduFx group).

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

6.3.2. Additional considerations

6.3.2.1. Case definition

The primary case definition of *P. falciparum* infection is an asexual blood stage *P. falciparum* parasite density > 0 detected by blood slide reading.

6.3.2.2. 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 protocol visit D314 (28 days post challenge), drop-out date, start date of antimalarial treatment or date meeting an endpoint, whichever occurs first. Time at risk will be calculated as: censor date – date challenge + 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 (visit D314 - 28 days post challenge).

6.4. Immunogenicity analysis

6.4.1. 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 study group, at each timepoint that a blood sample result is available:

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 in each group (AduFx, 2PedFx, PedFx, Adu2Fx, and Adu1Fx). Anti-CS antibody concentrations will be summarized by GMC. Anti-CS antibody concentrations will be displayed using reverse cumulative curves. Similar analysis will be performed for the anti-full length CS protein (proportion of subjects with anti-CS antibody titres ≥ 200 1/DIL) and anti-C-term antibodies (proportion of subjects with anti-CS antibody concentrations ≥100 EPT).

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 in each groups (AduFx, 2PedFx, PedFx, Adu2Fx, and Adu1Fx). Anti-HBs antibody concentrations will be summarized by GMC. Anti-HBs antibody concentrations will be displayed using reverse cumulative curves.

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.

6.4.2. 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.

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?).

6.5. Analysis of safety

6.5.1. Analysis of safety planned in the protocol

The analysis of safety will be performed on the ITTS.

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 30 day follow-up period after each vaccine dose and overall will be tabulated with exact 95% CI. The percentage of doses followed by at least one local AE (solicited and unsolicited), by at least one general AE (solicited and unsolicited) and by any AE during the 7-day or 30-day follow-up period will be tabulated with exact 95% CI. The 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 (Day 0-6) after each vaccine dose and overall will be tabulated for each group. Similarly, the percentage of doses followed by each individual solicited local and general AE will be tabulated, for the overall and for each vaccination course, with exact 95% CI.

For fever (fever is defined as temperature ≥ 37.5°C/99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C/100.4°F for rectal route), the number and percentage of subjects reporting fever by half degree (°C) cumulative increments during the first seven days (Day 0-6) after each vaccine dose and overall 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 (Day 0-6) overall doses will be tabulated.

The percentage of subjects reporting unsolicited AEs within 30 days (Day 0-29) after each vaccine dose (overall doses) and percentage of subjects reporting AEs after the sporozoite challenge 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 reporting SAEs (all, fatal, related) occurring within 30 days (day of vaccination and 29 subsequent days) after each dose of study vaccine, classified by the MedDRA preferred term level will be tabulated with exact 95% CI.

The percentage of subjects reporting SAEs (all, fatal, related) occurring from Dose 1 (Day 0) until last study visit (Day 376), classified by the MedDRA preferred term level will be tabulated with exact 95% CI.

The percentage of subjects reporting SAEs (all, fatal, related) occurring from day of challenge (Day 286) to the end of the challenge phase (Day 314), according to the MedDRA classification 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 further vaccination from Dose 1 (Day 0) until last study visit (Day 376), classified by MedDRA preferred term level, will be tabulated with exact 95% CI.

The percentage of vaccinated subjects reporting AEs of specific interest (meningitis and pIMDs) from Dose 1 (Day 0) until last study visit (Day 376), classified by MedDRA preferred term level, will be tabulated with exact 95% CI.

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 Table 4

Table 4 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)].

The percentage of subjects using concomitant medication (any medication, any antipyretic and any prophylactic medication, respectively) during the 7-day follow-up period (Day 0-6) after vaccination will be summarized by group after each dose and overall. The percentage of subjects using concomitant medication during the entire sporozoite challenge (D286-314) will be summarized by group.

6.5.2. Additional considerations

A summary of subjects with all combined solicited (regardless of their duration) and unsolicited adverse events will be provided. Solicited adverse events 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

The following analysis will be performed if at least 5 subjects have used concomitant vaccination during the 7-day follow-up period (Day 0-6) after study vaccination during the full study period.

The percentage of subjects using any concomitant vaccination during the 7-day follow-up period (Day 0-6) after study vaccination will be summarized by group after each dose and overall. The percentage of subjects using concomitant vaccination during the entire sporozoite challenge will be summarized by group.

Note that the study will be converted in CDISC. Accordingly protocol Day 0-Day N will be replaced by Day 1-Day N+1 for the statistical analysis.

