Clinical Study Protocol
Sponsor:
GlaxoSmithKline Biologicals
Rue de l'Institut 89, 1330 Rixensart
Belgium

Primary study vaccine and number	• GlaxoSmithKline (GSK) Biologicals' candidate *Plasmodium falciparum* malaria vaccine RTS,S/AS01$_E$ (SB257049)
Other study products	• Licensed measles and rubella vaccine (live), MR-VAC™ (Serum Institute of India) • Licensed World Health Organization (WHO) prequalified yellow fever vaccine • Vitamin A
eTrack study number and Abbreviated Title	200596 (MALARIA-073)
Date of protocol	Final Version 1: 03 June 2015
Date of protocol amendment	Amendment 1 Final: 09 August 2016
Title	Immunogenicity and safety study of GSK Biologicals' candidate malaria vaccine (SB257049) given at 6, 7.5 and 9 months of age in co-administration with measles, rubella and yellow fever vaccines followed by a booster of the malaria vaccine.
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.
Co-ordinating author	• PPD (Scientific Writer; Keyrus Biopharma contractor for GSK Biologicals)
Contributing authors	• PPD (Clinical Research and Development Lead, Director) • PPD (Lead Statistician) • PPD (Director, Biometrics) • PPD (Project Delivery Lead)

eTrack study number and Abbreviated Title	200596 (MALARIA-073)
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Contributing authors (continues) (Amended: 09 August 2016)	• PPD (Study Delivery Leads) • PPD (Study Delivery Manager) • PPD (Clinical ***Readout Team Leader***) • PPD (GVCL, Study Manager) • PPD ***(Clinical Laboratory Sciences Senior Lab Study Manager)*** • PPD (Clinical Regulatory Affairs representative) • PPD (Clinical Safety representative) • PPD (Safety and Pharmacovigilance) • PPD (Study Data Managers; TCS contractor for GSK Biologicals) • PPD, PPD ***and*** PPD (Project Data Managers) • PPD (Vaccine Supply Coordinator) • PPD (Global Patents representative) • PPD ***(Clinical Research and Development Lead)***

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Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	200596 (MALARIA-073)
Date of protocol amendment	Amendment 1 Final: 09 August 2016
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Sponsor signatory	François P Roman Clinical and Epidemiology R&D Project Lead Malaria vaccine GlaxoSmithKline Biologicals, SA.
Signature	_____
Date	_____

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Protocol Amendment 1 Rationale

Amendment number: Amendment 1
Rationale/background for changes: The protocol was amended for the following reasons: • The volumes of whole blood collected from subjects were considered insufficient. To ensure that an adequate blood volume is obtained for the analysis, the volumes of whole blood to be collected specified in the protocol were increased to take into account the dead volume due to aliquoting, and also to enable repeat testing of samples in case of invalid results. • It has been clarified that confirmatory testing for any subject showing clinical presentations compatible with yellow fever, rubella or measles will be performed only to identify cases of vaccine failure. • Clarification about the eCRF pages required to be filled in for pIMDs and seizures was provided. • The names and address of the laboratories performing the biological assays and study personnel at GSK were updated. Details of the safety lab tests were also added. • The Ghana FDA recommended that screening and vaccination should not be performed on the same day, so the screening will be performed up until one day before vaccination (Day -28 to Day -1).

Protocol Amendment 1 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals' investigational vaccine(s) and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally acceptable representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product(s), and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title	200596 (MALARIA-073)
Date of protocol amendment	Amendment 1 Final: 09 August 2016
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.
Investigator name	_____
Signature	_____
Date	_____

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Sponsor Information

1. Sponsor

GlaxoSmithKline Biologicals
Rue de l'Institut 89, 1330 Rixensart (Belgium)

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

4. Sponsor Study Contact for Reporting of a Serious Adverse Event

GSK Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 8.3.2.

SYNOPSIS

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.
Indication	Primary immunization against malaria disease caused by *Plasmodium falciparum* in children.
Rationale for the study and study design	**Rationale for the study vaccine and vaccination schedule** In sub-Saharan Africa, most of the Expanded Program on Immunization (EPI) vaccines are given in early infancy while measles, rubella and yellow fever (YF) vaccines are given at 9 months of age. Between the first EPI vaccines and the measles, rubella and YF vaccines, children receive Vitamin A supplementation at 6 months of age as recommended by the World Health Organization (WHO) [UNICEF, 1998]. To limit the number of clinic visits for young children and to optimize vaccine implementation, it would be more efficient to administer the first dose of RTS,S/AS01$_E$ during the EPI visit at 6 months of age when Vitamin A is given and to administer the third dose of RTS,S/AS01$_E$ on the same day as the YF, measles and rubella vaccines at 9 months of age according to the EPI schedule. This proposed schedule (0, 1.5, 3-month) is longer than the schedule currently evaluated in Phase III studies (0, 1, 2-month). Recent results from the phase III study MALARIA-055 PRI (110021) showed a decline in efficacy against clinical and severe malaria with time in both children and infants who did not receive a booster dose of the RTS,S/AS01$_E$ vaccine. Administration of a booster dose enhanced protection against clinical malaria in infants and children as well as the efficacy against severe malaria in the children. Vaccination with RTS,S/AS01$_E$ also significantly reduced the overall hospital admissions, admissions due to malaria, severe anemia, and the need for blood transfusion. These protective effects were more marked in children who received a booster dose [RTS,S Clinical Trials Partnership; 2015]. In order to provide the greatest benefit to children enrolled in this study, a booster dose of RTS,S/AS01$_E$ will be given 18 months post Dose 3. In this study, to ensure the same protection as the children vaccinated with RTS,S/AS01$_E$, children from the Control

group will also receive RTS,S/AS01$_E$.

Rationale for non-inferiority assessment

Non-inferiority of the immune response to measles and YF when the third dose of RTS,S/AS01$_E$ was co-administered with measles and YF vaccines compared to measles and YF vaccines given alone was demonstrated in study MALARIA-050 in infants 6 to 10 weeks of age at the time of first vaccination [Agnandji, 2010]. There are however no data of the anti-circumsporozoite protein of *Plasmodium falciparum* (anti-CS) immune response induced by RTS,S/AS01$_E$ when given in co-administration with measles, rubella and YF, in a 0, 1.5, 3-month schedule starting at an older age (5-17 months). Considering that the implementation of RTS,S/AS01$_E$ vaccine in EPI could occur in children aged 5-17 months, this study intends to demonstrate that anti-CS immune response of the candidate malaria vaccine RTS,S/AS01$_E$ is not inferior when RTS,S/AS01$_E$ is administered at 6, 7.5 and 9 months of age with the third dose given alone or in co-administration with a YF vaccine and a combined measles and rubella vaccine.

A secondary objective will assess the non-inferiority of the immune responses to YF vaccine and a combined measles and rubella vaccine when they are given in co-administration with RTS,S/AS01$_E$.

Rationale for safety follow-up

Safety and reactogenicity for the RTS,S/AS01$_E$ have previously been evaluated, alone or in co-administration with EPI vaccines given between 6-12 weeks of age. However, safety has not been evaluated in co-administration with measles, rubella and YF in a 0, 1.5, 3-month schedule starting at 6 months of age. This study will therefore provide safety information when RTS,S/AS01$_E$ is administered at 6, 7.5 and 9 months of age alone or in co-administration with YF vaccine and a combined measles and rubella vaccine.

A 12-month safety follow-up after the last dose of RTS,S/AS01$_E$ vaccine will be applied to all study groups.

Contrary to the 7-day follow-up period after RTS,S/AS01$_E$ vaccination in other malaria clinical studies, a 14-day follow-up safety period will be applied in this study following the study vaccines administered at 9 months of age (Visit 4) because, in combined measles and rubella vaccines, the peak of fever usually occurs between 5-12 days post-vaccination [Shinefield, 2005].

Objectives

Primary

- 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 titer (GMT) ratio (RTS,S group/Coad group) of the anti-CS, is below a limit of 2.

Secondary

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.

Tertiary

Immunogenicity

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

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:

  - **Coad group**: Children randomized to receive Vitamin A at 6 months of age, RTS,S/AS01$_E$ vaccine at 6, 7.5 and 9 months of age, and YF vaccine and a combined measles and rubella vaccine at 9 months of age. Children will receive a booster dose of RTS,S/AS01$_E$ vaccine 18 months post Dose 3 (i.e. at 27 months of age).
  - **RTS,S group**: Children randomized to receive Vitamin A at 6 months of age, RTS,S/AS01$_E$ vaccine at 6, 7.5 and 9 months of age, and YF vaccine and a combined measles and rubella vaccine at 10.5 months of age. Children will receive a booster dose of RTS,S/AS01$_E$ vaccine 18 months post Dose 3 (i.e. at 27 months of age).
  - **Control group**: Children randomized to receive Vitamin A at 6 months of age and YF vaccine and a combined measles and rubella vaccine at 9 months of age. These children will receive RTS,S/AS01$_E$ vaccine at 10.5, 11.5 and 12.5 months of age plus a booster dose 17.5 months post Dose 3 (i.e. at 30 months of age), so they can benefit from the same protection as children from the Coad and the RTS,S groups.

Synopsis 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.

Synopsis 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)

- Control: active control (Group receiving the EPI

interventions alone [Vitamin A at 6 months and YF vaccine and a combined measles and rubella vaccine at 9 months of age]). Children from this group will receive a 3-dose course (0, 1, 2-month) and a booster dose (17.5 months post Dose 3) of RTS,S/AS01$_E$ from Visit 6 onwards (10.5 months of age) so they can benefit from the same protection as the children from the Coad and the RTS,S groups.

