GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	Phase IIIb randomized, open, controlled, multi-center study to evaluate the immunogenicity and safety of the RTS,S/AS01$_E$ candidate malaria vaccine, when administered as primary vaccination at 6, 7.5 and 9 months of age with or without co-administration of measles, rubella and yellow fever vaccines followed by an RTS,S/AS01$_E$ booster vaccination 18 months post Dose 3, to children living in sub-Saharan Africa.
eTrack study number and Abbreviated Title	200596 (MALARIA-073)
Scope:	All data pertaining to the above study.
Date of Statistical Analysis Plan	Final: 09-Apr-2018
Co-ordinating author:	PPD (Statistician)
Reviewed by:	PPD (Clinical and Epidemiology Project Lead) PPD (Clinical Research and Development Lead) PPD (Lead statistician) PPD (Statistician) PPD (Lead statistical analyst) PPD (Scientific writer) PPD (Lead Scientific writer) PPD (Regulatory Affair) PPD (SERM physician) PPD (SERM Scientist) PPD (Public disclosure PM)
Approved by:	PPD (Clinical and Epidemiology Project Lead) delegating to PPD (Clinical Research and Development Lead) PPD (Lead statistician) PPD (Lead Scientific writer) PPD (Lead statistical analyst)

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

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LIST OF ABBREVIATIONS

AE	Adverse event
ANOVA	Analysis of Variance
Anti-CS	Antibody to the *Plasmodium falciparum* circumsporozoite (CS) repeat domain
Anti-HBs	Antibody to the hepatitis B surface antigen
Anti-Me	Anti-measles antibody
Anti-Ru	Anti-rubella antibody
Anti-YF	Anti-yellow fever antibody
$AS01_E$	GSK's proprietary Adjuvant System containing MPL, QS-21 Stimulon® and liposome (25 µg MPL and 25 µg QS-21 Stimulon®)
CI	Confidence interval
Coad	Co-administration
CS	Circumsporozoite protein of *Plasmodium falciparum*
eCRF	Electronic case report form
ED50	End point Dilution 50
EPI	Expanded Program on Immunization
ES	Exposed Set
EU/ml	ELISA unit per milliliter
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titre
GSK	GlaxoSmithKline
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IU/ml	International units per milliliter
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
N.A.	Not Applicable
PD	Protocol Deviation

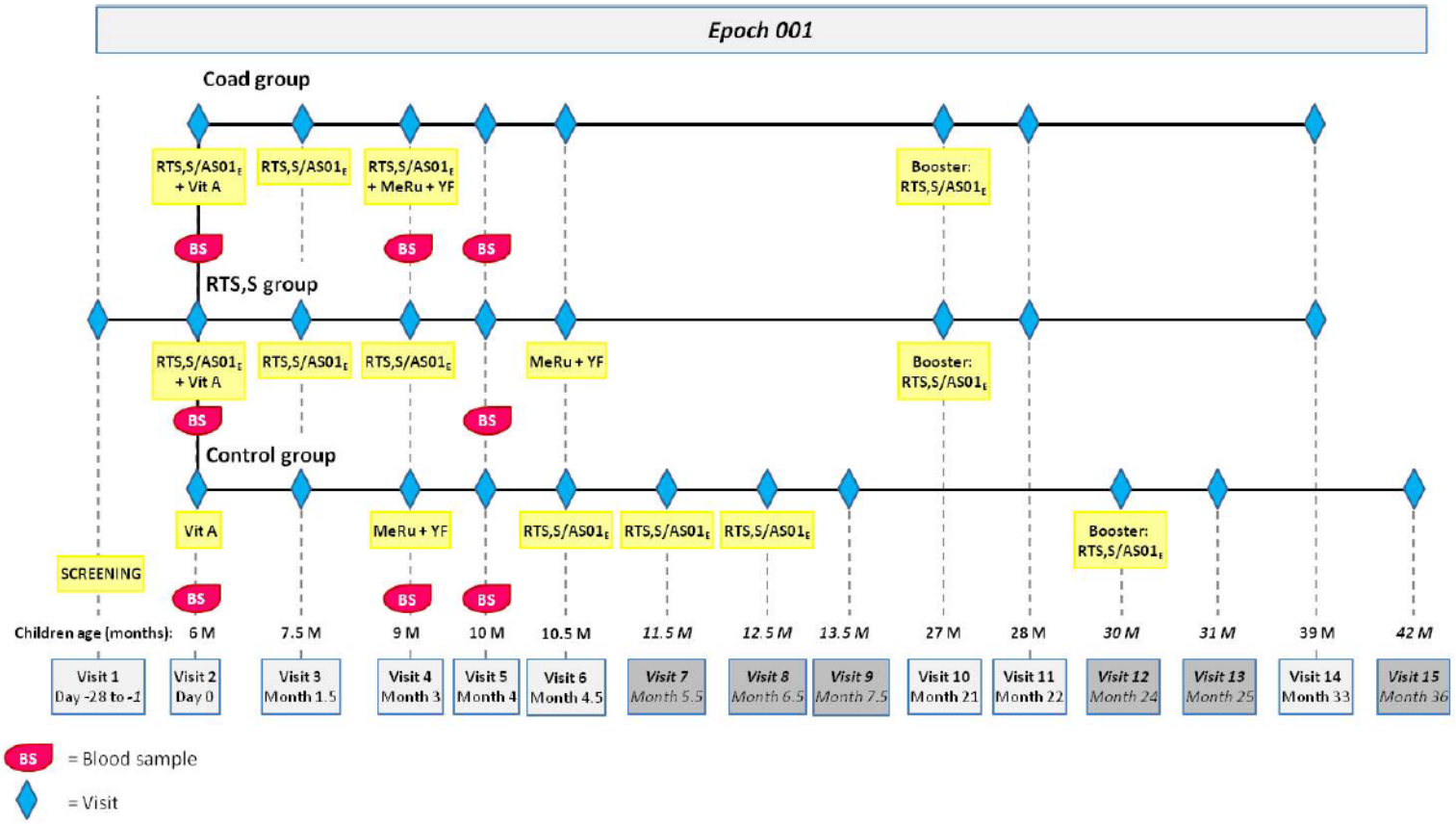
pIMD	Potential immune-mediated disease
PPS	Per Protocol Set
RCD	Reverse cumulative distribution
RTS,S	Particulate antigen, containing both RTS and S (hepatitis B surface antigen) proteins
RTS,S/AS01$_E$	GSK Biologicals' candidate *Plasmodium falciparum* malaria vaccine adjuvanted with GSK Biologicals' proprietary Adjuvant System AS01$_E$
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SR	Study Report
TFL	Tables Figures and Listings
TOC	Table of Content
UL	Upper Limit of the confidence interval
YF	Yellow fever

1. DOCUMENT HISTORY

Date	Description	Protocol Version
09-APR-2018	Final version	Amendment 1 Final – 09-AUG-2016

2. STUDY DESIGN

Figure 1 Study design



- Experimental design: Phase IIIB, open, randomized, controlled, multi-centric study with three parallel groups.
- Duration of the study: Approximately 33 months per participant in the Coad or the RTS,S group and 36 months in the Control group.
  - Epoch 001: Primary starting at Visit 1 (Screening) and ending at Visit 15 (Month 36).
- Study groups: 3 study groups are defined for the study (Coad group, RTS,S group and Control group). A description of the vaccination, blood sample and visit schedule is provided for each of the study groups in Figure 1.

Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age (Min)	Epoch 001
Coad group	233	6 months*	x
RTS,S group	233	6 months*	x
Control group	233	6 months*	x

* For clarity this corresponds from the day the child becomes 6 months of age until the day before the child achieves 7 months of age.

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study groups		
		Coad group	RTS,S group	Control group
RTS,S/AS01$_E$	RTS,S	x	x	x
	AS01E	x	x	x
Yellow fever	WHO prequalified Yellow Fever	x	x	x
Measles and Rubella	MR-VAC	x	x	x
Vitamin A	Vitamin A	x	x	x

MR-VAC: Live attenuated measles virus and rubella virus vaccine (Serum Institute of India)

- Treatment allocation: randomized in a 1:1:1 ratio to each study group.
- Blinding: open

Table 3 Blinding of study epoch

Study Epoch	Blinding
Epoch 001	open

- Type of study: self-contained.
- Data collection: Electronic Case Report Form (eCRF).
- Safety monitoring: description of safety monitoring is available in Table 5
- Immunogenicity monitoring:

Table 4 Immunological read-outs

Blood sampling timepoint		study group	No. subjects	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint				
Visit 2	Day 0	Coad group and RTS,S group	466	anti-CS	1
		Coad group and RTS,S group	466	anti-HBs	2
		Coad group and Control group	466	anti-catalase	3
Visit 4	Month 3	Coad group and Control group	466	anti-Me	1
		Coad group and Control group	466	anti-Ru	2
Visit 5	Month 4	Coad group and RTS,S group	466	anti-CS	1
		Coad group and RTS,S group	466	anti-HBs	5
		Coad group and Control group	466	anti-catalase	6
		Coad group and Control group	466	anti-Me	2
		Coad group and Control group	466	anti-Ru	3
		Coad group and Control group	466	anti-YF	4

Table 5 Reporting periods for adverse events and serious adverse events

Visit	1	2			3			4			5	6	7	8	9	10	11	12	13	14	15
Children age (Months)		6			7.5			9			10	10.5	11.5	12.5	13.5	27	28	30	31	39	42
Study Month		M0			M1.5			M3			M4	M4.5	M5.5	M6.5	M7.5	M21	M22	M24	M25	M33	M36
	D-28 to -1	D0	D6	D29	M1.5	M1.5 +6d	M1.5 +29d	M3	M3 +13d	M3 +41d											
Solicited local and general AEs		X[a]	X[a]		X[a]	X[a]		X[a]													
Unsolicited AEs		X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b,c]	X[c]	X[c]	X[c]	X[d]	X[d]	X[e]	X[e]		
SAEs related to study participation or concurrent GSK medication/vaccine																					
SAEs (All, fatal, related to the investigational vaccine)																					
AEs of specific interest**																					

M: study month; d: day

** AEs of specific interest include seizure (occurring within 30 days post-vaccination for vaccine doses administered at 6 and 7.5 months of age [Visits 2 and 3] or 42 days post-vaccination for vaccine doses administered at 9 months of age [Visit 4]), meningitis and pIMDs.

a In the Control group, only solicited general AE will be collected. In the Coad and the RTS,S groups, solicited local and general AEs will be collected.

b Unsolicited AEs will be collected from Visit 2 until 42 days after Visit 4 for children in Coad, RTS,S and Control groups.

c Unsolicited AEs will be collected from Visit 6 until 30 days after Visit 8 only for children from the Control group.

d Unsolicited AEs will be collected over a 30-day follow-up period after vaccination only for children from the Coad and the RTS,S groups.

e Unsolicited AEs will be collected over a 30-day follow-up period after vaccination only for children from the Control group.