7. ANALYSIS INTERPRETATION

All the analyses performed during this study will be descriptive.

8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

The analyses will be performed stepwise:

- An interim analysis to allow an internal decision for the choice of the booster dose in study Malaria-102 will be performed as soon as the results of the challenge phase will be available on data as clean as possible. This analysis will be descriptive and performed on the Adapted PPS for analysis of efficacy.
- When all the remaining data up to Day 376 will be available, the main analysis will be performed. An integrated study report will be written.

8.2. Statistical considerations for interim analyses

A descriptive analysis to evaluate VE against infection of *P. falciparum* will be performed on the Adapted PPS for analysis of efficacy at the time of the interim analysis. 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.

9. CHANGES FROM PLANNED ANALYSES

The Total vaccinated cohort (TVC) defined in the protocol has been replaced by the Intent-To-Treat Set (ITTS) to include both subjects vaccinated and subjects from the infectivity control group in the same cohort.

An interim analysis has been added to allow an internal decision for the choice of the booster dose in study Malaria-102. This analysis will be descriptive and performed on data as cleaned as possible.

To allow an interim analysis as close as possible to the main analysis, an Adapted PPS for analysis of efficacy has been created.

An analysis of concomitant vaccination has been added to assess any effect on immune response or safety.

10. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

The TFL TOC provides the list of tables/listings and figures needed for the study report. It also identifies the tables eligible for each analyses and their role (synopsis, in-text, post-text, SHS, CTRS, Annex). Note that all TFL aimed to be included as post-text are noted as post-text even if these are tabulations of individual data such as listings of SAEs. The post-text material contains all source material for the study report and accordingly a post-text table may be redundant with an in-text table.

11. ANNEX 1 STANDARD DATA DERIVATION RULE AND STATISTICAL METHODS

11.1. Statistical Method References

The exact two-sided 95% CIs for a proportion within a group will be the Clopper-Pearson exact CI [Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. *Biometrika*. 1934;26:404-413].

11.2. Standard data derivation

11.2.1. Date derivation

- SAS date derived from a character date: In case day is missing, 15 is used. In case day & month are missing, 30 June is used.
- Onset day for an event (AE, medication, vaccination): The onset day is the number of days between the last study vaccination & the onset/start date of the event. This is 1 for an event starting on the same day as a vaccination. See SAS date derived in case the start date of the event is incomplete.
- Duration: Duration of an event is expressed in days. It is the number of days between the start & the stop dates + 1. Therefore duration is 1 day for an event starting & ending on the same day.

11.2.2. Dose number

- The study dose number is defined in reference to the number of study visits at which vaccination occurred. More specifically dose 1 refers to all vaccines administered at the first vaccination visit while dose 2 corresponds to all vaccinations administered at the second vaccination visit even if this is the first time a product is administered to the subject.
- Relative dose: the relative dose for an event (AE, medication, vaccination) is the most recent study dose given before an event. In case the event takes place on the day a study dose is given, the related dose will be that of the study dose, even if the event actually took place before vaccination. For instance, if an AE begins on the day of the study vaccination but prior to administration of the vaccine, it will be assigned to this dose. In case a study dose is not administered (eg dose 2) and an event occurs after the subsequent study dose (eg 3rd study dose), the relative dose of the event will be study dose associated to the subsequent study dose (eg dose 3).
- The number of doses for a product is the number of times the product was administered to a subject.
- The incidence per dose is the number of vaccination visits at which an event was reported among all vaccination visits.

11.2.3. Demography

- Age: Age at the reference activity, computed as the number of years between the date of birth and the reference activity. Note that due to incomplete date, the derived age may be incorrect by 1 year when month is missing from the birthdate. This may lead to an apparent inconsistency between the derived age and the eligibility criteria/the age category used for randomization.
- Conversion of weight to kg

  The following conversion rule is used:

  – Weight in Kilogrammes= weight in Pounds / 2.2 + weight in Ounces / 35.2

  The result is rounded to 2 decimals.
- Conversion of height to cm

  The following conversion rule is used:

  – Height in Centimetres = Height in Feet * 30.48 + Height in Inches * 2.54

  The result is rounded to the unit (ie no decimal).
- Conversion of temperature to °C

  The following conversion rule is used:

  – Temperature in °Celsius = ((Temperature in °Fahrenheit -32) *5)/9

  The result is rounded to 1 decimal.