- Vaccination schedules:
  - For the **Coad group**, children will receive Vitamin A and RTS,S/AS01$_E$ vaccine on Day 0 (Visit 2 [6 months of age]), RTS,S/AS01$_E$ alone at Visit 3 (7.5 months of age), co-administration of RTS,S/AS01$_E$, YF vaccine and a combined measles and rubella vaccine at Visit 4 (9 months of age), and a booster dose of RTS,S/AS01$_E$ at Visit 10 (27 months of age).
  - For the **RTS,S group**, children will receive Vitamin A and RTS,S/AS01$_E$ vaccine on Day 0 (Visit 2 [6 months of age]), RTS,S/AS01$_E$ alone at Visit 3 and 4 (7.5 and 9 months of age), YF vaccine and a combined measles and rubella vaccine at Visit 6 (10.5 months of age), and a booster dose of RTS,S/AS01$_E$ at Visit 10 (27 months of age).
  - For the **Control group**, children will receive Vitamin A on Day 0 (Visit 2 [6 months of age]) and YF vaccine and a combined measles and rubella vaccine at Visit 4 (9 months of age). These children will also receive RTS,S/AS01$_E$ vaccine at Visit 6, 7 and 8 (10.5, 11.5 and 12.5 months of age) and a booster dose of RTS,S/AS01$_E$ vaccine at Visit 12 (30 months of age).
- Treatment allocation: randomized in a 1:1:1 ratio to each study group.
- Blinding: open

Synopsis Table 3 Blinding of study epochs

Study Epoch	Blinding
Epoch 001	open

- Sampling schedule:
  - For the **Coad group**, blood samples will be taken on Day 0, on the day of co-administration of RTS,S/AS01$_E$ with the YF vaccine and the combined measles and rubella vaccine (Month 3) and at one month post co-administration (Month 4).
  - For the **RTS,S group**, blood samples will be taken on Day 0 and at one month post Dose 3 of RTS,S/AS01$_E$ (Month 4).
  - For the **Control group**, blood samples will be taken on Day 0, on the day of administration of the YF vaccine and the combined measles and rubella vaccine (Month 3) and at one month post-vaccination with the YF vaccine and the combined measles and rubella vaccine (Month 4).
- Type of study: self-contained.
- Data collection: Electronic Case Report Form (eCRF).
- Safety monitoring:

  For the **Coad group** and the **RTS,S group,** there will be:
  - A 7-day follow-up period (day of vaccination and 6 subsequent days) following vaccines administered at 6 and 7.5 months of age (Visits 2 and 3) for recording of solicited local and general adverse events (AEs). On the day of vaccination the evaluation will be carried-out by the study physician at the study center. On Days 1, 2, 3, 4, 5 and 6 after vaccination, trained study personnel will visit the children to record solicited AEs on diary cards.
  - A 14-day follow-up period (day of vaccination and 13 subsequent days) following vaccines administered at 9 months of age (Visit 4) for recording of solicited local and general AEs. On the day of vaccination the evaluation will be carried-out by the study physician at the study center. On Days 1 to 13 after vaccination, trained study personnel will visit the children to record solicited AEs on diary cards.
  - Unsolicited AEs will be collected from the day of first vaccine administration (Visit 2) until 42 days after Visit 4. On the days of vaccinations (Visits 2, 3 and 4) the evaluation will be carried-out by the study physician at the study center. Unsolicited AEs will be captured through passive surveillance at inpatient and

outpatient facilities and during study visits. In addition on Days 1 to 6 after vaccinations at Visits 2 and 3 and on Days 1 to 13 after Visit 4, trained study personnel will visit the children to record any unsolicited AEs on diary cards.

– A 30-day follow-up period (day of vaccination and 29 subsequent days) after booster dose of RTS,S/AS01$_E$ vaccines administered at 27 months of age (Visit 10) for reporting unsolicited AEs. Unsolicited AEs will be captured through passive surveillance at inpatient and outpatient facilities and during study visits.

For the **Control group**, there will be:

– A 7-day follow-up period (day of administration and 6 subsequent days) following Vitamin A administered at 6 months of age (Visit 2) and a 7-day follow-up period following Visit 3 (7.5 months of age) for recording of solicited general AEs. On the day of Visits 2 and 3 the evaluation will be carried-out by the study physician at the study center. On Days 1, 2, 3, 4, 5 and 6 after Visits 2 and 3, trained study personnel will visit the children to record solicited general AEs on diary cards.

– A 14-day follow-up period (day of vaccination and 13 subsequent days) following vaccines administered at 9 months of age (Visit 4) for recording of solicited local and general AEs. On the day of vaccination the evaluation will be carried-out by the study physician at the study center. On Days 1 to 13 after vaccination, trained study personnel will visit the children to record solicited AEs on diary cards.

– Unsolicited AEs will be collected from the day of Vitamin A administration (Visit 2) until 42 days after Visit 4. On the day of Visits 2, 3 and 4 the evaluation will be carried-out by the study physician at the study center. Unsolicited AEs will be captured through passive surveillance at inpatient and outpatient facilities and during study visits. In addition on Days 1 to 6 after vaccinations at Visits 2 and 3 and on Days 1 to 13 after Visit 4, trained study personnel will visit the children to record any unsolicited AEs on diary cards.

– Unsolicited AEs will be collected from the day of the first dose of RTS,S/AS01$_E$ (Visit 6) until 30 days after Visit 8 and from the day of the booster dose of RTS,S/AS01$_E$ administered at 30 months of age (Visit 12) until 30 days after the booster dose. On the day of vaccination the evaluation will be carried-out by the

study physician at the study center. Unsolicited AEs will be captured through passive surveillance at inpatient and outpatient facilities and during study visits.

For all groups (**Coad group**, **RTS,S group** and **Control group**):

- Each subject will be observed for at least 60 minutes after vaccination to evaluate and treat any acute AEs.
- All serious adverse events (SAEs) will be reported until study end (Month 33 for Coad and RTS,S groups and Month 36 for the Control group).
- All AEs of specific interest will be reported until study end (Month 33 for Coad and RTS,S groups and Month 36 for the Control group). AEs of specific interest include seizure (occurring within 30 days post-vaccination for vaccine doses administered at 6 and 7.5 months of age or 42 days post-vaccination for vaccine doses administered at 9 months of age), meningitis and potential immune-mediated diseases (pIMDs).
- This study will be overseen by a formally constituted Independent Data Monitoring Committee (IDMC) operating under a charter. Information about the rescue plan for measles and rubella can be found in Section 5.7.5.1.

- Immunogenicity monitoring:
  - Immune response to the CS antigen will be assessed before vaccination (Day 0) and one month post Dose 3 of RTS,S/AS01$_E$ vaccine (Month 4) (i.e. in the Coad group and RTS,S group).
  - Immune response to the HBs antigen will be assessed before vaccination (Day 0) and one month post Dose 3 of RTS,S/AS01$_E$ vaccine (Month 4) (i.e. in the Coad group and RTS,S group).
  - Immune response to the catalase antigen will be assessed at Day 0 for the Control and the Coad groups, one month post Dose 3 of RTS,S/AS01$_E$ vaccine for the Coad group (Month 4) and before the first RTS,S/AS01$_E$ vaccine dose for the Control group (Month 4).
  - Immune response to the YF vaccine will be assessed one month post-vaccination with the YF vaccine and the combined measles and rubella vaccines when administered at 9 months of age (Month 4) (i.e. in the

Coad group and Control group).

- Immune response to the combined measles and rubella vaccine will be assessed before vaccination at Month 3 and one month post-vaccination with the YF vaccine and the combined measles and rubella vaccines when administered at 9 months of age (Month 4) (i.e. in the Coad group and Control group).

Number of subjects Approximately 700 subjects (233 subjects per group) will be enrolled in this study.

Endpoints

Primary

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

Secondary

Immunogenicity

- Antibody response to the candidate vaccine RTS,S/AS01$_E$ (RTS,S group and Coad group):
  - Anti-CS antibody titers and seropositivity at Day 0 and at one month post Dose 3 of RTS,S/AS01$_E$ (Month 4).
  - Anti-HBs antibody titers and seroprotection 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 titer below 150 mIU/ml and a post-vaccination titer $\geq$ 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 titers and seropositivity ($\geq$ 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 titer below 4 IU/ml and a post-vaccination titer ≥ 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 titers 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 titers 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 administrations.
  - 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).

Tertiary

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.

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LIST OF ABBREVIATIONS (AMENDED: 09 August 2016)

AE:	Adverse event
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®)
ATP:	According-to-protocol
CEVAC:	Center for Vaccinology
CI:	Confidence interval
CLIA:	Chemiluminescence enzyme immunoassay
CLS:	***Clinical Laboratory Sciences***
Coad:	Co-administration
CS:	Circumsporozoite protein of *Plasmodium falciparum*
DTPwHepB:	Diphtheria, tetanus, whole-cell pertussis; hepatitis B vaccine
eCRF:	Electronic case report form
ED50:	End point Dilution 50
ELISA:	Enzyme-linked immunosorbent assay
EPI:	Expanded Program on Immunization
eTDF:	Electronic Temperature excursion Decision Form
FDA:	Food and Drug Administration, United States of America
GCP:	Good Clinical Practice

GMT:	Geometric mean titer
GSK:	GlaxoSmithKline
HIV:	Human immunodeficiency virus
ICF:	Informed Consent Form
ICH:	International Conference on Harmonization
IDMC:	Independent Data Monitoring Committee
IEC:	Independent Ethics Committee
IM:	Intramuscular
IMP:	Investigational Medicinal Product
IRB:	Institutional Review Board
IU:	International units
LAR:	Legally acceptable representative
MedDRA:	Medical Dictionary for Regulatory Activities
MPL:	3-O-desacyl-4'-monophosphoryl lipid A (produced by GSK)
pIMD:	Potential immune-mediated disease
PRN:	Plaque neutralization assay
QS-21 Stimulon®:	*Quillaja saponaria* Molina, fraction 21 (Licensed by GSK from Antigenics Inc., a wholly owned subsidiary of Agenus Inc., Lexington, MA, USA)
RDE:	Remote Data Entry
RE:	Retinol equivalent
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

SBIR:	Randomization system on internet
SC:	Subcutaneous
SDV:	Source Document Verification
SPM:	Study Procedures Manual
TVC:	Total vaccinated cohort
UL:	Upper limit
WHO:	World Health Organization
YF:	Yellow fever

GLOSSARY OF TERMS

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an open-label study, no blind is used. Both the investigator and the subject know the identity of the treatment assigned.
Child in care:	A child who has been placed under the control or protection of an agency, organization, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Epoch:	An epoch is a self-contained set of consecutive timepoints or a single timepoint from a single protocol. Self-contained means that data collected for all subjects at all timepoints within that epoch allows to draw a complete conclusion to define or precise the targeted label of the product. Typical examples of epochs are primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or

	safety.
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see Sections 6.7.2 and 10.5 for details on criteria for evaluability).
Immunological correlate of protection:	The defined immune response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.
Investigational vaccine/product: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Legally acceptable representative **(The terms legal representative or legally authorized representative are used in some settings.)**	An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.
Potential immune-mediated disease:	Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.
Protocol amendment:	The International Conference on Harmonization (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.

Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.
Randomization:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Self-contained study:	Study with objectives not linked to the data of another study.
Serious adverse event:	A serious adverse event (SAE) is any untoward medical occurrence that: a. results in death; b. is life-threatening; c. requires hospitalization or prolongation of existing hospitalization; d. results in disability/incapacity; Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm or blood dyscrasias. In this study, the following AEs of specific interest (pIMDs, meningitis and seizure within 30 or 42 days of vaccination) will be reported as SAEs.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Solicited adverse event:	AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccine(s)/product(s) or as a control.

Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomization or treatment allocation.
Treatment number:	A number identifying a treatment to a subject, according to the study randomization or treatment allocation.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

TRADEMARKS

The following trademarks are used in the present protocol.

Note: In the body of the protocol (including the synopsis), the names of the vaccines and medications will be written without the superscript symbol ™ or ® and in *italics*.

Trademarks not owned by the GlaxoSmithKline group of companies	Generic description
MR-VAC™ (Serum Institute of India)	Live attenuated measles virus and rubella virus vaccine
QS-21 *Stimulon*® (*Quillaja saponaria* Molina, fraction 21) (licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., Lexington, MA, USA)	Triterpene glycoside immune enhancer

1. INTRODUCTION

1.1. Background

Measles vaccine, yellow fever (YF) vaccine and Vitamin A are part of the standard Expanded Program on Immunization (EPI) in several African countries and the rubella vaccine is currently being rolled-out in African countries and is expected to be part of the routine vaccination program in some countries when RTS,S/AS01$_E$ will be available.

Please refer to the current Investigator Brochure for information regarding the pre-clinical and clinical studies of RTS,S/AS01$_E$.

1.2. Rationale for the study and study design

1.2.1. Rationale for the study vaccine and vaccination schedule

In sub-Saharan Africa, most of the EPI vaccines are given in early infancy while measles, rubella and YF vaccines are given at 9 months of age. Between the first EPI vaccines and the measles, rubella and YF vaccines, children receive Vitamin A supplementation at 6 months of age as recommended by the World Health Organization (WHO) [UNICEF, 1998]. To limit the number of clinic visits for young children and to optimize vaccine implementation, it would be more efficient to administer the first dose of RTS,S/AS01$_E$ during the EPI visit at 6 months of age when Vitamin A is given and to administer the third dose of RTS,S/AS01$_E$ on the same day as the YF, measles and rubella vaccines at 9 months of age according to the EPI schedule. This proposed schedule (0, 1.5, 3-month) is longer than the schedule currently evaluated in Phase III studies (0, 1, 2-month).

Recent results from the phase III study MALARIA-055 PRI (110021) showed a decline in efficacy against clinical and severe malaria with time in both children and infants who did not receive a booster dose of the RTS,S/AS01$_E$ vaccine. Administration of a booster dose enhanced protection against clinical malaria in infants and children as well as the efficacy against severe malaria in the children. Vaccination with RTS,S/AS01$_E$ also significantly reduced the overall hospital admissions, admissions due to malaria, severe anemia, and the need for blood transfusion. These protective effects were more marked in children who received a booster dose [RTS,S Clinical Trials Partnership, 2015]. In order to provide the greatest benefit to children enrolled in this study, a booster dose of RTS,S/AS01$_E$ will be given 18 months post Dose 3.

In this study, to ensure the same protection as the children vaccinated with RTS,S/AS01$_E$, children from the Control group will also receive RTS,S/AS01$_E$.

1.2.2. Rationale for non-inferiority assessment

Non-inferiority of the immune response to measles and YF when the third dose of RTS,S/AS01$_E$ was co-administered with measles and YF vaccines compared to measles and YF vaccines given alone was demonstrated in study MALARIA-050 in infants 6 to 10 weeks of age at the time of first vaccination [Agnandji, 2010]. There are however no data of the anti-circumsporozoite protein of *Plasmodium falciparum* (anti-CS) immune

response induced by RTS,S/AS01$_E$ when given in co-administration with measles, rubella and YF, in a 0, 1.5, 3-month schedule starting at an older age (5-17 months). Considering that the implementation of RTS,S/AS01$_E$ vaccine in EPI could occur in children aged 5-17 months, this study intends to demonstrate that anti-CS immune response of the candidate malaria vaccine RTS,S/AS01$_E$ is not inferior when RTS,S/AS01$_E$ is administered at 6, 7.5 and 9 months of age with the third dose given alone or in co-administration with a YF vaccine and a combined measles and rubella vaccine.

A secondary objective will assess the non-inferiority of the immune responses to YF vaccine and a combined measles and rubella vaccine when they are given in co-administration with RTS,S/AS01$_E$.

1.2.3. Rationale for safety follow-up

Safety and reactogenicity for the RTS,S/AS01$_E$ have previously been evaluated, alone or in co-administration with EPI vaccines given between 6-12 weeks of age. However, safety has not been evaluated in co-administration with measles, rubella and YF in a 0, 1.5, 3-month schedule starting at 6 months of age. This study will therefore provide safety information when RTS,S/AS01$_E$ is administered at 6, 7.5 and 9 months of age alone or in co-administration with YF vaccine and a combined measles and rubella vaccine.

A 12-month safety follow-up after the last dose of RTS,S/AS01$_E$ vaccine will be applied to all study groups.

Contrary to the 7-day follow-up period after RTS,S/AS01$_E$ vaccination in other malaria clinical studies, a 14-day follow-up safety period will be applied in this study following the study vaccines administered at 9 months of age (Visit 4) because, in combined measles and rubella vaccines, the peak of fever usually occurs between 5-12 days post-vaccination [Shinefield, 2005].

1.3. Benefit : Risk Assessment

Please refer to the current Investigator Brochure for the summary of potential risks and benefits of RTS,S/AS01$_E$.

Please refer to the Prescribing Information for information regarding the summary potential risks and benefits of *MR-VAC*, YF vaccine and Vitamin A.

The following section outlines the risk assessment and mitigation strategy for this study protocol:

1.3.1. Risk Assessment

Important Potential/Identified	Data/Rationale for Risk	Mitigation Strategy
Investigational study vaccine (RTS,S/AS01$_E$)		
Important identified risk: **Febrile convulsion**	The increased risk of febrile convulsion within seven days post-vaccination has been identified.	Seizure is an adverse event of specific interest (see Section 8.1.5).

Important Potential/Identified	Data/Rationale for Risk	Mitigation Strategy
		A previous history of febrile seizures is not an exclusion criterion for the study. Vaccinees with a history of febrile convulsions should be closely followed up as vaccine related fever may occur after vaccination.
Important potential risk: **Meningitis**	An imbalance of meningitis cases of any etiologies (i.e. including cases with confirmed etiology and cases with no etiology found) has been identified.	Meningitis is an adverse event of specific interest (see Section 8.1.5). A high level of medical supervision is in place to detect and treat meningitis if it occurs. All centers participating to this study have diagnostic microbiological facilities available.
Important potential risk: **Rebound effect**	In the large phase III study, MALARIA-055 PRI, an increased incidence of severe malaria relative to control group has been observed, starting around two years after RTS,S/AS01$_E$ primary vaccination course, in children 5-17 month of age at first dose that did not receive a RTS,S/AS01$_E$ booster dose. This higher risk of severe malaria might result from a rebound effect; a delay into the acquisition of natural immunity due to decreased exposure in vaccine relative to control.	A booster dose with RTS,S/AS01$_E$ is included in the vaccination schedule. Study data have shown that in those that received a booster there is no evidence of rebound up to two years post booster.
Important potential risk: **Hypersensitivity (including anaphylaxis)**	As with other vaccines, anaphylaxis to one or several components of the vaccine can rarely occur. Few cases of hypersensitivity (3) have been reported within 30 days following vaccination with RTS,S/AS01$_E$. No case of hypersensitivity has been reported after booster dose.	The subjects will be observed closely for at least 60 minutes following the administration of the vaccines, with appropriate medical treatment readily available in case of anaphylaxis (see Section 5.6.11). Previous anaphylactic reaction with a vaccine is a contraindication to vaccination in this study (see Section 6.5)
Important potential risk: **potential immune-mediated disease (pIMD)**	pIMDs is a theoretical concern with adjuvanted vaccines as no evidence of autoimmune disease caused by RTS,S/AS01$_E$ has been observed.	pIMD is an adverse event of specific interest (see Section 8.1.5).

Important Potential/Identified	Data/Rationale for Risk	Mitigation Strategy
Other		
Important identified risk with measles vaccine: **Febrile convulsion**	Febrile convulsions have been reported associated with the administration of measles containing vaccines.	Seizure is an adverse event of specific interest (see Section 8.1.5). No preventability measures are available so no particular mitigation strategy is deemed necessary.
Important identified risk with measles-rubella vaccine and YF vaccine: **Anaphylaxis**	The measles and rubella vaccine may contain traces of neomycin and YF vaccine is produced in specified pathogen-free chick embryos. Anaphylactic reaction to neomycin, eggs, chicken proteins or any other components of the vaccine has been reported.	Anaphylactic or anaphylactoid reactions to neomycin, eggs, chicken proteins or any other component of the vaccine, history of anaphylactic or anaphylactoid reactions are absolute contraindications.
Important potential risk with measles-rubella vaccine: **Thrombocytopenia**	Thrombocytopenia has been reported associated with the administration of measles containing vaccines. Most post-immunization episodes of thrombocytopenia resolve within three months, although low platelet counts may rarely persist for more than six months [Farrington, 1995].	In case of thrombocytopenia following previous vaccination with measles containing vaccines, the risk-benefit of further immunizing with measles vaccines should be carefully evaluated.