3. OBJECTIVES

3.1. Primary objective

- To demonstrate the non-inferiority of the antibody response to the CS antigen when RTS,S/AS01$_E$ is co-administered with YF vaccine and a combined measles and rubella vaccine versus RTS,S/AS01$_E$ administered alone.
  - *Criteria for non-inferiority: one month post Dose 3 of RTS,S/AS01$_E$, the upper limit (UL) of the 2-sided 95% confidence interval (CI) on the geometric mean titre (GMT) ratio (RTS,S group/Coad group) of the anti-CS, is below a limit of 2.*

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

3.2. Secondary objectives

Immunogenicity

- To describe the antibody response to the CS antigen when RTS,S/AS01$_E$ is administered at 6, 7.5 and 9 months of age in co-administration with YF vaccine and a combined measles and rubella vaccine versus RTS,S/AS01$_E$ administered alone.
- To describe the antibody response to the hepatitis B surface (HBs) antigen when RTS,S/AS01$_E$ is administered at 6, 7.5 and 9 months of age in co-administration with YF vaccine and a combined measles and rubella vaccine versus RTS,S/AS01$_E$ administered alone.
- To demonstrate the non-inferiority of the antibody response to the measles vaccine antigen when YF vaccine and a combined measles and rubella vaccine are co-administered with RTS,S/AS01$_E$ versus administration without RTS,S/AS01$_E$.
  - *Criteria for non-inferiority: one month post-vaccination with the combined measles and rubella vaccine, the UL of the 95% CI on the difference in seroconversion rates of the anti-measles antibody (anti-Me), is below 10% (Control group minus Coad group).*
- To describe the antibody response to the measles vaccine antigen when YF vaccine and a combined measles and rubella vaccine are co-administered with RTS,S/AS01$_E$ versus administration without RTS,S/AS01$_E$.
- To demonstrate the non-inferiority of the antibody response to the rubella vaccine antigen when YF vaccine and a combined measles and rubella vaccine are co-administered with RTS,S/AS01$_E$ versus administration without RTS,S/AS01$_E$.
  - *Criteria for non-inferiority: one month post-vaccination with the combined measles and rubella vaccine, the UL of the 95% CI on the difference in seroconversion rates of the anti-rubella antibody (anti-Ru), is below 10% (Control group minus Coad group).*

- To describe the antibody response to the rubella vaccine antigen when YF vaccine and a combined measles and rubella vaccine are co-administered with RTS,S/AS01$_E$ versus administration without RTS,S/AS01$_E$.
- To demonstrate the non-inferiority of the antibody response to the YF vaccine antigen when YF vaccine and a combined measles and rubella vaccine are co-administered with RTS,S/AS01E versus administration without RTS,S/AS01E.
  - *Criteria for non-inferiority: one month post-vaccination with the YF vaccine, the UL of the 95% CI on the difference in seropositivity rates of the anti-yellow fever antibody (anti-YF), is below 10% (Control group minus Coad group).*
- To describe the antibody response to the YF vaccine antigen when YF vaccine and a combined measles and rubella vaccine are co-administered with RTS,S/AS01$_E$ versus administration without RTS,S/AS01$_E$.

Safety

- Evaluation of the safety profile of RTS,S/AS01$_E$ when administered at 6, 7.5 and 9 months of age in co-administration with YF vaccine and a combined measles and rubella vaccine versus RTS,S/AS01$_E$ administered alone.

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

3.3. Tertiary objective

Immunogenicity

- To describe the antibody response to the human catalase after administration of a 3-dose course of RTS,S/AS01$_E$.

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

4. ENDPOINTS

4.1. Primary endpoints

- Non-inferiority of the antibody response to the CS antigen (RTS,S group/Coad group):
  - Anti-CS antibody titres at one month post Dose 3 of RTS,S/AS01$_E$ (Month 4).

4.2. Secondary endpoints

Immunogenicity

- Antibody response to the candidate vaccine RTS,S/AS01$_E$ (RTS,S group and Coad group):
  - Anti-CS antibody titres and seropositivity (≥ **1.9** EU/ml) at Day 0 and at one month post Dose 3 of RTS,S/AS01$_E$ (Month 4).
  - Anti-HBs antibody titres and seroprotection (≥ 10 mIU/ml) at Day 0 and at one month post Dose 3 of RTS,S/AS01$_E$ (Month 4).
- Non-inferiority of the antibody response to the measles vaccine antigen in the combined measles and rubella vaccine (Control group minus Coad group):
  - Seroconversion for anti-Me at one month post-vaccination with the combined measles and rubella vaccine (Month 4). Seroconversion is defined as children with an anti-Me pre-vaccination titre below 150 mIU/ml and a post-vaccination titre ≥ 150 mIU/ml.
- Antibody response to the measles vaccine antigen in the combined measles and rubella vaccine (Control group and Coad group):
  - Anti-Me antibody titres and seropositivity (≥ 150 mIU/ml) pre-vaccination (Month 3) and one month post-vaccination with the combined measles and rubella vaccine (Month 4).
- Non-inferiority of the antibody response to the rubella vaccine antigen in the combined measles and rubella vaccine (Control group minus Coad group):
  - Seroconversion for anti-Ru at one month post-vaccination with the combined measles and rubella vaccine (Month 4). Seroconversion is defined as children with an anti-Ru pre-vaccination titre below 4 IU/ml and a post-vaccination titre ≥ 4 IU/ml.
- Antibody response to the rubella vaccine antigen in the combined measles and rubella vaccine (Control group and Coad group):
  - Anti-Ru antibody titres and seropositivity (≥ 4 IU/ml) pre-vaccination (Month 3) and one month post-vaccination with the combined measles and rubella vaccine (Month 4).
- Non-inferiority of the antibody response to the YF vaccine antigen (Control group minus Coad group):
  - Seropositivity (≥10 ED50) for anti-YF at one month post-vaccination with the YF vaccine (Month 4).
- Antibody response to the YF vaccine antigen (Control group and Coad group):
  - Anti-YF antibody titres and seropositivity (≥ 10 ED50) one month post-vaccination with the YF vaccine (Month 4).

Safety

- Solicited local and general AEs.
  - For the Coad and the RTS,S groups, the occurrence of solicited local and general AEs over a 7-day follow-up period (day of administration and 6 subsequent days) after administration of Vitamin A and study vaccines at 6 months of age (Visit 2).
  - For the Control group, the occurrence of solicited general AEs over a 7-day follow-up period (day of administration and 6 subsequent days) after administration of Vitamin A at 6 months of age (Visit 2).
  - For the Coad and the RTS,S groups, the occurrence of solicited local and general AEs over a 7-day follow-up period (day of vaccination and 6 subsequent days) after dose of study vaccines administered at 7.5 months of age (Visit 3).
  - For the Control group, the occurrence of solicited general AEs over a 7-day follow-up period (day of visit and 6 subsequent days) after Visit 3 (7.5 months of age).
  - For all groups, the occurrence of solicited general and local AEs over a 14-day follow-up period (day of vaccination and 13 subsequent days) after dose of study vaccines administered at 9 months of age (Visit 4).
- Unsolicited AEs.
  - For all groups, the occurrence of unsolicited AEs over a 30-day follow-up period (day of administration and 29 subsequent days) after administration of Vitamin A and study vaccines at 6 months of age (Visit 2).
  - For the Coad and the RTS,S groups, the occurrence of unsolicited AEs over a 30-day follow-up period (day of vaccination and 29 subsequent days) after dose of study vaccines administered at 7.5 months of age (Visit 3).
  - For the Control group, the occurrence of unsolicited AEs over a 30-day follow-up period (day of visit and 29 subsequent days) after Visit 3 (7.5 months of age).
  - For all groups, the occurrence of unsolicited AEs over a 42-day follow-up period (day of vaccination and 41 subsequent days) after dose of study vaccines administered at 9 months of age (Visit 4).
  - For the Coad and the RTS,S groups, the occurrence of unsolicited AEs over a 30-day follow-up period (day of vaccination and 29 subsequent days) after the booster dose of study vaccine administered at 27 months of age (Visit 10).
  - For the Control group, the occurrence of unsolicited AEs over a 30-day follow-up period (day of vaccination and 29 subsequent days) after dose of study vaccines administered at 10.5, 11.5, 12.5 and 30 months of age (Visit 6, 7, 8 and 12).

- SAEs: all, fatal and related SAEs.
  - The occurrence of SAEs occurring within 30 days (day of vaccination and 29 subsequent days) after each administration.
  - The occurrence of SAEs from Screening visit (Visit 1) until Month 4.5.
  - The occurrence of SAEs from Screening visit (Visit 1) until study end (Month 33 for Coad and RTS,S groups and Month 36 for the Control group).
  - The occurrence of pIMDs from Day 0 until Month 4.5.
  - The occurrence of pIMDs from Day 0 until study end (Month 33 for Coad and RTS,S groups and Month 36 for the Control group).
  - The occurrence of meningitis from Day 0 until Month 4.5.
  - The occurrence of meningitis from Day 0 until study end (Month 33 for Coad and RTS,S groups and Month 36 for the Control group).
  - The occurrence of seizure (occurring within 30 days post-vaccination for vaccine doses administered at 6 and 7.5 months of age [Visits 2 and 3] or 42 days post-vaccination for vaccine doses administered at 9 months of age [Visit 4]) from Day 0 until Month 4.5.
  - The occurrence of seizure occurring within 30 days post-vaccination for vaccine doses administered at 6, 7.5 and 27 months of age (Visits 2, 3 and 10 for Coad and RTS,S group) and at 10.5, 11.5, 12.5 and 30 months of age (Visits 6, 7, 8 and 12 for Control group) or 42 days post-vaccination for vaccine doses administered at 9 months of age (Visit 4 for all groups).
  - The occurrence of generalized convulsive seizure occurring within 7 days after vaccines administered at Visit 2 and 3 (Coad and RTS,S groups) and 14 days after vaccines administered at Visit 4 (all groups).

4.3. Tertiary endpoints

Immunogenicity

- Antibody response to component of the candidate vaccine RTS,S/AS01$_E$ (Coad group and Control group):
  - Anti-catalase antibody concentrations and seropositivity at Day 0 and before administration of RTS,S/AS01$_E$ (Month 4) for the Control group and at Day 0 and at one month post Dose 3 of RTS,S/AS01$_E$ (Month 4) for the Coad group.

5. ANALYSIS SETS

5.1. Definition

5.1.1. Enrolled Set

The enrolled set will include all subjects who signed informed consent.

5.1.2. Exposed Set (ES)

The exposed set (ES) will include all subjects who received at least one dose of the study treatment (i.e. receiving at least one dose of study vaccine or Vitamin A). The ES analysis will be performed per treatment actually administered.