11.2.4. Immunogenicity

- For a given subject and given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.
- The Geometric Mean Concentrations (GMCs) calculations are performed by taking the anti-log of the mean of the log titre 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.
- The percentage of subjects seropositive/seroprotected and associated two-sided 95% Clopper-Pearson confidence intervals (CIs) will be computed by vaccine group for each available immunogenicity monitoring.
- A subject seropositive for anti-CS antibody will be a subject whose antibody concentration will be greater than or equal to the cut-off value (anti-CS ≥ 1.9 EU/ml).
- Seroprotection rate for anti-HBs antibody is defined as the percentage of subjects with antibody concentration greater than or equal to an established cut-off (anti-HBs ≥ 10 mIU/ml).

11.2.5. Safety

- Handling of missing data: subjects who missed reporting symptoms (unsolicited or concomitant medications) will be treated as subjects without symptoms (unsolicited or concomitant medications, respectively). In case of significant non-compliance of study procedures for reporting symptoms, the analysis plan will be reassessed to ensure more accurate reporting of study data by further analysis.
- For the analysis of solicited symptoms, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the ES will include only subjects/doses with documented safety data (i.e. symptom screen/sheet completed).
- For a given subject and the analysis of solicited symptoms within 7 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the ES will include only vaccinated subjects for doses with documented safety data (i.e., symptom screen completed). More specifically the following rules will be used:
  - Subjects who documented the absence of a solicited symptom after one dose will be considered not having that symptom after that dose.
  - Subjects who documented the presence of a solicited symptom and fully or partially recorded daily measurement over the solicited period will be included in the summaries at that dose and classified according to their maximum observed daily recording over the solicited period.
  - Subjects who documented the presence of a solicited symptom after one dose without having recorded any daily measurement will be assigned to the lowest intensity category at that dose (i.e., 37.5°C for fever or grade 1 for other symptoms).
  - Doses without symptom sheets documented will be excluded.
- For analysis of unsolicited AEs, such as SAEs or AEs by primary MedDRA term, and for the analysis of concomitant medications, all vaccinated subjects will be considered.
- For the analysis, temperatures will be coded as follows:

Grade	Temperature
0	< 37.5°C (< 99.5°F)
1	≥ 37.5°C (≥ 99.5°F) to ≤ 38.0°C (100.4°F)
2	> 38.0°C (> 100.4°F) to ≤ 39.0°C (102.1°F)
3	> 39.0°C (102.1°F)

- For the analysis, local injection site redness and swelling will be coded as follows:

Grade	Temperature
0	0 mm
1	> 0 to ≤ 50 mm
2	> 50 mm to ≤ 100 mm
3	> 100 mm

Note that for all tables described in this section, the way the percentage of subjects will be derived will depend on the event analysed (see table below for details). As a result, the N value will differ from one table to another.

Event	N used for deriving % per subject for Vaccination phase	N used for deriving % per dose for Vaccination phase
Concomitant vaccination	All subjects with study vaccine administered	All study visits with study vaccine administered
Solicited general symptom	All subjects with at least one solicited general symptom documented as either present or absent (i.e., symptom screen completed)	All study visits with study vaccine administered and with at least one solicited general symptom documented as either present or absent (i.e., symptom screen completed)
Solicited local symptom	All subjects with at least one solicited local symptom documented as either present or absent (i.e., symptom screen completed)	All study visits with study vaccine administered and with at least one solicited local symptom documented as either present or absent (i.e., symptom screen completed)
Unsolicited symptom	All subjects with study vaccine administered	All study visits with study vaccine administered
Concomitant medication	All subjects with study vaccine administered	All study visits with study vaccine administered

- Related dose: The related dose for an event (e.g., AE, medication, vaccination,…) is the study dose given before an event. In case the event takes place on a day a study dose is given, if the investigator has indicated the timing (before or after the vaccination) the related dose for this event is the most recent study dose given before this event. If the investigator has not indicated the timing, the related dose will be that of the study dose even if the event actually took place before.

Number of decimals displayed:

The following decimal description from the decision rules will be used for demography, efficacy, immunogenicity and safety/reactogenicity results.

Display Table	Parameters	Number of decimal digits
Demographic characteristics	Mean, median age	1
Demographic characteristics	SD (age)	1
Reactogenicity	Mean, Min, Q1, Median, Q3, Max for duration	1
All summaries	% of count, including LL & UL of CI	1
All summaries	p-value	3