1.3.2. Benefit Assessment

The results of the clinical trials showed a significant efficacy of RTS,S/AS01$_E$ against malaria disease caused by *Plasmodium falciparum*.

All the children in the study can benefit of the vaccine as they will all receive RTS,S/AS01$_E$. The Control group will receive it later (start of primary vaccination at the age of 10.5 months [Visit 6]) than the other groups.

1.3.3. Overall Benefit : Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential or identified risks identified in association with RTS,S/AS01$_E$ (SB257049) are justified by the potential benefits (prevention / treatment) that may be afforded to subject(s) receiving primary immunization against malaria disease caused by *Plasmodium falciparum*.

2. OBJECTIVES

2.1. 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 titer (GMT) ratio (RTS,S group/Coad group) of the anti-CS, is below a limit of 2.*

Refer to Section 10.1 for the definition of the primary endpoints.

2.2. 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 10.2 for the definition of the secondary endpoints.

2.3. Tertiary objective

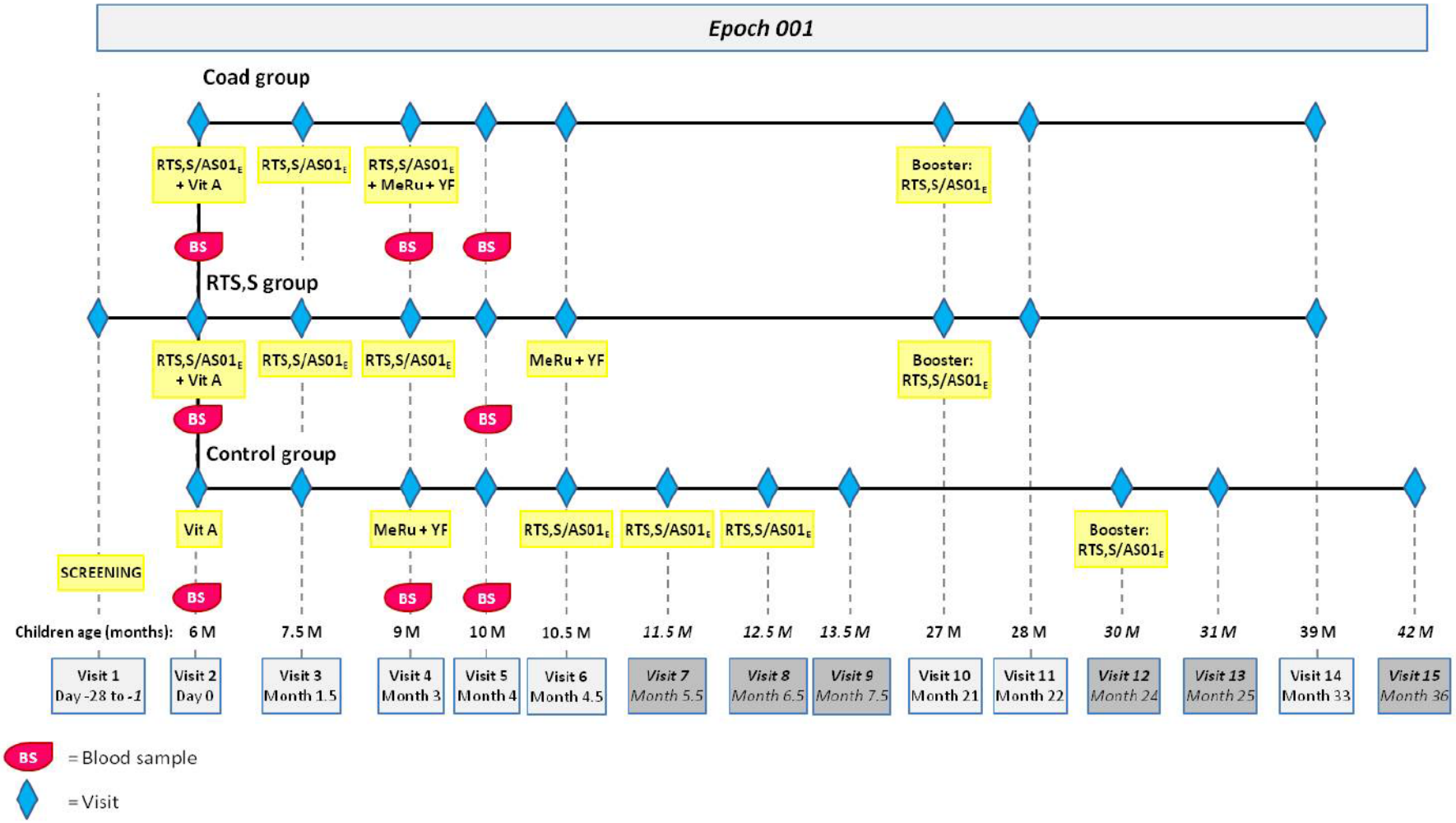
Immunogenicity

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

Refer to Section 10.3 for the definition of the tertiary endpoint.

3. STUDY DESIGN OVERVIEW

Figure 1 Study design (Amended: 09 August 2016)



Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 5.5), are essential and required for study conduct.

- 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:
  - **Coad group**: Children randomized to receive Vitamin A at 6 months of age, RTS,S/AS01$_E$ vaccine at 6, 7.5 and 9 months of age, and YF vaccine and a combined measles and rubella vaccine at 9 months of age. Children will receive a booster dose of RTS,S/AS01$_E$ vaccine 18 months post Dose 3 (i.e. at 27 months of age).
  - **RTS,S group**: Children randomized to receive Vitamin A at 6 months of age, RTS,S/AS01$_E$ vaccine at 6, 7.5 and 9 months of age, and YF vaccine and a combined measles and rubella vaccine at 10.5 months of age. Children will receive a booster dose of RTS,S/AS01$_E$ vaccine 18 months post Dose 3 (i.e. at 27 months of age).
  - **Control group**: Children randomized to receive Vitamin A at 6 months of age and YF vaccine and a combined measles and rubella vaccine at 9 months of age. These children will receive RTS,S/AS01$_E$ vaccine at 10.5, 11.5 and 12.5 months of age plus a booster dose 17.5 months post Dose 3 (i.e. at 30 months of age), so they can benefit from the same protection as children from the Coad and the RTS,S groups.

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)

- Control: active control (Group receiving the EPI interventions alone [Vitamin A at 6 months and YF vaccine and a combined measles and rubella vaccine at 9 months of age]). Children from this group will receive a 3-dose course (0, 1, 2-month) and a booster dose (17.5 months post Dose 3) of RTS,S/AS01$_E$ from Visit 6 onwards (10.5 months of age) so they can benefit from the same protection as the children from the Coad and the RTS,S groups.

- Vaccination schedules:

  - For the **Coad group**, children will receive Vitamin A and RTS,S/AS01$_E$ vaccine on Day 0 (Visit 2 [6 months of age]), RTS,S/AS01$_E$ alone at Visit 3 (7.5 months of age), co-administration of RTS,S/AS01$_E$, YF vaccine and a combined measles and rubella vaccine at Visit 4 (9 months of age), and a booster dose of RTS,S/AS01$_E$ at Visit 10 (27 months of age).
  - For the **RTS,S group**, children will receive Vitamin A and RTS,S/AS01$_E$ vaccine on Day 0 (Visit 2 [6 months of age]), RTS,S/AS01$_E$ alone at Visit 3 and 4 (7.5 and 9 months of age), YF vaccine and a combined measles and rubella vaccine at Visit 6 (10.5 months of age), and a booster dose of RTS,S/AS01$_E$ at Visit 10 (27 months of age).
  - For the **Control group**, children will receive Vitamin A on Day 0 (Visit 2 [6 months of age]) and YF vaccine and a combined measles and rubella vaccine at Visit 4 (9 months of age). These children will also receive RTS,S/AS01$_E$ vaccine at Visit 6, 7 and 8 (10.5, 11.5 and 12.5 months of age) and a booster dose of RTS,S/AS01$_E$ vaccine at Visit 12 (30 months of age).

- 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

- Sampling schedule:

  - For the **Coad group**, blood samples will be taken on Day 0, on the day of co-administration of RTS,S/AS01$_E$ with the YF vaccine and the combined measles

and rubella vaccine (Month 3) and at one month post co-administration (Month 4).

- For the **RTS,S group**, blood samples will be taken on Day 0 and at one month post Dose 3 of RTS,S/AS01$_E$ (Month 4).
- For the **Control group**, blood samples will be taken on Day 0, on the day of administration of the YF vaccine and the combined measles and rubella vaccine (Month 3) and at one month post-vaccination with the YF vaccine and the combined measles and rubella vaccine (Month 4).

- Type of study: self-contained.
- Data collection: Electronic Case Report Form (eCRF).
- Safety monitoring:

  For the **Coad group** and the **RTS,S group,** there will be:

  - A 7-day follow-up period (day of vaccination and 6 subsequent days) following vaccines administered at 6 and 7.5 months of age (Visits 2 and 3) for recording of solicited local and general adverse events (AEs). On the day of vaccination the evaluation will be carried-out by the study physician at the study center. On Days 1, 2, 3, 4, 5 and 6 after vaccination, trained study personnel will visit the children to record solicited AEs on diary cards.
  - A 14-day follow-up period (day of vaccination and 13 subsequent days) following vaccines administered at 9 months of age (Visit 4) for recording of solicited local and general AEs. On the day of vaccination the evaluation will be carried-out by the study physician at the study center. On Days 1 to 13 after vaccination, trained study personnel will visit the children to record solicited AEs on diary cards.
  - Unsolicited AEs will be collected from the day of first vaccine administration (Visit 2) until 42 days after Visit 4. On the days of vaccinations (Visits 2, 3 and 4) the evaluation will be carried-out by the study physician at the study center. Unsolicited AEs will be captured through passive surveillance at inpatient and outpatient facilities and during study visits. In addition on Days 1 to 6 after vaccinations at Visits 2 and 3 and on Days 1 to 13 after Visit 4, trained study personnel will visit the children to record any unsolicited AEs on diary cards.
  - A 30-day follow-up period (day of vaccination and 29 subsequent days) after booster dose of RTS,S/AS01$_E$ vaccines administered at 27 months of age (Visit 10) for reporting unsolicited AEs. Unsolicited AEs will be captured through passive surveillance at inpatient and outpatient facilities and during study visits.