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

The PPS for analysis of immunogenicity will include all evaluable subjects meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study. Subjects with incomplete vaccination course or blood sampling performed outside the protocol defined windows will be eliminated.

Note that in order to align to ICH terminology the Total Vaccinated Cohort and the According To Protocol cohort have been renamed Exposed Set (ES) and Per-Protocol Set (PPS) respectively.

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. Time intervals were defined in advance and are stored in the elimination form document (MALARIA-073 (200596) Criteria for Eliminating Subjects from the Analysis (main analysis visit 6) (12-Feb-2017) version 2.5) in eTMF.

5.2.1. Elimination from Exposed Set (ES)

Code 1030 (Study vaccine not administered at all) and code 900 (invalid informed consent or fraud data) will be used for identifying subjects eliminated from ES.

5.2.2. Elimination from Per-protocol analysis Set (PPS)

5.2.2.1. Excluded subjects

A subject will be excluded from the PPS analysis under the following conditions. These apply to the period from Day 0 to Visit 6.

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
1050	Randomization failure
1070	Vaccination not according to protocol: Incomplete vaccination course before treatment withdrawal. Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number). Administered study vaccine reported as being the correct one but is not compatible with the vaccine regimen associated to the treatment number.
1080	Vaccine temperature deviation (non GMP use)
1090	Expired vaccine administered
2010	Protocol violation (inclusion/exclusion criteria)
2040	Administration of any medication forbidden by the protocol
2050	Underlying medical condition forbidden by the protocol
2080	Subjects did not comply with vaccination schedule
2090	Subjects did not comply with blood sample schedule
2100	Serological results not available post-vaccination
2120	Obvious incoherence or abnormality or error in data

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

Important protocol deviations not leading to elimination from PPS are defined in MALARIA-073 Protocol Deviation Management Plan.

6. STATISTICAL ANALYSES

Note that standard data derivation rule and stat methods are described in Section 11and will not be repeated below.

All statistical analyses will be performed using SAS 9.2 or later versions.

6.1. Demography

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

Demographic characteristics (age, gender, length for age Z-score, and weight for age Z-score) of each cohort (ES and PPS for immunogenicity) will be tabulated per study group.

The mean age at first vaccination [Vitamin A administration for Control group] (in months, 1 decimal digit) (plus range and standard deviation) of the vaccinated subjects, as a whole, and per group, will be calculated.

6.1.2. Additional considerations

Demographic characteristics, cohort description, withdrawal status will be summarized by group using descriptive statistics:

- Frequency tables will be generated for categorical variables such as gender.
- Mean, median, standard deviation, minimum and maximum will be provided for continuous data such as age.
- The 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 analyses will be tabulated.
- The numbers of withdrawn subjects will be tabulated according to the main reason for withdrawal.

6.2. Exposure

6.2.1. Analysis of exposure planned in the protocol

The number and percentage of subjects who received study vaccine doses will be tabulated for each study group (ES).

6.2.2. Additional considerations

Not Applicable.

6.3. Efficacy/Effectiveness

6.3.1. Analysis of efficacy planned in the protocol

Not Applicable.

6.3.2. Additional considerations

Not Applicable.

6.4. Immunogenicity

6.4.1. Analysis of immunogenicity planned in the protocol

The primary analysis will be based on the PPS for immunogenicity.

For the primary endpoint, the 95% CIs of the anti-CS GMT ratio between the groups (RTS,S group over Coad group) at one month post Dose 3 of RTS,S/AS01$_E$ will be calculated. Non-inferiority of anti-CS immune response will be concluded if the UL of this CI is below 2.

For the secondary endpoints, the 95% CIs of the difference in anti-Me, anti-Ru and anti-YF seroconversion/seropositivity rates between the groups (Control group minus Coad group) at one month post-vaccination will be calculated (standardized asymptotic). The seroconversion rate is defined as the percentage of initially seronegative that are seropositive post-vaccination. Non-inferiority will be concluded if the UL of this CI is below 10%.

The percentage of subjects with seropositive levels of anti-CS (proportion of subjects with anti-CS antibody titres ≥ **1.9** EU/ml) with 95% CI will be determined at Day 0 and one month post Dose 3 of RTS,S/AS01$_E$ in the RTS,S group and Coad group. Antibody titres will be summarized by GMT with 95% CI. Antibody titres at one month post Dose 3 of RTS,S/AS01$_E$ will also be investigated using reverse cumulative curves.

Seroprotection level for anti-HBs with 95% CI will be determined at Day 0 and one month post Dose 3 of RTS,S/AS01$_E$ in the RTS,S group and Coad group. Anti-HBs titres will be summarized by GMT with 95% CI. Anti-HBs titres one month post Dose 3 of RTS,S/AS01$_E$ will also be investigated using reverse cumulative curves.

Seropositivity levels of anti-Ru (≥ 4 IU/ml) and seropositivity levels of anti-Me (≥ 150 mIU/ml) with 95% CI will be determined pre-vaccination and one month post-vaccination with the YF vaccine and the combined measles and rubella vaccine in the Control group and Coad group. Antibody titres will be summarized by GMT with 95% CI. Anti-Ru and anti-Me titres at one month post-vaccination with the YF vaccine and the combined measles and rubella vaccine will also be investigated using reverse cumulative curves.

Seropositivity levels of anti-YF (≥ 10 ED50) with 95% CI will be determined one month post-vaccination with the YF vaccine and the combined measles and rubella vaccine in the Control group and Coad group. Antibody titres will be summarized by GMT with 95% CI. Anti-YF titres at one month post-vaccination with the YF vaccine and the combined measles and rubella vaccine will also be investigated using reverse cumulative curves.

For the tertiary endpoints, the anti-catalase concentrations will be summarized by seropositivity and geometric mean concentration with 95% CI at Day 0 (Control and Coad groups), at one month post Dose 3 of RTS,S/AS01$_E$ in the Coad group and before administration of the first dose of RTS,S/AS01$_E$ in the Control group.

6.4.2. Additional considerations

Standard data derivation procedures for immunogenicity are available in Section 11 (see Section 11.2.4).

The primary analysis will be based on the PPS cohort for analysis of immunogenicity. If, the percentage of vaccinated subjects with serological results excluded from the PPS cohort for analysis of immunogenicity is 5% or more, a second analysis based on the ES will be performed to complement the PPS analysis.

Statistical methods for Geometric Mean Titres/Concentrations and GMT ratio

Within group assessment

GMTs and GMCs and associated two-sided 95% CIs will be computed for each group and for each strain at each available immunogenicity monitoring (see Section 6.4– Immunogenicity monitoring). The 95% CI for the mean of log-transformed titre (or concentration) will be first obtained assuming that log-transformed titres (or concentrations) are normally distributed with unknown variance. Logarithmic transformations use base 10. The 95% CI for the GMT (or GMC) will then be obtained by exponential transformation (base 10) of the 95% CI for the mean of the log-transformed titres (or concentrations).

Between group assessment

The group GMT ratio (RTS,S group over Coad group) of anti-CS at one month post Dose 3 of RTS,S/AS01$_E$ will be obtained using an ANOVA model on the logarithm-transformed titres. The ANOVA model will include the study group as fixed effect. The GMT ratio and its two-sided 95% CI will be derived as exponential-transformation (base 10) of the corresponding group contrast in the model.

Reverse cumulative distribution curves

Reverse cumulative distribution (RCD) curves for antibody titres will be plotted: the x-axis represents the antibody titres value (log-10 scale), while the y-axis the percentage of subjects having a log-transformed antibody value greater or equal to the corresponding x-value. RCD curves analysis is performed by study group for the following immunogenicity monitoring:

- one month post Dose 3 of RTS,S/AS01E for anti-CS and anti-HBs titres
- one month post-vaccination with the YF vaccine and the combined measles and rubella vaccine for anti-Me, anti-Ru and anti-YF titres

Statistical methods for seropositivity/seroprotection rates and for seroconversion/seropositivity rates differences

The percentage of subjects seropositive/seroprotected and associated two-sided 95% Clopper-Pearson confidence intervals (CIs) will be computed by vaccine group for each strain at each available immunogenicity monitoring. In addition, differences in percentages (for seroconversion rates of anti-Me and anti-Ru and for the seropositivity rate of anti-YF at one month post-vaccination) between the groups (Control group minus Coad group) will be calculated and the associated confidence interval for the difference will be constructed using the method of Miettinen and Nurminen.

6.5. Analysis of safety

6.5.1. Analysis of safety planned in the protocol

The primary analysis will be based on the ES.

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 solicited follow-up period [7 days post Dose 1, post Dose 2 and 14 days post Dose 3]will be tabulated with exact 95% CI after each vaccine dose and overall. 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 will be tabulated for the overall vaccination course, with exact 95% CI. Similar tables will be generated for Grade 3 AEs and AEs considered as causally related to vaccination.

The percentage of subjects reporting each individual solicited local and general AE during the solicited follow-up period will be tabulated with exact 95% CI. The percentage of doses followed by each individual solicited local and general AE will be tabulated for each dose and for the overall vaccination course, with exact 95% CI. Similar tables will be generated for Grade 3 AEs, causal events and for fever, temperature in 0.5°C increments.

The proportion of subjects reporting an AE (unsolicited) until 30 days (Days 0-29) post each dose of RTS,S/AS01$_E$, classified by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term level will be tabulated with exact 95% CI. The proportion of subjects reporting an AE (unsolicited) until 42 days (Days 0-41) after the administration of the YF vaccine and the combined measles and rubella vaccine (restricted to the Coad group and Control group), classified by the MedDRA preferred term level will be tabulated with exact 95% CI. Similar tables will be generated for Grade 3 AEs and AEs considered as causally related to vaccination.

The proportion of subjects reporting an SAE (all, fatal, related) occurring within 30 days (day of vaccination and 29 subsequent days) after each visit where a study product is potentially administered, classified by the MedDRA preferred term level will be tabulated with exact 95% CI.

The proportion of subjects reporting an SAE (all, fatal, related) from Day 0 to Month 4.5 and over the whole study duration (Day 0 to Month 33 for Coad and RTS,S groups and Month 36 for the Control group), classified by the MedDRA preferred term level will be tabulated with exact 95% CI.

The proportion of subjects reporting an AEs of specific interest (pIMDs, meningitis and seizures) from Day 0 to Month 4.5 and over the whole study duration (Day 0 to Month 33 for Coad and RTS,S groups and Month 36 for the Control group), classified by the MedDRA preferred term level will be tabulated with exact 95% CI.

For generalized convulsive seizures occurring within 7 days after vaccines administered at Visit 2 and 3 (Coad and RTS,S groups) and 14 days after vaccines administered at Visit 4 (all groups) an analysis will be performed based on the Brighton Collaborations guidelines [**Bonhoeffer**, 2004]. This includes descriptive tables of the time relationship of seizures to vaccination, the duration of seizures and the level of diagnostic certainty.

6.5.2. Additional considerations

Standard data derivation procedures for safety are available in Section 11 (see Section 11.2.5).

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

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

Solicited symptom	Lower level term code	Corresponding Lower level term decode
Pain at injection site	10022086	Injection site pain
Redness at injection site	10022098	Redness at injection site
Swelling at injection site	10053425	Swelling at injection site
Drowsiness	10013649	Drowsiness
Fever	10016558	Fever
Irritability/Fussiness	10057224	Irritability post vaccinal
Loss of appetite	10003028	Appetite lost
Measles-like rash	10027022	Measles-like rash

Cases of measles and rubella will be listed.

6.5.2.1. Concomitant Medication and Concomitant Vaccination

Medications will be coded using the GSKDRUG dictionary.

The frequencies and percentages of subjects reporting antipyretic medications will be tabulated by vaccine group for each study dose and across doses. All concomitant medication will be provided in individual listings.

Antipyretics will be further considered prophylactic when administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination.

Concomitant vaccinations administered in the period starting seven days before the first dose of study vaccine and ending at Visit 5 (Month 4) will be listed.

7. ANALYSIS INTERPRETATION

Except for analyses on objectives with a pre-defined success criterion (see Section 3), comparative analyses will be descriptive with the aim to characterize the difference in immunogenicity and safety between groups.

8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

Description	**Analysis ID**	**Disclosure Purpose (CTRS=public posting, SR=study report, internal)**	**Dry run review needed (Y/N)**	***Study Headline Summary (SHS)*requiring expedited communication to upper management (Yes/No)**	**Reference for TFL**
Final analysis	E1_01	SR, CTRS	Y	Yes	TFL_TOC_MAL-073
Primary Epoch Analysis	E1_02	SR, CTRS	Y	Yes	TFL_TOC_MAL-073

The primary analysis will be performed on data collected up to and including 42 days post-measles/rubella/YF vaccination and will include all immunogenicity data (primary secondary and tertiary endpoints) and safety data (secondary endpoints) up to Month 4.5 (Visit 6). A clinical study report will be written after this analysis.

An analysis with remaining safety data will be performed when all data up to and including the Month 33 for Coad and RTS,S groups (Visit 14) and Month 36 for the Control group (Visit 15) will be available. Additional safety information will be added to the clinical study report prepared after Visit 6.

8.2. Statistical considerations for interim analyses

No interim analyses are planned.

9. CHANGES FROM PLANNED ANALYSES

The seropositivity threshold for anti-CS has been updated from 0.5 EU/ml to 1.9 EU/ml.

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 analysis and their role (synopsis, in-text, post-text, SHS, CTRS,…). Note that all TFL aimed to be included as post-text are noted as post-text even if these are tabulation of individual data such as listing of SAE. 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.

The mock tables referred under column named 'layout' can be found in Section 13 of this SAP.

The following group names will be used in the TFLs, to be in line with the T-domains:

Group order in tables	Group label in tables	Group definition for footnote	Pooled Groups label in tables	Pooled definition for footnote
1	Coad	Group receiving co-administration regimen of RTS,S/AS01$_{E,}$ YF vaccine and a combined measles and rubella vaccine	NA	NA
2	RTS,S	Group receiving regimen of RTS,S/AS01$_{E}$ vaccine	NA	NA
3	Control	Group receiving regimen of YF vaccine and a combined measles and rubella vaccine	NA	NA

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].

The standardised asymptotic two-sided 95% CI for the group difference in proportions is based on the method described in the following paper: Robert G. Newcombe, interval estimation for the difference between independent proportions: comparison of eleven methods, *Statist Med.* 1998; 17, 873-890]. The standardised asymptotic method used is the method six.

11.1.1. Other references

Bonhoeffer J, Menkes J, Gold MS et al. Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis and presentation. *Vaccine*. 2004; 22:557-562.

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, 30June is used.
- The onset day for a safety event is the number of days between the last study vaccination and the onset/start date of the event (onset date – last study vaccination+1). This is 1 for an event starting on the same day as a vaccination.
- 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 adverse event 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 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 time 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 days between the date of birth and the reference activity and converted in months (= days *12 /365.25) (keeping 1 decimal digit).

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/Titres (GMC/Ts) calculations are performed by taking the anti-log of the mean of the log titre transformations (base 10). Antibody titres 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 GMT calculation. The cut-off value is defined by the laboratory before the analysis.
- A subject seropositive for anti-CS antibody will be a subject whose antibody titre will be greater than or equal to the cut-off value (anti-CS $\geq$ 1.9 EU/ml).
- A subject seropositive for anti-HBs antibody will be a subject whose antibody titre will be greater than or equal to the cut-off value (anti-HBs $\geq$ 6.2 mIU/ml).
- Seroprotection rate for anti-HBs antibody is defined as the percentage of subjects with antibody titres greater than or equal to 10 mIU/ml (anti-HBs $\geq$ 10 mIU/ml).

- Seroconversion rate for anti-Me is defined as the percentage of children with an anti-Me pre-vaccination titre below 150 mIU/ml and a post-vaccination titre ≥ 150 mIU/ml (i.e. the subject is seropositive post-vaccination and seronegative pre-vaccination for anti-Me).
- Seroconversion rate for anti-Ru is defined as the percentage of children with an anti-Ru pre-vaccination titre below 4 IU/ml and a post-vaccination titre ≥ 4 IU/ml (i.e. the subject is seropositive post-vaccination and seronegative pre-vaccination for anti-Ru).
- Seroprotection rate for anti-Ru antibody is defined as the percentage of subjects with antibody titres greater than or equal to 10 IU/ml (anti-Ru ≥ 10 IU/ml).
- A subject seropositive for anti-YF antibody will be a subject whose antibody titre will be greater than or equal to the cut-off value (anti-YF ≥ 10 ED50).
- A subject seropositive for anti-catalase antibody will be a subject whose antibody concentration is greater than or equal to 65 ng/ml.
- The assay cut-off is the value under which there is no quantifiable result available. For an assay with a specific 'cut_off' , numerical immuno result is derived from a character field (rawres):
  - If rawres is 'NEG' or '-' or '(-)', numeric result= cutt_off/2,
  - if rawres is 'POS' or '+' or '(+)', numeric result = cut_off,
  - if rawres is '< value' and value<=cut_off, numeric result =cut_off/2,
  - if rawres is '< value' and value>cut_off, numeric result =value,
  - if rawres is '> value' and value<cut_off, numeric result =cut_off/2,
  - if rawres is '> value' and value>=cut_off, numeric result =value,
  - if rawres is '<= value' or '>= value' and value<cut_off, numeric result =cut_off/2,
  - if rawres is '<= value' or '>= value' and value>=cut_off, numeric result =value,
  - if rawres is a value < cut_off, numeric result = cut_off/2,
  - if rawres is a value >= cut_off, numeric result = rawres,
  - if rawres is a value >= cut_off, numeric result = rawres,
  - else numeric result is left blank.
  - All CI computed will be two-sided 95% CI.

11.2.5. Safety

- For a given subject and the analysis of solicited symptoms, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the Exposed Set 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 adverse events, such as serious adverse events or adverse events by primary MedDRA term, and for the analysis of concomitant medications, all vaccinated subjects (or receiving Vitamin A) will be considered. Subjects who did not report the event or the concomitant medication will be considered as subjects without the event or the concomitant medication respectively.
- The maximum intensity of local injection site redness/swelling will be coded as follows:

Grade	Redness/swelling
0	Absent
1	> 0 mm and < 5 mm
2	≥ 5 mm and ≤ 20 mm
3	> 20 mm

- For the analysis, temperatures will be coded as follows:

Grade	Temperature
0	< 37.5°C
1	≥ 37.5°C - ≤ 38.0°C
2	> 38.0°C - ≤ 39.0°C
3	> 39.0°C

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

Number of decimals displayed:

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

Display Table	**Parameters**	**Number of decimal digits**
Demographic characteristics	Mean, median, SD	1
Immunogenicity	GMT/C, including LL & UL of CI	1
Immunogenicity	Ratio of GMT, including LL & UL of CI	2
All summaries, Reactogenicity	% of count, including LL & UL of CI	1
All summaries	% of difference, including LL & UL of CI	2

12. ANNEX 2: SUMMARY ON ELIMINATION CODES

Table 6 Safety Sets

PD code	PD Description	Study Objective/ Period	All Exposed Set
	Exclusion code		EXPFL
1030	Study vaccine not administered AT ALL	All Study	EXC
900	Invalid inform consent or fraud data		EXC

EXC = excluded from this analysis set.

Table 7 Immunogenicity Sets

PD code	PD Description	Study Objective/ Period	All Exposed	PPS
	Exclusion code		EXPFL	PPSFL
1030	Study vaccine not administered AT ALL	All Study	EXC	EXC
900	Invalid inform consent or fraud data		EXC	EXC
1040	Administration of forbidden vaccine			EXC
1050	Randomization failure			EXC
1070	Wrong replacement of study vaccine administered			EXC
1070	Administered study vaccine reported as correct but not compatible with regimen associated to treatment number			EXC
1070	Incomplete vaccination course			EXC
1080	Administration of temperature-deviated vaccine			EXC
1090	Administration of expired vaccine			EXC
2010	Subject did not meet entry criteria			EXC
2040	Administration of forbidden medication			EXC
2050	Underlying medical condition forbidden by the protocol			EXC

PD code	PD Description	Study Objective/ Period	All Exposed	PPS
	Exclusion code		EXPFL	PPSFL
2080	Did not comply with study vaccination schedule			EXC
2090	Did not comply with blood draw schedule			EXC
2100	Serological results are not available			EXC
2120	Obvious deviation from Laboratory Manual or error in laboratory data			EXC
2120	Incoherence between CRF and CLS database in terms of sample availability (e.g. sample not collected but result is available)			EXC
2120	Label error of blood samples that could not be resolved			EXC

PPS=Per Protocol Set; EXC = excluded from this analysis set

13. ANNEX 3: STUDY SPECIFIC MOCK TFL

The following drafted study specific mocks will be used.

The data display, title and footnote is for illustration purpose and will be adapted to the study specificity as indicated in the TFL TOC. These templates were copied from MALARIA-063 and additional tables required for public disclosure were added.

Note that there may be few changes between the study specific SAP mock TFL and the final TFLs as editorial/minor changes do not require a SAP amendment.