  For the **Control group**, there will be:

  A 7-day follow-up period (day of administration and 6 subsequent days) following Vitamin A administered at 6 months of age (Visit 2) and a 7-day follow-up period following Visit 3 (7.5 months of age) for recording of solicited general AEs. On the day of Visits 2 and 3 the evaluation will be carried-out by the study physician at the study center. On Days 1, 2, 3, 4, 5 and 6 after Visits 2

and 3, trained study personnel will visit the children to record solicited general AEs on diary cards.

- A 14-day follow-up period (day of vaccination and 13 subsequent days) following vaccines administered at 9 months of age (Visit 4) for recording of solicited local and general AEs. On the day of vaccination the evaluation will be carried-out by the study physician at the study center. On Days 1 to 13 after vaccination, trained study personnel will visit the children to record solicited AEs on diary cards.
- Unsolicited AEs will be collected from the day of Vitamin A administration (Visit 2) until 42 days after Visit 4. On the day of Visits 2, 3 and 4 the evaluation will be carried-out by the study physician at the study center. Unsolicited AEs will be captured through passive surveillance at inpatient and outpatient facilities and during study visits. In addition on Days 1 to 6 after vaccinations at Visits 2 and 3 and on Days 1 to 13 after Visit 4, trained study personnel will visit the children to record any unsolicited AEs on diary cards.
- Unsolicited AEs will be collected from the day of the first dose of RTS,S/AS01$_E$ (Visit 6) until 30 days after Visit 8 and from the day of the booster dose of RTS,S/AS01$_E$ administered at 30 months of age (Visit 12) until 30 days after the booster dose. On the day of vaccination the evaluation will be carried-out by the study physician at the study center. Unsolicited AEs will be captured through passive surveillance at inpatient and outpatient facilities and during study visits.

For all groups (**Coad group**, **RTS,S group** and **Control group**):

- Each subject will be observed for at least 60 minutes after vaccination to evaluate and treat any acute AEs.
- All serious adverse events (SAEs) will be reported until study end (Month 33 for Coad and RTS,S groups and Month 36 for the Control group).
- All AEs of specific interest will be reported until study end (Month 33 for Coad and RTS,S groups and Month 36 for the Control group). AEs of specific interest include seizure (occurring within 30 days post-vaccination for vaccine doses administered at 6 and 7.5 months of age or 42 days post-vaccination for vaccine doses administered at 9 months of age), meningitis and potential immune-mediated diseases (pIMDs).
- This study will be overseen by a formally constituted Independent Data Monitoring Committee (IDMC) operating under a charter. Information about the rescue plan for measles and rubella can be found in Section 5.7.5.1.

- Immunogenicity monitoring:
  - Immune response to the CS antigen will be assessed before vaccination (Day 0) and one month post Dose 3 of RTS,S/AS01$_E$ vaccine (Month 4) (i.e. in the Coad group and RTS,S group).
  - Immune response to the HBs antigen will be assessed before vaccination (Day 0) and one month post Dose 3 of RTS,S/AS01$_E$ vaccine (Month 4) (i.e. in the Coad group and RTS,S group).

- Immune response to the catalase antigen will be assessed at Day 0 for the Control and the Coad groups, one month post Dose 3 of RTS,S/AS01$_E$ vaccine for the Coad group (Month 4) and before the first RTS,S/AS01$_E$ vaccine dose for the Control group (Month 4).
- Immune response to the YF vaccine will be assessed one month post-vaccination with the YF vaccine and the combined measles and rubella vaccines when administered at 9 months of age (Month 4) (i.e. in the Coad group and Control group).
- Immune response to the combined measles and rubella vaccine will be assessed before vaccination at Month 3 and one month post-vaccination with the YF vaccine and the combined measles and rubella vaccines when administered at 9 months of age (Month 4) (i.e. in the Coad group and Control group).

4. STUDY COHORT

4.1. Number of subjects/centers

Approximately 700 subjects (233 subjects per group) will be enrolled in this study. Refer to Section 10.4 for the determination of sample size.

4.1.1. Overview of the recruitment plan

Upon completion of all screening procedures (Refer to Table 4, Table 5 and Table 6), the investigator, or designee, will review the inclusion/exclusion criteria for each subject. Subjects meeting all eligibility criteria will be enrolled in the study. Their screening information will be recorded on the appropriate screen of eCRF.

If the investigator believes there is a reasonable reason to do so, screening procedures may be repeated once only.

4.2. Inclusion criteria for enrolment

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

All subjects must satisfy ALL the following criteria at study entry:

- Subjects' parent(s)/Legally Acceptable Representative(s) (LAR[s]) who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. return for follow-up visits).
- A male or female 6 months of age (from the day the child becomes 6 months of age until the day before the child achieves 7 months of age) at the time of the first vaccination.
- Signed or thumb-printed informed consent obtained from the parent(s)/LAR(s) of the subject. Where parent(s)/LAR(s) are illiterate, the consent form will be countersigned by an independent witness.

- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Previously received three documented doses of diphtheria, tetanus, and whole-cell pertussis, hepatitis B vaccine (DTPwHepB), and a 3-dose course of oral polio vaccine and, if locally recommended, pneumococcal and rotavirus vaccines.

4.3. Exclusion criteria for enrolment

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria should be checked at the time of study entry. If ANY exclusion criterion applies, the subject must not be included in the study:

- Child in care
  Please refer to the glossary of terms for the definition of child in care.
- Use of a drug or vaccine that is not approved for that indication (by one of the following regulatory authorities: Food and Drug Administration [FDA; United States] or European Union member state or WHO [with respect to prequalification]) other than the study vaccines within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs within six months prior to the first vaccine dose. For corticosteroids, this will mean prednisone (0.5 mg/kg/day, or equivalent. Inhaled and topical steroids are allowed.
- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting seven days before the first dose of RTS,S/AS01$_E$ / measles, rubella and YF vaccines and ending 42 days after the last dose of vaccines given at 9 months of age (Visit 4), with the exception of oral polio vaccine which could be given for unforseen public health threat.
- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
- Previous vaccination against measles, YF or rubella.
- Previous administration of Vitamin A.
- Moderate or severe malnutrition at screening defined as weight for age Z-score < -2 (by WHO growth standard) [WHO, 2006].
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Family history of congenital or hereditary immunodeficiency.

- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine(s). See also Section 1.3.
- Major congenital defects or serious chronic illness.
- History of any neurological disorders or seizures.
- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature ≥ 37.5°C /99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C /100.4°F on rectal route. The preferred route for recording temperature in this study will be axillary.
  - Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator.
- Administration of immunoglobulins and/or any blood products within the 3 months preceding the first dose of study vaccine or planned administration during the study period.
- Same sex twin (to avoid misidentification).
- Maternal death.
- Previous participation in any other malaria study.

5. CONDUCT OF THE STUDY

5.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with the ICH Guideline for Good Clinical Practice (GCP), all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

The study has been designed and will be conducted in accordance with the ICH Harmonized Tripartite Guideline for clinical investigation of medicinal products in the pediatric population (ICH E11) and all other applicable ethical guidelines.

GSK will obtain favorable opinion/approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site initiating the study in that country.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favorable opinion/approval of study protocol and any subsequent amendments.
- Subject's parent(s)/LAR(s) informed consent, as appropriate.
- Investigator reporting requirements as stated in the protocol.

GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.

Freely given and written or witnessed/ thumb printed informed consent must be obtained from each subject's parent(s)/LAR(s), as appropriate, prior to participation in the study.

GSK Biologicals will prepare a model Informed Consent Form (ICF) which will embody the ICH GCP and GSK Biologicals required elements. While it is strongly recommended that this model ICF is to be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgment, local regulations and requirements should guide the final structure and content of the local version of the ICF.

The investigator has the final responsibility for the final presentation of the ICF, respecting the mandatory requirements of local regulations. The ICF generated by the investigator with the assistance of the sponsor's representative must be acceptable to GSK Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

5.2. Subject identification and randomization of treatment

5.2.1. Subject identification

Subject identification numbers will be assigned sequentially to the subjects who have consented to participate in the study, according to the range of subject identification numbers allocated to each study center. Study subjects will receive study identification cards with their picture with their parents/LAR(s) and subject number.

5.2.2. Randomization of treatment

5.2.2.1. Randomization of supplies

The randomization of supplies within blocks will be performed at GSK Biologicals, using MATerial EXcellence (MATEX), a program developed for use in Statistical Analysis System (SAS®) (Cary, NC, USA) by GSK Biologicals. Entire blocks will be shipped to the study centers /warehouse(s).

To allow GSK Biologicals to take advantage of greater rates of recruitment than anticipated at individual centers in this multi-center study and to thus reduce the overall study recruitment period, an over-randomization of supplies will be prepared.

5.2.2.2. Treatment allocation to the subject

The treatment numbers will be allocated by dose.

5.2.2.2.1. Study group and treatment number allocation

The target will be to enroll approximately 700 eligible subjects who will be randomly assigned to three study groups in a (1:1:1) ratio (approximately 233 subjects in each group).

Allocation of the subject to a study group at the investigator site will be performed using a randomization system on internet (SBIR). The randomization algorithm will use a minimization procedure accounting for center.

After obtaining the signed and dated ICF from the subject's parents/LAR(s) and having checked the eligibility of the subject, the site staff will access SBIR. Upon providing the subject identification number, the randomization system will determine the study group and will provide the treatment number for the products to be administered at Visit 2 (Day 0).

The number of each administered vaccines must be recorded in the eCRF on the Vaccine Administration screen.

When SBIR is not available, please refer to the SBIR user guide or the Study Procedures Manual (SPM) for specific instructions.

5.2.2.2.2. Treatment number allocation for subsequent doses

For each visit where vaccines are administered, the study staff will access SBIR, provide the subject identification number, and the system will provide treatment numbers consistent with the allocated study group.