Template 1 Number of subjects enrolled by center, per study group (Exposed Set)

	Coad N =		RTS,S N =		Control N =		Total N =	
Center	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
PPD (Ghana)								
PPD (Ghana)								

Coad =
RTS,S =
Control =
N = Number of subjects
n = Number of subjects enrolled by center
Center = GSK Biologicals assigned center number
% = n / Number of subjects with available results x 100

Template 2 Number of enrolled subjects by country (All Enrolled Set)

	Coad N =	RTS,S N =	Control N =	Total N =
Country	**N**	**n**	**n**	**n**
Ghana				

Coad =
RTS,S =
Control =
N = number of subjects
n= number of enrolled subjects included in each group or in total

Template 3 Number of enrolled subjects by age category (All Enrolled Set)

		Coad N =	RTS,S N =	Control N =	Total N =
Characteristics	**Categories**	**n**	**n**	**n**	**n**
Age category	Infants and toddlers (28 days-23 months)				

Coad =
RTS,S =
Control =
N = Number of enrolled subjects
n= number of enrolled subjects included in each group or in total for a given age category or for all age categories
Missing = <describe missing>

Template 4 Consort, per study group (Month 4.5)(all screened set)

	Total	Coad	RTS,S	Control
Screened				
Reasons for not being vaccinated				
Did not meet eligibility criteria				
Migrated/Lost to FU before first vaccination				
Other				
Protocol violation				
Vaccinated (at least one vaccination)				
Reasons for incomplete vaccination course				
Other				
Protocol violation				
Serious adverse event				
Subjects with full vaccination course				
Reasons for elimination from PPS for immunogenicity				
Serological results not available				
Administration of concomitant vaccination				
Wrong replacement				
Inclusion criteria not met				
Out of interval				
PPS for immunogenicity				

Coad =
RTS,S =
Control =

Template 5 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal until Month 4.5, per study group (Exposed Set)

	Coad	RTS,S	Control	Total
Number of subjects vaccinated				
Number of subjects completed				
Number of subjects withdrawn				
Reasons for withdrawal :				
Serious Adverse Event				
Non-Serious Adverse Event				
Protocol violation				
Consent withdrawal (not due to an adverse event)				
Migrated/moved from study area				
Lost to follow-up (subjects with incomplete vaccination course)				
Lost to follow-up (subjects with complete vaccination course)				
Sponsor study termination				
Others				

Coad =
RTS,S =
Control =
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed Month 4.5 visit
Withdrawn = number of subjects who did not come for the last visit

Template 6 Deviations from specifications for age and intervals between study visits (Exposed Set)

		Age	Dose1-Dose2	Dose1-Dose3	Dose1-PI(D30)	Dose2-PII(D90)	Dose3-PIII(D210)	Dose1-PIII(D420)
Group		Protocol	Protocol	Protocol	Protocol	Protocol	Protocol	Protocol
		from 50 to 70 year	from 60 to 70 days	from 180 to 194 days	from 30 to 40 days	from 30 to 40 days	from 30 to 40 days	from 420 to 440 days
10-PLAIN	N							
	n							
	%							
	range							
30-PLAIN	N							
	n							
	%							
	range							
10-AL	N							
	n							
	%							
	range							
30-AL	N							
	n							
	%							
	range							
10-AS01E	N							
	n							
	%							
	range							
30-AS01E	N							
	n							
	%							
	range							
10-AS04C	N							
	n							
	%							
	range							
30-AS04C	N							
	n							
	%							
	range							
Placebo	N							
	n							
	%							
	range							

10-PLAIN = 3 doses of non-adjuvanted vaccine containing 10 mcg of each antigen
30-PLAIN = 3 doses of non-adjuvanted vaccine containing 30 mcg of each antigen
10-AL = 3 doses of aluminium adjuvanted vaccine containing 10 mcg of each antigen
30-AL = 3 doses of aluminium adjuvanted vaccine containing 30 mcg of each antigen
10-AS01E = 2 doses of AS01e adjuvanted vaccine containing 10 mcg of each antigen and 1 dose of saline solution
30-AS01E = 2 doses of AS01e adjuvanted vaccine containing 30 mcg of each antigen and 1 dose of saline solution

10-AS04C = 2 doses of AS04c adjuvanted vaccine containing 10 mcg of each antigen and 1 dose of saline solution
30-AS04C = 2 doses of AS04c adjuvanted vaccine containing 30 mcg of each antigen and 1 dose of saline solution
Placebo = 3 doses of saline solution
N = total number of subjects with available results
n/% = number / percentage of subjects with results outside of the interval
range = minimum-maximum for age and intervals
PI(D30) = One month post-dose 1 blood sample time point - Day 30 (visit 3)
PII(D90) = One month post-dose 2 blood sample time point - Day 90 (visit 6)
PIII(D210) = One month post-dose 3 blood sample time point - Day 210 (visit 9)
PIII(D420) = Eight months post-dose 3 blood sample time point - Day 420 (visit 10)

Template 7 Number of subjects at each visit and list of withdrawn subjects until Month 4.5, per study group (Exposed Set)

Group	VISIT	N	Withdrawn Subject numbers	Reason for withdrawal
Coad	SCREENING			
	VISIT2			
	VISIT3			
	VISIT4			
	VISIT5			
	VISIT6			
RTS,S	SCREENING			
	VISIT2			
	VISIT3			
	VISIT4			
	VISIT5			
	VISIT6			
Control	SCREENING			
	VISIT2			
	VISIT3			
	VISIT4			
	VISIT5			
	VISIT6			

Coad =
RTS,S =
Control =
N = Number of subjects who are still in the study up to the visit
Withdrawn = Subject who did not return after the visit

Template 8 Number and percentage of subjects who received study vaccine doses by vaccine, per study group (Exposed Set)

	CoadRTS,SAS01E N =		Coad Measles and Rubella N =		Coad Yellow fever N =		RTS,S RTS,SAS01E N =		RTS,S Measles and Rubella N =		RTS,S Yellow fever N =		Control RTS,SAS01E N =	
Total number of doses received	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
0														
1														
2														
3														
Any														

	Control Measles and Rubella N =		Control Yellow fever N =	
Total number of doses received	**n**	**%**	**n**	**%**
0				
1				
2				
3				
Any				

Coad =
RTS,S =
Control =
N = number of subjects in each group included in the considered cohort
n/% = number/percentage of subjects receiving the specified total number of doses
Any = number and percentage of subjects receiving at least one dose

Template 9 Number of subjects enrolled into the study as well as the number excluded from PPS analyses with reasons for exclusion, per study group (all enrolled set)

	Total			Coad		RTS,S		Control	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**	**n**	**s**
Total cohort									
Study vaccine dose not administrated but subject number allocated (code 1030)									
Exposed Set									
Administration of vaccine(s) forbidden in the protocol (code 1040)									
Randomisation failure (code 1050)									
Protocol violation (inclusion/exclusion criteria) (code 2010)									
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)									
Essential serological data missing (code 2100)									
PPS for immunogenicity									

Coad =
RTS,S =
Control =
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered PPS relative to the ES

Template 10 Summary of demographic characteristics at baseline, per study group (Exposed Set)

		Coad N =		RTS,S N =		Control N =		Total N =	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at first vaccination in months	Mean								
	SD								
	Median								
	Minimum								
	Maximum								
Gender	Female								
	Male								
Length for age z-score [HAZ]	Mean								
	SD								
	Minimum								
	Maximum								
	Missing								
Weight for age z-score [WAZ]	Mean								
	SD								
	Minimum								
	Maximum								
	Missing								

Coad =
RTS,S =
Control =
N = number of subject number
n = number of subject number in a given category
Value = value of the considered parameter
% = n / Number of subject number with available results x 100

Template 11 Minimum and maximum activity dates, per study group (Exposed Set)

Group	Activity number	Activity Description	Minimum date	Maximum date
each group	each activity			

Coad =
RTS,S =
Control =

Template 12 Eligibility (Total cohort) (all screened set)

Eligibility criteria	N	%
A male or female infant aged between 8 and 12 weeks inclusive at the time of first vaccination		
Any other findings that would increase the risk of having an adverse outcome from participation		
Any other findings that would result in data collected being incomplete or of poor quality		
Born after a normal gestation period of 36 to 42 weeks inclusive		
Healthy subjects as established by medical history and clinical examination before study entry		
Laboratory screening tests out of range (see protocol)		
Previous vaccination with diphtheria, tetanus, pertussis (whole-cell or acellular), Haemophilus influenzae type b, Streptococcus pneumoniae, hepatitis B vaccine or rotavirus vaccines.		
Serious acute or chronic illness determined by clinical or physical exam and lab screening tests		
Subjects whom parent(s)/LAR(s) can and will comply with the requirements of the protocol		

N = Number of times each eligibility criterion was reported as a reason for a subject failing screening
Note: Subjects could fail multiple eligibility criteria. Therefore, the sum of N in this table is greater than the number of subjects that were screening failures due to not meeting the eligibility criteria
LAR : Legally Acceptable Representative
ICF : Informed Consent Form

Template 13 Primary objective assessment: Non-inferiority assessment of anti-CS antibody response to RTS,S/AS01E in Coad and RTS,S groups, GMT ratio, Month 4 (Per-Protocol Set)

					GMT ratio (RTS,S / Coad)		
	RTS,S		Coad			95% CI	
Antibody	N	GMT	N	GMT	Value	LL	UL
Anti-CS							

RTS,S =
Coad =
GMT = geometric mean antibody titre
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit
PIII(M4) = Post Dose 3, Month 4

Template 14 Non-inferiority assessment of anti-Me and anti-Ru antibody seroconversion rates in Coad and Control groups, Differences, Month 4 (Per-Protocol Set)

							Difference in seroconversion rate (Group 1 minus Group 2)			
									95 % CI	
Antibody	Group 1	N	%	Group 2	N	%	Difference	%	LL	UL
Anti-Me	Control			Coad			Control - Coad			
Anti-Ru	Control			Coad			Control - Coad			

Control =
Coad =
N = number of subjects with available results
% = percentage of subjects with Anti-Me/Anti-Ru titre >= . MIU-ML post-vaccination and < .MIU-ML pre-vaccination
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
PIII(M4) = Post Dose 3, Month 4

Template 15 Non-inferiority assessment of anti-YF antibody seropositivity rate in Coad and Control groups, Difference, Month 4 (Per-Protocol Set)

						Difference in seropositivity rate (Group 1 minus Group 2)			
								95 % CI	
Group 1	N	%	Group 2	N	%	Difference	%	LL	UL
Control			Coad			Control - Coad			

Control =
Coad =
N = number of subjects with available results
% = percentage of subjects with Anti-YF titre >= . MIU-ML
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
PIII(M4) = Post Dose 3, Month 4

Template 16 Anti-CS seropositivity rates and GMTs in Coad and RTS,S groups, Month 4 (Per-Protocol Set)

				>= 1.9 EU/ml				GMT				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Anti-CS	RTS,S	Pre										
		PIII(M4)										
	Coad	Pre										
		PIII(M4)										

RTS,S =
Coad =
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
Pre = Day 0
PIII(M4) = Post Dose 3, Month 4

Template 17 Anti-HBs seropositivity and seroprotection rates and GMTs in Coad and RTS,S groups, Month 4 (Per-Protocol Set)

				>= 6.2 mIU/mL				>= 10 mIU/mL				GMT				
						95% CI				95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL	Min	Max
Anti-HBs	Coad	Pre														
		PIII(M4)														
	RTS,S	Pre														
		PIII(M4)														

RTS,S =
Coad =
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
Pre = Day 0
PIII(M4) = Post Dose 3, Month 4

Template 18 Anti-HBs response to RTS,S/AS01E in Coad and RTS,S groups, GMT ratio, Month 4 (Per-Protocol Set)

						GMT ratio			
								95% CI	
Group description	N	GMT	Group description	N	GMT	Ratio order	Value	LL	UL
RTS,S			Coad			RTS,S /Coad			

RTS,S =
Coad =
GMT = geometric mean antibody titer
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance with more than 2 groups);
LL = lower limit,
UL = upper limit

Template 19 Anti-Measles seropositivity rates and GMTs in Coad and Control groups, Month 4 (Per-Protocol Set)

				>= 150 mIU/ml				GMT				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Anti-Measles	Coad	Pre										
		PIII(M4)										
	Control	Pre										
		PIII(M4)										

Control =
Coad =
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE = Month 3
PIII(M4) = Post Dose 3, Month 4

Template 20 Anti-Rubella seropositivity and seroprotection rates and GMTs in Coad and Control groups, Month 4 (Per-Protocol Set)

				>= 4 IU/ml				>= 10 IU/ml				GMT				
						95% CI				95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL	Min	Max
Anti-Ru	Coad	Pre														
		PIII(M4)														
	Control	Pre														
		PIII(M4)														

Control =
Coad =
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE = Month 3
PIII(M4) = Post Dose 3, Month 4

Template 21 Anti-YF seropositivity rates and GMTs in Coad and Control groups, Month 4 (Per-Protocol Set)

				>= 10 ED50				GMT				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Anti-YF	Coad	PIII(M4)										
	Control	PIII(M4)										

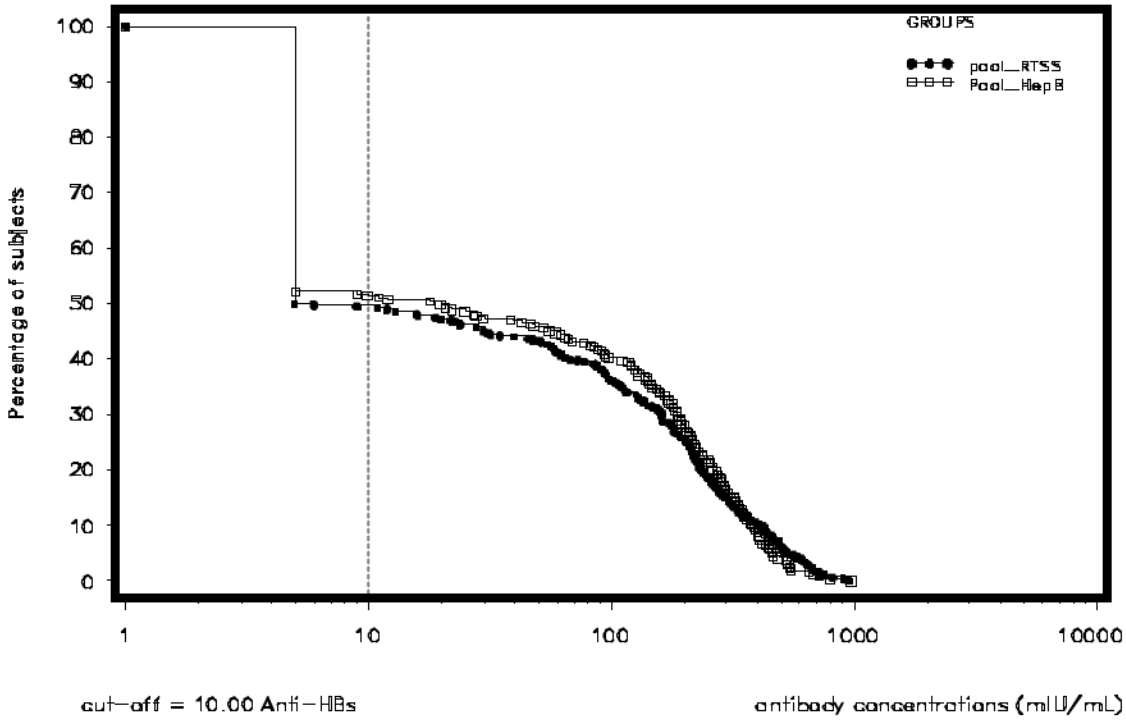
Control =
Coad =
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PIII(M4) = Post Dose 3, Month 4

Template 22 Anti-catalase seropositivity rates and GMCs in Coad and Control groups, Month 4 (Per-Protocol Set)

				>= 65 ng/ml				GMC				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Anti-catalase	Coad	Pre										
		PIII(M4)										
	Control	Pre										
		PIII(M4)										

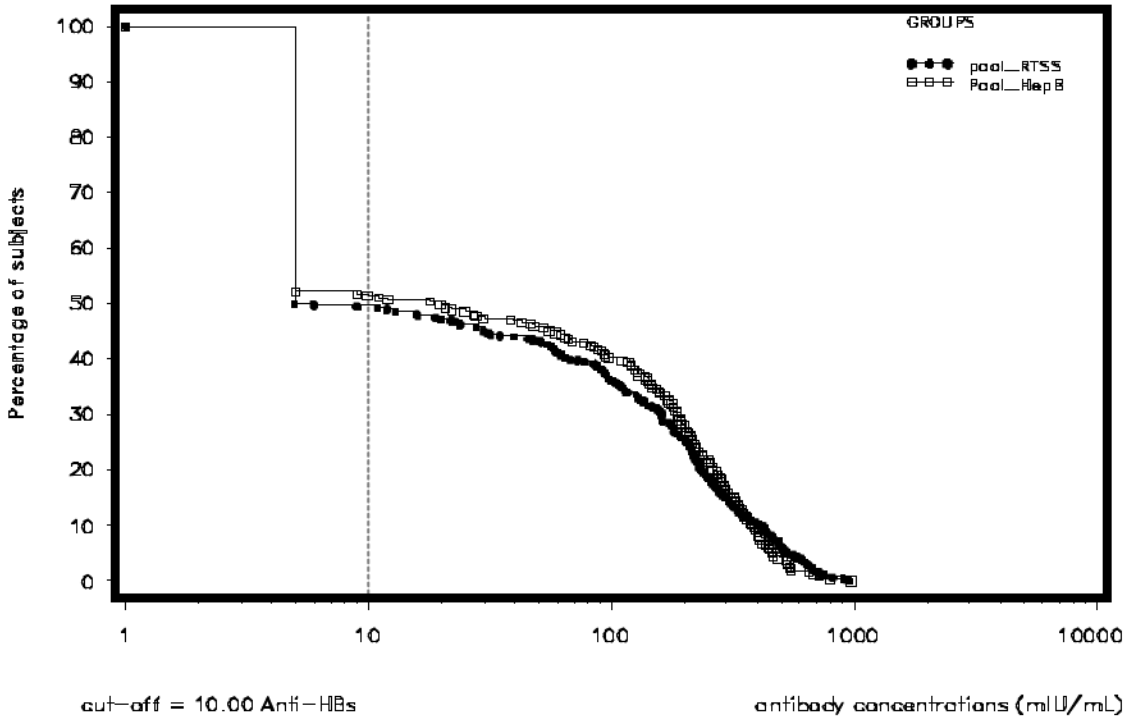
Control =
Coad =
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
Pre = Day 0
PIII(M4) = Post Dose 3, Month 4

Template 23 Reverse Cumulative Distributions of Anti-CS Titres at Month 4, Coad and RTS,S groups (Per-Protocol Set)



RTS,S =
Coad =

Template 24 Reverse Cumulative Distributions of Anti-Me titres at Month 4, Coad and Control groups (Per-Protocol Set)



Control =
Coad =

Template 25 Compliance to data capture per study group (Exposed Set)

	Each group (Coad/RTS,S/Control/ Total)									
	Dose 1		Dose 2		Dose 3		All doses		Per subject	
Criteria	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
With visit done										
With dose received										
With Vitamin A received										
With RTS,S AS01E dose received										
With Measles and Rubella vaccine dose received										
With Yellow fever dose received										
With local solicited data available										
With RTS,S AS01E local solicited data available										
With Measles and Rubella local solicited data available										
With Yellow fever local solicited data available										
With general solicited data available										

Coad =
RTS,S =
Control =
n = for each dose: number of subjects enrolled in the considered cohort and fulfilling specific criteria for the considered dose
for all doses : sum of n from individual doses
per subject : number of subjects enrolled in the considered cohort and fulfilling specific criteria for at least one dose
% = percentage of doses with solicited/unsolicited data available among the number of administered doses

Template 26 Incidence and nature of solicited and unsolicited symptoms over 7 days post vaccination (Days 1-7) by dose and overall, per study group (Exposed Set)

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	Coad															
	RTS,S															
	Control											NA	NA	NA	NA	NA
Dose 2	Coad															
	RTS,S															
	Control											NA	NA	NA	NA	NA
Dose 3 (over 14 days)	Coad															
	RTS,S															
	Control															
Dose 3 (over 7 days)	Coad															
	RTS,S															
	Control															
Overall/ dose	Coad															
	RTS,S															
	Control															
Overall/ subject	Coad															
	RTS,S															
	Control															

Coad =
RTS,S =
Control =
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
Over 14 days post vaccination at Dose 3

Template 27 Incidence and nature of local solicited and unsolicited symptoms reported for each vaccine over 7 days post vaccination (Days 1-7) by dose and overall, per study group (Exposed Set)

		RTS,SAS01E					Measles and Rubella					Yellow fever				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	Coad						NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	RTS,S						NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Dose 2	Coad						NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	RTS,S						NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Dose 3 (over 14 days)	Coad															
	RTS,S						NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Control	NA	NA	NA	NA	NA										
Dose 3 (over 7 days)	Coad															
	RTS,S						NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Control	NA	NA	NA	NA	NA										
Overall/dose	Coad															
	RTS,S						NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Control	NA	NA	NA	NA	NA										
Overall/subject	Coad															
	RTS,S						NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Control	NA	NA	NA	NA	NA										

Coad =
RTS,S =
Control =
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 at the study vaccine site
For overall/dose:
N= number of administered doses
n/%= number/percentage of doses followed by at least one type of symptom at the study vaccine site
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Over 14 days post vaccination at Dose 3

Template 28 Incidence and nature of grade 3 solicited and unsolicited symptoms over 7 days post vaccination (Days 1-7) by dose and overall, per study group (Exposed Set)