The number of each administered vaccines must be recorded in the eCRF on the Vaccine Administration screen.

5.2.3. Allocation of subjects to assay subsets

There will be no subsets of subjects.

5.3. Method of blinding

This study is an open-label study.

The laboratory in charge of the laboratory testing will be blinded to the treatment, and codes will be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

5.4. General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects.

5.4.1. Independent Data Monitoring Committee (IDMC) oversight

This study will be overseen by IDMC operating under a charter and assisted by a Local Safety Monitor at each site. Overall, the role of the IDMC includes the review and protection of data integrity and rights and safety of study participants throughout the study period. It will provide initial, regular, and closing advice to GSK Biologicals on medical, ethical, scientific and safety-related issues. Its advice will be based on the interpretation of study data with reference to the study protocol.

The IDMC will review the Protocol and Statistical Analysis Plan. Meetings will be documented and minutes of open sessions of the IDMC meetings made available to the sponsor. The IDMC may, if deemed necessary, convene a meeting with, or request further information from the Principal Investigators, the Medical Monitor/Local Safety Monitor and GSK Biologicals' designated project representatives at any stage of the study.

The IDMC may recommend to the sponsor to suspend the enrollment to the study and/or vaccination based on their review of safety data arising in this study or other relevant study of the same product.

The IDMC will receive the following safety data:

- Periodic safety reports.

In addition, the IDMC will receive from the sponsor, GSK Biologicals:

- New information that may adversely affect the safety of the subjects or the conduct of the study.
- All subsequent protocol amendments, informed consent changes or revisions or other documents originally submitted for review.
- All subsequent protocol administrative changes (for information).

5.4.2. Standard of care provided to the subjects during the study

During the study, subjects will receive standard medical care according to national guidelines.

5.5. Outline of study procedures

Table 4 List of study procedures for the Coad group (Amended: 09 August 2016)

Epoch	*Epoch 001*								
Type of contact	Visit 1 (Screening)*	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 10	Visit 11	Visit 14
Timepoints	Day -28 to *-1*	Day 0	Month 1.5	Month 3	Month 4	Month 4.5	Month 21	Month 22	Month 33
Children age (Months)		6	7.5	9	10	10.5	27	28	39
Informed consent	●								
Check inclusion/exclusion criteria	●	O							
Collect demographic data	●								
Check medical history	●								
Physical examination	●	O	O	O	O	O	O	O	O
Measure/record length and weight	●								
Issuing identification card	O								
Check identification card		O	O	O	O	O	O	O	O
Randomization		●							
Treatment number allocation		O	O	O			O		
Recording of administered vaccine treatment number		●	●	●			●		
Check contraindications and warnings and precautions		●	●	●			●		
Pre-vaccination body temperature		●	●	●			●		
Vitamin A administration		●							
RTS,S/AS01$_E$ vaccine administration		●	●	●			●		
YF vaccine and measles and rubella vaccine administration				●					
Blood sampling for anti-HBs and anti-CS antibody determination		●			●				
Blood sampling for anti-Me and anti-Ru antibody determination				●	●				
Blood sampling for anti-catalase antibody determination		●			●				
Blood sampling for anti-YF antibody determination					●				
Record of solicited symptoms (Days 0-6)		●[a]	●[a]						
Record of solicited symptoms (Days 0-13)				●[b,c]					

Epoch	*Epoch 001*								
Type of contact	**Visit 1 (Screening)***	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 10**	**Visit 11**	**Visit 14**
Timepoints	**Day -28 to *-1***	**Day 0**	**Month 1.5**	**Month 3**	**Month 4**	**Month 4.5**	**Month 21**	**Month 22**	**Month 33**
Children age (Months)		**6**	**7.5**	**9**	**10**	**10.5**	**27**	**28**	**39**
Record of unsolicited AEs		●[a]	●[a]	●[b]	●	●	●	●	
Record any concomitant medication/vaccination		●	●	●	●	●	●	●	●
Record any case of measles and rubella †		●	●	●	●	●	●	●	●
Record of SAEs related to study participation or to a concurrent GSK medication/vaccine	●	●	●	●	●	●	●	●	●
Record of SAEs (all, fatal, SAEs related to investigational vaccine)		●	●	●	●	●	●	●	●
Record AEs of specific interest (including seizure occurring within 30 or 42 days post-vaccination, meningitis and pIMDs)[d]		●	●	●	●	●	●	●	●
Study Conclusion									●

[a] Study personnel will visit the children on Days 1, 2, 3, 4, 5 and 6 after each vaccination to record solicited and unsolicited AEs on diary cards.
[b] Study personnel will visit the children on Days 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 13 after vaccination to record solicited and unsolicited AEs on diary cards.
[c] Collection of solicited local AE for the three injection sites.
[d] Seizures 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).
Note: The double-line border following Month 4.5 (Visit 6) indicates the analyses which will be performed on all data (i.e. data that are as clean as possible) obtained up to Month 4.5.
* If the investigator believes there is a reasonable reason to do so, screening procedures may only be repeated once.
† Confirmatory serology tests should be performed to identify cases of vaccine failure.
● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.

Table 5 List of study procedures for the RTS,S group (Amended: 09 August 2016)

Epoch	*Epoch 001*								
Type of contact	Visit 1 (Screening)*	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 10	Visit 11	Visit 14
Timepoints	Day -28 to -1	Day 0	Month 1.5	Month 3	Month 4	Month 4.5	Month 21	Month 22	Month 33
Children age (Months)		6	7.5	9	10	10.5	27	28	39
Informed consent	●								
Check inclusion/exclusion criteria	●	O							
Collect demographic data	●								
Check medical history	●								
Physical examination	●	O	O	O	O	O	O	O	O
Measure/record length and weight	●								
Issuing identification card	O								
Check identification card		O	O	O	O	O	O	O	O
Randomization		●							
Treatment number allocation		O	O	O		O	O		
Recording of administered vaccine treatment number		●	●	●		●	●		
Check contraindications and warnings and precautions		●	●	●		●	●		
Pre-vaccination body temperature		●	●	●		●	●		
Vitamin A administration		●							
RTS,S/AS01$_E$ vaccine administration		●	●	●			●		
YF vaccine and measles and rubella vaccine administration						●			
Blood sampling for anti-HBs and anti-CS antibody determination		●			●				
Record of solicited symptoms (Days 0-6)		●[a]	●[a]						
Record of solicited symptoms (Days 0-13)				●[b]					
Record of unsolicited AEs		●[a]	●[a]	●[b]	●	●	●	●	
Record any concomitant medication/vaccination		●	●	●	●	●	●	●	●
Record any case of measles and rubella †		●	●	●	●	●	●	●	●
Record of SAEs related to study participation or to a concurrent GSK medication/vaccine	●	●	●	●	●	●	●	●	●
Record of SAEs (all, fatal, SAEs related to investigational vaccine)		●	●	●	●	●	●	●	●

Epoch	*Epoch 001*								
Type of contact	**Visit 1 (Screening)***	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 10**	**Visit 11**	**Visit 14**
Timepoints	**Day -28 to *-1***	**Day 0**	**Month 1.5**	**Month 3**	**Month 4**	**Month 4.5**	**Month 21**	**Month 22**	**Month 33**
Children age (Months)		**6**	**7.5**	**9**	**10**	**10.5**	**27**	**28**	**39**
Record AEs of specific interest (including seizure occurring within 30 or 42 days post-vaccination, meningitis and pIMDs)[c]		●	●	●	●	●	●	●	●
Study Conclusion									●

[a] Study personnel will visit the children on Days 1, 2, 3, 4, 5 and 6 after each vaccination to record solicited and unsolicited AEs on diary cards.
[b] Study personnel will visit the children on Days 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 13 after vaccination to record solicited and unsolicited AEs on diary cards.
[c] Seizures 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).
Note: The double-line border following Month 4.5 (Visit 6) indicates the analyses which will be performed on all data (i.e. data that are as clean as possible) obtained up to Month 4.5.
* If the investigator believes there is a reasonable reason to do so, screening procedures may only be repeated once.
[†] Confirmatory serology tests should be performed to identify cases of vaccine failure.
● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.

Table 6 List of study procedures for the Control group (Amended: 09 August 2016)

Epoch	*Epoch 001*											
Type of contact	**Visit 1 (Screening)***	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 12**	**Visit 13**	**Visit 15**
Timepoints	**Day -28 to *-1***	**Day 0**	**Month 1.5**	**Month 3**	**Month 4**	**Month 4.5**	**Month 5.5**	**Month 6.5**	**Month 7.5**	**Month 24**	**Month 25**	**Month 36**
Children age (Months)		**6**	**7.5**	**9**	**10**	**10.5**	**11.5**	**12.5**	**13.5**	**30**	**31**	**42**
Informed consent	●											
Check inclusion/exclusion criteria	●	O										
Collect demographic data	●											
Check medical history	●											
Physical examination	●	O	O	O	O	O	O	O	O	O	O	O
Measure/record length and weight	●											
Issuing identification card	O											
Check identification card		O	O	O	O	O	O	O	O	O	O	O
Randomization		●										
Treatment number allocation		O		O		O	O	O		O		
Recording of administered vaccine treatment number				●		●	●	●		●		
Check contraindications and warnings and precautions				●		●	●	●		●		
Pre-vaccination body temperature		●	●	●		●	●	●		●		
Vitamin A administration		●										
YF vaccine and measles and rubella vaccine administration				●								
RTS,S/AS01$_E$ vaccine administration						●	●	●		●		
Blood sampling for anti-Me and anti-Ru antibody determination				●	●							
Blood sampling for anti-YF antibody determination					●							
Blood sampling for anti-catalase antibody determination		●			●							
Record of solicited symptoms (Days 0-6)		●[a]	●[a]									
Record of solicited symptoms (Days 0-13)				●[b,c]								
Record of unsolicited AEs		●[a]	●[a]	●[b]	●	●	●	●	●	●	●	