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	Coad															
	RTS,S															
	Control											NA	NA	NA	NA	NA
Dose 2	Coad															
	RTS,S															
	Control											NA	NA	NA	NA	NA
Dose 3 (over 14 days)	Coad															
	RTS,S															
	Control															
Overall/dose	Coad															
	RTS,S															
	Control															
Overall/subject	Coad															
	RTS,S															
	Control															

Coad =
RTS,S =
Control =
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
Over 14 days post vaccination at Dose 3

Template 29 Incidence and nature of local grade 3 solicited and unsolicited symptoms reported for each vaccine over 7 days post vaccination (Days 1-7) by dose and overall, per study group (Exposed Set)

		RTS,SAS01E					Measles and Rubella					Yellow fever				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	Coad						NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	RTS,S						NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Dose 2	Coad						NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	RTS,S						NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Dose 3 (over 14 days)	Coad															
	RTS,S						NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Control	NA	NA	NA	NA	NA										
Overall/dose	Coad															
	RTS,S						NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Control	NA	NA	NA	NA	NA										
Overall/subject	Coad															
	RTS,S						NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Control	NA	NA	NA	NA	NA										

Coad =
RTS,S =
Control =
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 at the study vaccine site
For overall/dose:
N= number of administered doses
n/%= number/percentage of doses followed by at least one type of symptom at the study vaccine site
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Over 14 days post vaccination at Dose 3

Template 30 Incidence and nature of solicited and unsolicited symptoms considered as causally related over 7 days post vaccination (Days 1-7) by dose and overall, per study group (Exposed Set)

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	Coad															
	RTS,S															
	Control	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Dose 2	Coad															
	RTS,S															
	Control	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Dose 3 (over 14 days)	Coad															
	RTS,S															
	Control															
Overall/dose	Coad															
	RTS,S															
	Control															
Overall/subject	Coad															
	RTS,S															
	Control															

Coad =
RTS,S =
Control =
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
Over 14 days post vaccination at Dose 3

Template 31 Incidence and nature of solicited and unsolicited symptoms with considered causal relationship to vaccination, reported for each vaccine, over 7 days post vaccination (Days 1-7) by dose and overall, per study group (Exposed Set)

		RTS,SAS01E					Measles and Rubella					Yellow fever				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	Coad						NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	RTS,S						NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Dose 2	Coad						NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	RTS,S						NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Dose 3 (over 14 days)	Coad															
	RTS,S						NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Control	NA	NA	NA	NA	NA										
Overall/dose	Coad															
	RTS,S						NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Control	NA	NA	NA	NA	NA										
Overall/subject	Coad															
	RTS,S						NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Control	NA	NA	NA	NA	NA										

Coad =
RTS,S =
Control =
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 at the study vaccine site
For overall/dose:
N= number of administered doses
n/%= number/percentage of doses followed by at least one type of symptom at the study vaccine site
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Over 14 days post vaccination at Dose 3

Template 32 Incidence of solicited local symptoms over 7 days post vaccination (Days 1-7) by dose and overall, per study group (Exposed Set)

		Coad					RTS,S					Control				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1																
Pain	All											NA	NA	NA	NA	NA
	Grade 3											NA	NA	NA	NA	NA
Redness (mm)	All											NA	NA	NA	NA	NA
	>20.0											NA	NA	NA	NA	NA
Swelling (mm)	All											NA	NA	NA	NA	NA
	>20.0											NA	NA	NA	NA	NA
Dose 2																
Pain	All											NA	NA	NA	NA	NA
	Grade 3											NA	NA	NA	NA	NA
Redness (mm)	All											NA	NA	NA	NA	NA
	>20.0											NA	NA	NA	NA	NA
Swelling (mm)	All											NA	NA	NA	NA	NA
	>20.0											NA	NA	NA	NA	NA
Dose 3																
Pain	All															
	Grade 3															
Redness (mm)	All															
	>20.0															
Swelling (mm)	All															
	>20.0															
Overall/dose																
Pain	All															
	Grade 3															
Redness (mm)	All															
	>20.0															
Swelling (mm)	All															
	>20.0															

		Coad					RTS,S					Control				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Overall/subject																
Pain	All															
	Grade 3															
Redness (mm)	All															
	>20.0															
Swelling (mm)	All															
	>20.0															

Coad =
RTS,S =
Control =
For each dose and overall/subject:
N= number of subjects with at least one administered dose
n/%= number/percentage of subjects reporting the symptom at least once
For Overall/dose:
N= number of administered doses
n/%= number/percentage of doses followed by at least one type of symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
Solicited symptoms are reported over 14 days post Dose 3

Template 33 Incidence of solicited local symptoms over 7 days post vaccination (Days 1-7) by dose and overall, by vaccine, per study group (Exposed Set)

			Coad					RTS,S					Control				
						95 % CI					95 % CI					95 % CI	
Symptom	Product	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1																	
Pain	RTSAS01E	All											NA	NA	NA	NA	NA
		Grade 3											NA	NA	NA	NA	NA
Redness (mm)	RTSAS01E	All											NA	NA	NA	NA	NA
		>20.0											NA	NA	NA	NA	NA
Swelling (mm)	RTSAS01E	All											NA	NA	NA	NA	NA
		>20.0											NA	NA	NA	NA	NA
Dose 2																	
Pain	RTSAS01E	All											NA	NA	NA	NA	NA
		Grade 3											NA	NA	NA	NA	NA
Redness (mm)	RTSAS01E	All											NA	NA	NA	NA	NA
		>20.0											NA	NA	NA	NA	NA
Swelling (mm)	RTSAS01E	All											NA	NA	NA	NA	NA
		>20.0											NA	NA	NA	NA	NA
Dose 3																	
Pain	RTSAS01E	All											NA	NA	NA	NA	NA
		Grade 3											NA	NA	NA	NA	NA
	Measles and Rubella	All						NA	NA	NA	NA	NA					
		Grade 3						NA	NA	NA	NA	NA					
	Yellow fever	All						NA	NA	NA	NA	NA					
		Grade 3						NA	NA	NA	NA	NA					
Redness (mm)	RTSAS01E	All											NA	NA	NA	NA	NA
		>20.0											NA	NA	NA	NA	NA
	Measles and Rubella	All						NA	NA	NA	NA	NA					
		>20.0						NA	NA	NA	NA	NA					
	Yellow fever	All						NA	NA	NA	NA	NA					
		>20.0						NA	NA	NA	NA	NA					

			Coad					RTS,S					Control				
						95 % CI					95 % CI					95 % CI	
Symptom	**Product**	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Swelling (mm)	RTSAS01E	All											NA	NA	NA	NA	NA
		>20.0											NA	NA	NA	NA	NA
	Measles and Rubella	All						NA	NA	NA	NA	NA					
		>20.0						NA	NA	NA	NA	NA					
	Yellow fever	All						NA	NA	NA	NA	NA					
		>20.0						NA	NA	NA	NA	NA					
Overall/dose																	
Pain	RTSAS01E	All											NA	NA	NA	NA	NA
		Grade 3											NA	NA	NA	NA	NA
	Measles and Rubella	All						NA	NA	NA	NA	NA					
		Grade 3						NA	NA	NA	NA	NA					
	Yellow fever	All						NA	NA	NA	NA	NA					
		Grade 3						NA	NA	NA	NA	NA					
Redness (mm)	RTSAS01E	All											NA	NA	NA	NA	NA
		>20.0											NA	NA	NA	NA	NA
	Measles and Rubella	All						NA	NA	NA	NA	NA					
		>20.0						NA	NA	NA	NA	NA					
	Yellow fever	All						NA	NA	NA	NA	NA					
		>20.0						NA	NA	NA	NA	NA					
Swelling (mm)	RTSAS01E	All											NA	NA	NA	NA	NA
		>20.0											NA	NA	NA	NA	NA
	Measles and Rubella	All						NA	NA	NA	NA	NA					
		>20.0						NA	NA	NA	NA	NA					
	Yellow fever	All						NA	NA	NA	NA	NA					
		>20.0						NA	NA	NA	NA	NA					
Overall/subject																	
Pain	RTSAS01E	All											NA	NA	NA	NA	NA
		Grade 3											NA	NA	NA	NA	NA
	Measles and Rubella	All						NA	NA	NA	NA	NA					
		Grade 3						NA	NA	NA	NA	NA					
	Yellow fever	All						NA	NA	NA	NA	NA					
		Grade 3						NA	NA	NA	NA	NA					

			Coad					RTS,S					Control				
						95 % CI					95 % CI					95 % CI	
Symptom	**Product**	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Redness (mm)	RTSAS01E	All											NA	NA	NA	NA	NA
		>20.0											NA	NA	NA	NA	NA
	Measles and Rubella	All						NA	NA	NA	NA	NA					
		>20.0						NA	NA	NA	NA	NA					
	Yellow fever	All						NA	NA	NA	NA	NA					
		>20.0						NA	NA	NA	NA	NA					
Swelling (mm)	RTSAS01E	All											NA	NA	NA	NA	NA
		>20.0											NA	NA	NA	NA	NA
	Measles and Rubella	All						NA	NA	NA	NA	NA					
		>20.0						NA	NA	NA	NA	NA					
	Yellow fever	All						NA	NA	NA	NA	NA					
		>20.0						NA	NA	NA	NA	NA					

Coad =
RTS,S =
Control =
For each dose and overall/subject:
N= number of subjects with at least one administered dose
n/%= number/percentage of subjects reporting the symptom at least once
For Overall/dose:
N= number of administered doses
n/%= number/percentage of doses followed by at least one type of symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
Solicited symptoms are reported over 14 days post Dose 3

Template 34 Incidence of solicited general symptoms over 7 days post vaccination (Days 1-7) by dose and overall, per study group (Exposed Set)

		Coad					RTS,S					Control				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1																
Drowsiness	All															
	Related															
	Grade 3															
	Grade 3*Related															
Irritability / fussiness	All															
	Related															
	Grade 3															
	Grade 3*Related															
Loss of appetite	All															
	Related															
	Grade 3															
	Grade 3*Related															
Temperature/ (Axillary) (°C)	All															
	Related															
	>39.0															
	>39.0*Related															
Measles/rubella-like rash	All															
	Related															
	>39.0															
	>39.0*Related															
Drowsiness	All															
	Related															
	Grade 3															
	Grade 3*Related															
Irritability / fussiness	All															
	Related															
	Grade 3															
	Grade 3*Related															
Loss of appetite	All															
	Related															
	Grade 3															
	Grade 3*Related															
Temperature/ (Axillary) (°C)	All															
	Related															
	>39.0															
	>39.0*Related															
Measles/rubella-like rash	All															
	Related															
	>39.0															
	>39.0*Related															

		Coad					RTS,S					Control				
					95 % CI					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Dose 3																
Drowsiness	All															
	Related															
	Grade 3															
	Grade 3*Related															
Irritability / fussiness	All															
	Related															
	Grade 3															
	Grade 3*Related															
Loss of appetite	All															
	Related															
	Grade 3															
	Grade 3*Related															
Temperature/ (Axillary) (°C)	All															
	Related															
	>39.0															
	>39.0*Related															
Measles/rubella-like rash	All															
	Related															
	>39.0															
	>39.0*Related															
Overall/dose																
Drowsiness	All															
	Related															
	Grade 3															
	Grade 3*Related															
Irritability / fussiness	All															
	Related															
	Grade 3															
	Grade 3*Related															
Loss of appetite	All															
	Related															
	Grade 3															
	Grade 3*Related															
Temperature/ (Axillary) (°C)	All															
	Related															
	>39.0															
	>39.0*Related															
Measles/rubella-like rash	All															
	Related															
	>39.0															
	>39.0*Related															

		Coad					RTS,S					Control				
					95 % CI					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Overall/subject																
Drowsiness	All															
	Related															
	Grade 3															
	Grade 3*Related															
Irritability / fussiness	All															
	Related															
	Grade 3															
	Grade 3*Related															
Loss of appetite	All															
	Related															
	Grade 3															
	Grade 3*Related															
Temperature/ (Axillary) (°C)	All															
	Related															
	>39.0															
	>39.0*Related															
Measles/rubella -like rash	All															
	Related															
	>39.0															
	>39.0*Related															

Coad =
RTS,S =
Control =
For each dose and overall/subject:
N= number of subjects with at least one administered dose
n/%= number/percentage of subjects reporting the symptom at least once
For Overall/dose:
N= number of administered doses
n/%= number/percentage of doses followed by at least one type of symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
Solicited symptoms are reported over 14 days post Dose 3

Template 35 Maximum temperature reported during the 7-day (Days 1-7) post-vaccination period (overall doses), per study group (Exposed Set)

		Coad N =				RTS,S N =				Control N =			
				95% CI				95% CI				95% CI	
Characteristics	Categories	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Maximum temperature	No fever												
	Unknown temperature												
	[37.5-38.0]												
	[38.1-38.5]												
	[38.6-39.0]												
	[39.1-39.5]												
	[39.6-40.0]												
	>40.0												

Coad =
RTS,S =
Control =
N = number of doses
n = number of doses in a given category
% = n / Number of doses with available results x 100
LL, UL for percentage = Exact 95% Lower and Upper confidence limits
Temperature is reported over 14 days post Dose 3

Template 36 Maximum temperature reported during the <7>-day (Days 1-<7>) post-vaccination period (<Dose 1>), per study group (Exposed Set)

		Coad N =				RTS,S N =				Control N =			
				95% CI				95% CI				95% CI	
Characteristics	Categories	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Maximum temperature	No fever												
	[37.5-38.0]												
	[38.1-38.5]												
	[38.6-39.0]												

Coad =
RTS,S =
Control =
N = number of subjects
n = number of subjects in a given category
% = n / Number of subjects with available results x 100
LL, UL for percentage = Exact 95% Lower and Upper confidence limits

Template 37 Percentage of subjects reporting unsolicited adverse events classified by MedDRA Primary System Organ Class and Preferred Term over 30 days (Days 1-30) post vaccination, per study group (Exposed Set)

		Coad N =				RTS,S N =				Control N =			
				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom													

Coad =
RTS,S =
Control =
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Unsolicited adverse events are reported over 42 days post Dose 3

Template 38 Percentage of subjects reporting Serious Adverse Events (SAEs) classified by MedDRA Primary System Organ Class and Preferred Term within 30 days post vaccination, per study group, Month 4.5 (Exposed Set)

		Coad N =				RTS,S N =				Control N =			
				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom													

Coad =
RTS,S =
Control =
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Template 39 Percentage of subjects with fatal SAEs classified by MedDRA Primary System Organ Class and Preferred Term within 30 days post vaccination, per study group, Month 4.5 (Exposed Set)

		Coad N =				RTS,S N =				Control N =			
				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom													

Coad =
RTS,S =
Control =
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Template 40 Percentage of subjects reporting SAEs with causal relationship to vaccination classified by MedDRA Primary System Organ Class and Preferred Term within 30 days post vaccination, per study group, Month 4.5 (Exposed Set)

		Coad N =				RTS,S N =				Control N =			
				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom													

Coad =
RTS,S =
Control =
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of administered doses
n/% = number/percentage of doses with the symptom
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Template 41 Listing of SAEs reported until Month 4.5 visit, per study group (Exposed Set)

Group	Sub. No.	Case Id	Age at onset (Year)	Sex	Verbatim	Preferred term	System Organ Class	MA type	Dose	Day of onset	Duration	Causality	Outcome

Coad =
RTS,S =
Control =

Template 42 Incidence of seizures by diagnostic certainty level within 7 days (1-7) post vaccination overall doses (Diagnostic certainty 1-5), per study group (Exposed Set)

		Coad N =				RTS,S N =				Control N =			
				95% CI				95% CI				95% CI	
Characteristics	Categories	n	n/1000	LL	UL	n	n/1000	LL	UL	n	n/1000	LL	UL
Generalized convulsive seizure	Level 1 to 3												
Convulsive seizure	Level 1 to 5												
Diagnostic certainty level	Level 1												
	Level 2												
	Level 3												
	Level 4												
	Level 5												

Coad =
RTS,S =
Control =
Total = Total
N = number of doses
n = number of doses in a given category
n/1000 = n / Number of doses with available results x 1000
LL, UL for percentage = Exact 95% Lower and Upper confidence limits
Level 1: Witnessed sudden loss of consciousness AND generalized, tonic, clonic, tonic-clonic, or atonic motor manifestations
Level 2: History of unconsciousness AND generalized, tonic, clonic, tonic-clonic, or atonic motor manifestations
Level 3: History of unconsciousness AND other generalized motor manifestations
Level 4: Reported generalized convulsive seizure with insufficient evidence to meet the case definition
Level 5: Not a case of generalized convulsive seizure
Within 14 days post Dose 3

Template 43 Incidence of seizures by diagnostic certainty level and history of fever within 7 days (1-7) post vaccination overall doses (Diagnostic certainty 1-5), per study group (Exposed Set)

		Coad N =				RTS,S N =				Control N =			
				95% CI				95% CI				95% CI	
Characteristics	Categories	n	n/1000	LL	UL	n	n/1000	LL	UL	n	n/1000	LL	UL
Level 1	History of fever												
	No history of fever												
Level 2	History of fever												
	No history of fever												
Level 3	History of fever												
	No history of fever												
Level 4 and 5	History of fever												
	No history of fever												

Coad =
RTS,S =
Control =
Total = Total
N = number of generalized convulsive seizures
n = number of generalized convulsive seizures in a given category
% = n / Number of generalized convulsive seizures with available results x 100
LL, UL for percentage = Exact 95% Lower and Upper confidence limits
Level 1: Witnessed sudden loss of consciousness AND generalized, tonic, clonic, tonic-clonic, or atonic motor manifestations

Level 2: History of unconsciousness AND generalized, tonic, clonic, tonic-clonic, or atonic motor manifestations
Level 3: History of unconsciousness AND other generalized motor manifestations
Level 4: Reported generalized convulsive seizure with insufficient evidence to meet the case definition
Level 5: Not a case of generalized convulsive seizure
Within 14 days post Dose 3

Template 44 Incidence of seizures by diagnostic certainty level and fever within 7 days (1-7) post vaccination overall doses (Diagnostic certainty 1-5), per study group (Exposed Set)

		Coad N =				RTS,S N =				Control N =			
				95% CI				95% CI				95% CI	
Characteristics	Categories	n	n/1000	LL	UL	n	n/1000	LL	UL	n	n/1000	LL	UL
Level 1	<38°C												
	≥38°C												
	Missing temperature												
Level 2	<38°C												
	≥38°C												
	Missing temperature												
Level 3	<38°C												
	≥38°C												
	Missing temperature												
Level 4 and 5	<38°C												
	≥38°C												
	Missing temperature												

Coad =
RTS,S =
Control =
Total = Total
N = number of generalized convulsive seizures
n = number of generalized convulsive seizures in a given category
% = n / Number of generalized convulsive seizures with available results x 100
LL, UL for percentage = Exact 95% Lower and Upper confidence limits
Level 1: Witnessed sudden loss of consciousness AND generalized, tonic, clonic, tonic-clonic, or atonic motor manifestations
Level 2: History of unconsciousness AND generalized, tonic, clonic, tonic-clonic, or atonic motor manifestations
Level 3: History of unconsciousness AND other generalized motor manifestations
Level 4: Reported generalized convulsive seizure with insufficient evidence to meet the case definition
Level 5: Not a case of generalized convulsive seizure
Within 14 days post Dose 3

Template 45 Incidence of concomitant medication administered during the <30-day (Days 1-30)> post-vaccination period by dose and overall, per study group (Exposed Set)

	Coad					RTS,S					Control				
				95% CI					95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1															
Any antipyretic															
Prophylactic antipyretic															
Dose 2															
Any antipyretic															
Prophylactic antipyretic															
Dose 3															
Any antipyretic															
Prophylactic antipyretic															
Overall/dose															
Any antipyretic															
Prophylactic antipyretic															
Overall/subject															
Any antipyretic															
Prophylactic antipyretic															

Coad =
RTS,S =
Control =
For each dose and overall/subject:
N= number of subjects with at least one administered dose
n/%= number/percentage of subjects who started to take the specified concomitant medication at least once during the mentioned period
For overall/dose:
N= number of administered doses
During the < 42-day> post-vaccination period post Dose 3

Template 46 Number (%) of subjects with serious adverse events including number of events reported during the study period (Exposed Set)

			Coad N =			RTS,S N =			Control N =		
Type of Event	Primary System Organ Class	Preferred Term (CODE)	n*	n	%	n*	n	%	n*	n	%
SAE	At least one symptom										
	<each SOC>	<each PT term>									
Related SAE	At least one symptom										
	<each SOC>	<each PT term>									
Fatal SAE	At least one symptom										
	<each SOC>	<each PT term>									
Related fatal SAE	At least one symptom										
	<each SOC>	<each PT term>									

Coad =
RTS,S =
Control =
N = number of subjects with the administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once

Template 47 Solicited and unsolicited symptoms, classified by MedDRA Primary System Organ Class and Preferred Term within the 42-day (Days 1-42) post-vaccination period including number of events - SAE excluded (Exposed Set)

		CoadN =			RTS,S N =			Control N =		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n*	n	%	n*	n	%	n*	n	%
At least one symptom										
<each SOC>	<each PT term>									

Coad =
RTS,S =
Control =
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with the administered dose
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once

Template 48 Listing of dropouts due to AEs, SAEs and solicited symptoms (Exposed Set)

Group	Study - Subject	Country	Gender	Race	AE Description	SAE	Causality	Outcome	Type of discontinuation