Epoch	*Epoch 001*											
Type of contact	**Visit 1 (Screening)***	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 12**	**Visit 13**	**Visit 15**
Timepoints	**Day -28 to *-1***	**Day 0**	**Month 1.5**	**Month 3**	**Month 4**	**Month 4.5**	**Month 5.5**	**Month 6.5**	**Month 7.5**	**Month 24**	**Month 25**	**Month 36**
Children age (Months)		**6**	**7.5**	**9**	**10**	**10.5**	**11.5**	**12.5**	**13.5**	**30**	**31**	**42**
Record any concomitant medication/vaccination		●	●	●	●	●	●	●	●	●	●	●
Record any case of measles and rubella †		●	●	●	●	●	●	●	●	●	●	●
Record of SAEs related to study participation or to a concurrent GSK medication/vaccine	●	●	●	●	●	●	●	●	●	●	●	●
Record of SAEs (all, fatal, SAEs related to investigational vaccine)		●	●	●	●	●	●	●	●	●	●	●
Record AEs of specific interest (including seizure occurring within 30 or 42 days post-vaccination, meningitis and pIMDs)[d]		●	●	●	●	●	●	●	●	●	●	●
Study Conclusion												●

[a] Study personnel will visit the children on Days 1, 2, 3, 4, 5 and 6 after Vitamin A administration (Visit 2) and after Visit 3 to record solicited general and unsolicited AEs on diary cards.
[b] Study personnel will visit the children on Days 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 13 after vaccination to record solicited and unsolicited AEs on diary cards.
[c] Collection of solicited local AE for the two injection sites.
[d] Seizures 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).
Note: The double-line border following Month 4.5 (Visit 6) indicates the analyses which will be performed on all data (i.e. data that are as clean as possible) obtained up to Month 4.5.
* If the investigator believes there is a reasonable reason to do so, screening procedures may only be repeated once.
† Confirmatory serology tests should be performed to identify cases of vaccine failure.
● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.

Table 7 Intervals between study visits (Amended: 09 August 2016)

Study visit	Timing of visit[a]	Allowed interval[b]
Visit 1 (Screening)[c]	*1*-28 days before Visit 2	-
Visit 2	6 months of age	Child should be 6[c] months of age
Visit 3	7.5 months of age	Child should be 7[d] or 8[e] months of age but respecting a minimum of 4 weeks (28 days) since previous dose (Visit 2)
Visit 4	9 months of age	Child should be 9[f] months of age but respecting a minimum of 4 weeks (28 days) since previous dose (Visit 3)
Visit 5	4 weeks after Visit 4	Minimum 4 weeks (28 days) - Maximum 6 weeks (42 days)
Visit 6	2 weeks after Visit 5	Minimum 2 weeks (14 days) - Maximum 3 weeks (21 days)
Visit 7	4 weeks after Visit 6	Minimum 4 weeks (28 days) - Maximum 6 weeks (42 days)
Visit 8	4 weeks after Visit 7	Minimum 4 weeks (28 days) - Maximum 6 weeks (42 days)
Visit 9	4 weeks after Visit 8	Minimum 4 weeks (28 days) - Maximum 6 weeks (42 days)
Visit 10	18 months after Visit 4	17 months (516 days) after Visit 4 – 19 months (577 days) after Visit 4
Visit 11	4 weeks after Visit 10	Minimum 4 weeks (28 days) - Maximum 6 weeks (42 days)
Visit 12	17.5 months after Visit 8	17 months (516 days) after Visit 8 – 19 months (577 days) after Visit 8
Visit 13	4 weeks after Visit 12	Minimum 4 weeks (28 days) - Maximum 6 weeks (42 days)
Visit 14	12 months after Visit 10	11 months (334 days) after Visit 10 - 13 months (396 days) after Visit 10
Visit 15	12 months after Visit 12	11 months (334 days) after Visit 12 - 13 months (396 days) after Visit 12

[a] Whenever possible the investigator should arrange study visits within this interval.
[b] Subjects will not be eligible for inclusion in the ATP cohort for analysis of immunogenicity if they make the study visit outside this interval.
[c] 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.
[d] For clarity this corresponds from the day the child becomes 7 months of age until the day before the child achieves 8 months of age.
[e] For clarity this corresponds from the day the child becomes 8 months of age until the day before the child achieves 9 months of age.
[f] For clarity this corresponds from the day the child becomes 9 months of age until the day before the child achieves 10 months of age.

5.6. Detailed description of study procedures

5.6.1. Informed consent

The signed/witnessed/thumb printed informed consent of the subject's parent(s)/LAR(s) must be obtained before study participation. Refer to Section 5.1 for the requirements on how to obtain informed consent and assent, as appropriate.

5.6.2. Check inclusion and exclusion criteria

Check all inclusion and exclusion criteria as described in Sections 4.2 and 4.3 before enrolment.

5.6.3. Collect demographic data

Record demographic data such as date of birth, gender, and ethnicity in the subject's eCRF.

5.6.4. Medical history

Obtain the subject's medical history by interview of subject's parent(s)/LAR(s) and/or review of the subject's medical records and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the first study vaccination in the eCRF.

5.6.5. Physical examination

Perform a physical examination of the subject, including assessment of body temperature, heart rate and respiratory rate. Collected information needs to be recorded in the eCRF (Visit 1 only).

Physical examination at each study visit subsequent to the first vaccination visit, will be performed only if the subject indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the Investigator or delegate.

Treatment of any abnormality observed during physical examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

5.6.6. Measure/record length and weight

Perform anthropometric measurements of the subject (length and weight) at the Screening visit (Visit 1). Collected information needs to be recorded in the eCRF.

The methodologies used for length and weight measurements have been adapted from Cogill [Cogill, 2003] and are based on guidelines of the United Nations [United Nations, 1986]. These procedures are fully described in the SPM.

5.6.7. Issuing subject identification card

At the Screening visit (Visit 1), take a picture of the subject and his/her parent(s)/LAR(s) to make an identification card with subject's picture and number. Give this identification card to the subject's parent(s)/LAR(s).

At each subsequent visits, check this identification card.

5.6.8. Study group and treatment number allocation

Study group and treatment number allocation will be performed as described in Section 5.2.2. The number of each administered vaccines must be recorded in the eCRF.

5.6.9. Check contraindications, warnings and precautions to vaccination

Contraindications, warnings and precautions to vaccination must be checked at the beginning of each vaccination visit. Refer to Sections 6.5 and 6.6 for more details.

5.6.10. Assess pre-vaccination body temperature

The axillary, rectal, oral or tympanic body temperature of all subjects needs to be measured prior to any study vaccine/ product administration. The preferred route for recording temperature in this study will be axillary. If the subject has fever [fever is defined as temperature ≥ 37.5°C/99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C/100.4°F for rectal route] on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 7).

5.6.11. Study Vaccines/product administration

- After completing all prerequisite procedures prior to vaccination, study vaccines will be administered (refer to Section 6.3 for detailed description of the vaccines/product administration procedure). If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccines/product administration, the visit will be rescheduled within the allowed interval for this visit (refer to Table 7).
- The subjects will be observed closely for at least 60 minutes following the administration of the vaccines, with appropriate medical treatment readily available in case of anaphylaxis.
- Vaccination will take place at the vaccination center. All vaccinations will be given by a qualified person: a nurse or a doctor. A staff member experienced in the resuscitation of children will be available at all vaccination sessions.

5.6.12. Sampling

Refer to the Module on Biospecimen Management in the SPM for detailed instructions for the collection, handling and processing of the samples.

5.6.12.1. Blood sampling for anti-HBs and anti-CS immune response assessments (Amended: 09 August 2016)

Blood samples will be taken during certain study visits as specified in Section 5.5 List of Study Procedures.

- A volume of at least ***1.2*** ml of whole blood (to provide at least ***500*** µl of serum for anti-CS and anti-HBs) should be drawn from all subjects from the **Coad group** and the **RTS,S group** for each analysis of humoral immune response at each pre-defined timepoint. After centrifugation, serum samples should be kept at –20°C/ –4°F or below until shipment. Refer to the SPM for more details on sample storage conditions.

5.6.12.2. Blood sampling for anti-catalase immune response assessments (Amended: 09 August 2016)

Blood samples will be taken during certain study visits as specified in Section 5.5 List of Study Procedures.

- A volume of at least ***600*** µl of whole blood (to provide at least ***250*** µl of serum) should be drawn from all subjects from the **Coad** and the **Control groups** for analysis of anti-catalase immune response at each pre-defined timepoint. After centrifugation, serum samples should be kept at –20°C/ –4°F or below until shipment. Refer to the SPM for more details on sample storage conditions.

5.6.12.3. Blood sampling for anti-Me and anti-Ru immune response assessments (Amended: 09 August 2016)

Blood samples will be taken during certain study visits as specified in Section 5.5 List of Study Procedures.

- A volume of at least ***600 µl*** of whole blood (to provide at least ***250*** µl of serum for anti-Me and anti-Ru) should be drawn from all subjects from the **Coad group** and the **Control group** for each analysis of humoral immune response at each pre-defined timepoint. After centrifugation, serum samples should be kept at –20°C/ –4°F or below until shipment. Refer to the SPM for more details on sample storage conditions.

5.6.12.4. Blood sampling for anti-YF immune response assessments (Amended: 09 August 2016)

Blood samples will be taken during certain study visits as specified in Section 5.5 List of Study Procedures.

- A volume of at least ***600*** µl of whole blood (to provide at least 250 µl of serum for anti-YF) should be drawn from all subjects from the **Coad group** and the **Control group** for each analysis of humoral immune response at each pre-defined timepoint. After centrifugation, serum samples should be kept at –20°C/ –4°F or below until shipment. Refer to the SPM for more details on sample storage conditions.

5.6.13. Check and record concomitant medication/vaccination and cases of measles and rubella

Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.7.

Capture of cases of measles and rubella is described in Section 6.8.

5.6.14. Recording of AEs, SAEs, and AEs of specific interest

- Refer to Section 8.2 for procedures for the investigator to record AEs, SAEs and AEs of specific interest (pIMDs, meningitis and seizure within 30 or 42 days of vaccination). Refer to Section 8.3 for guidelines on how to submit SAE and AEs of specific interest reports to GSK Biologicals.
- The subjects' parent(s)/LAR(s) will be instructed to contact the investigator immediately should the subjects manifest any signs or symptoms they perceive as serious.
- For the **Coad group** and the **RTS,S group,** there will be:
  - A 7-day follow-up period (day of vaccination and 6 subsequent days) following vaccines administered at 6 and 7.5 months of age (Visits 2 and 3) for recording of solicited local and general AEs. On the day of vaccination the evaluation will be carried-out by the study physician at the study center. On Days 1, 2, 3, 4, 5 and 6 after vaccination, trained study personnel will visit the children to record solicited AEs on diary cards.
  - A 14-day follow-up period (day of vaccination and 13 subsequent days) following vaccines administered at 9 months of age (Visit 4) for recording of solicited local and general AEs. On the day of vaccination the evaluation will be carried-out by the study physician at the study center. On Days 1 to 13 after vaccination, trained study personnel will visit the children to record solicited AEs on diary cards.
  - Unsolicited AEs will be collected from the day of first vaccine administration (Visit 2) until 42 days after Visit 4. On the days of vaccinations (Visits 2, 3 and 4) the evaluation will be carried-out by the study physician at the study center. Unsolicited AEs will be captured through passive surveillance at inpatient and outpatient facilities and during study visits. In addition on Days 1 to 6 after vaccinations at Visits 2 and 3 and on Days 1 to 13 after Visit 4, trained study personnel will visit the children to record any unsolicited AEs on diary cards.
  - A 30-day follow-up period (day of vaccination and 29 subsequent days) after booster dose of RTS,S/AS01$_E$ vaccines administered at 27 months of age (Visit 10) for reporting unsolicited AEs. Unsolicited AEs will be captured through passive surveillance at inpatient and outpatient facilities and during study visits.
- For the **Control group**, there will be:
  - A 7-day follow-up period (day of administration and 6 subsequent days) following Vitamin A administered at 6 months of age (Visit 2) and a 7-day

follow-up period following Visit 3 (7.5 months of age) for recording of solicited general AEs. On the day of Visits 2 and 3 the evaluation will be carried out by the study physician at the study center. On Days 1, 2, 3, 4, 5 and 6 after Visits 2 and 3, trained study personnel will visit the children to record solicited general AEs on diary cards.

- A 14-day follow-up period (day of vaccination and 13 subsequent days) following vaccines administered at 9 months of age (Visit 4) for recording of solicited local and general AEs. On the day of vaccination the evaluation will be carried-out by the study physician at the study center. On Days 1 to 13 after vaccination, trained study personnel will visit the children to record solicited AEs on diary cards.
- Unsolicited AEs will be collected from the day of Vitamin A administration (Visit 2) until 42 days after Visit 4. On the day of Visits 2, 3 and 4 the evaluation will be carried-out by the study physician at the study center. Unsolicited AEs will be captured through passive surveillance at inpatient and outpatient facilities and during study visits. In addition on Days 1 to 6 after vaccinations at Visits 2 and 3 and on Days 1 to 13 after Visit 4, trained study personnel will visit the children to record any unsolicited AEs on diary cards.
- Unsolicited AEs will be collected from the day of the first dose of RTS,S/AS01$_E$ (Visit 6) until 30 days after Visit 8 and from the day of the booster dose of RTS,S/AS01$_E$ administered at 30 months of age (Visit 12) until 30 days after the booster dose. On the day of vaccination the evaluation will be carried-out by the study physician at the study center. Unsolicited AEs will be captured through passive surveillance at inpatient and outpatient facilities and during study visits.

- For all groups (**Coad group**, **RTS,S group** and **Control group**):
  - All SAEs will be reported until study end (Month 33 for Coad and RTS,S groups and Month 36 for the Control group).
  - All AEs of specific interest will be reported until study end (Month 33 for Coad and RTS,S groups and Month 36 for the Control group). AEs of specific interest include seizure (occurring within 30 days post-vaccination for vaccine doses administered at 6 and 7.5 months of age or 42 days post-vaccination for vaccine doses administered at 9 months of age), meningitis and pIMDs.

5.6.15. Study conclusion

The investigator will:

- Review data collected to ensure accuracy and completeness
- Complete the Study Conclusion screen in the eCRF.

5.7. Biological sample handling and analysis

Please refer to the SPM for details on biospecimen management (handling, storage and shipment).

Samples will not be labeled with information that directly identifies the subject but will be coded with the identification number for the subject (subject number).

- Collected samples will be used for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.
- It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all subjects in countries where this is allowed, will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to the laws and regulations in the respective countries and will only be performed once an independent Ethics Committee or Review Board has approved this research.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the individual subject's parent(s)/LAR(s).

Refer also to the Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

If additional testing is performed, the marker priority ranking given in Section 5.7.4 may be changed.

Collected samples will be stored for a maximum of 20 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

5.7.1. Use of specified study materials

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.5 for the definition of cohorts to be analyzed). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, appropriate materials from the investigator's site must be used. Refer to the Module on Clinical Trial Supplies in the SPM.

5.7.2. Biological samples

Details of the quantity of blood to be taken at each timepoint during the study are provided in Table 8.

Table 8 Biological samples (Amended: 09 August 2016)

Timepoint	Group	Sample type	Quantity	Unit
Visit 2 (Day 0)	Coad group	Blood	***1.8***	ml
	RTS,S group	Blood	***1.2***	ml
	Control group	Blood	***0.6***	ml
Visit 4 (Month 3)	Coad group	Blood	***0.6***	ml
	Control group	Blood	***0.6***	ml
Visit 5 (Month 4)	Coad group	Blood	***3.5***	ml
	RTS,S group	Blood	***1.2***	ml
	Control group	Blood	***1.8***	ml

5.7.3. Laboratory assays

Please refer to APPENDIX A for a detailed description of the assays performed in the study. Please refer to APPENDIX B for the address of the clinical laboratories used for sample analysis.

Serological assays for the determination of anti-CS antibodies will be performed by enzyme-linked immunosorbent assay (ELISA) at a laboratory designated by GSK Biologicals using standardized and validated procedures (refer to Table 9).

Serological assays for the determination of anti-HBs antibodies will be performed by chemiluminescence enzyme immunoassay (CLIA) at a GSK Biologicals laboratory using standardized and validated procedures (refer to Table 9).

Serological assays for the determination of anti-catalase antibodies will be performed by ELISA at a GSK Biologicals laboratory using optimized procedures (refer to Table 9).

Serological assays for the determination of anti-Me and anti-Ru antibodies will be performed by ELISA at a GSK Biologicals laboratory using standardized and qualified procedures (refer to Table 9).

Serological assays for the determination of anti-YF antibodies will be performed by plaque neutralization assay (PRN) at a laboratory designated by GSK Biologicals using standardized and validated procedures (refer to Table 9).

Table 9 Humoral Immunity (Antibody determination) (Amended: 09 August 2016)

System	Component	Method	Kit / Manufacturer	Unit	Cut-off	Laboratory
SERUM	Plasmodium falciparum.Circumsporozoite Protein.R32LR Ab.IgG	ELISA	Not Applicable	EU/ml	0.5	CEVAC
SERUM	Hepatitis B Virus.Surface Ab	CLIA	ADVIA Centaur anti-HBs2 (Siemens Healthcare)	mIU/ml	6.2	GSK Biologicals*
SERUM	catalase Ab.IgG	ELISA	In house	ng/ml	65	GSK Biologicals*
SERUM	Measles Virus Ab.IgG	ELISA	Dade Behring Enzygnost Anti-measles virus IgG	mIU/ml	150	GSK Biologicals*
SERUM	Yellow Fever Virus Ab	PRN	in house	ED50	10	Focus Diagnostics
SERUM	Rubella Virus Ab.IgG	ELISA	Dade Behring Enzygnost Anti-rubella virus IgG	IU/ml	4	GSK Biologicals*

*GSK Biologicals laboratory refers to the ***Clinical Laboratory Sciences*** (***CLS***) in Rixensart, Belgium; Wavre, Belgium; ***NEOMED- LABS Inc, Canada.***
CEVAC: Center for Vaccinology, Ghent, Belgium
Focus Diagnostics, Inc.: 5785 Corporate Avenue; Cypress, CA 90630, United States
CLIA: chemiluminescence enzyme immunoassay
ELISA: Enzyme linked immunosorbent assay
PRN: Plaque neutralization assay
ED50: End point Dilution 50
EU/ml: ELISA unit per milliliter
mIU/ml : milli-international unit per milliliter
IU/ml : International unit per milliliter

The GSK Biologicals' clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals' clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

5.7.4. Biological samples evaluation

5.7.4.1. Immunological read-outs

Blood samples will be collected for assessment of serology.

Table 10 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

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analyzed according to priority ranking provided in Table 10.

5.7.5. Immunological correlates of protection

No correlate of protection has been demonstrated so far for the CS and YF antigens.

For the hepatitis B surface antigen, the conventional correlate of protection is anti-HBs antibody titers above 10 mIU/ml [European Consensus Group on Hepatitis B Immunity, 2000].

Anti-Me and anti-Ru antibody titers will be determined using ELISA kits. The seroprotection threshold is 150 mIU/ml and 10 IU/ml for anti-Me and anti-Ru antibodies, respectively.

5.7.5.1. Rescue Plan

Assessment of the protection level for measles and rubella will be done one month post-vaccination (Visit 5 for the Coad and Control groups). The results of the immunological assay will be communicated to the investigator as soon as they become available and in any case no later than 12 months after the visit date at which sampling allows the assessment of protection. Children with antibodies below the seroprotection thresholds of 150 mIU/ml (anti-Me antibodies) and 10 IU/ml (anti-Ru antibodies) will be considered as non-responders. The list of non-responders will be provided to the IDMC and investigators. Investigators based on their clinical judgment will decide whether families should be offered additional measles or rubella vaccine doses.

The investigator is encouraged to share the immunological assay results for non-responders with the study subjects/subjects' parent(s)/LAR(s).

For the subjects identified as non-responders, it remains the responsibility of the investigator in charge of the subject's clinical management to determine the medical need for re-vaccination and to re-vaccinate the subjects as per local/regional practices.

6. STUDY VACCINES/PRODUCT AND ADMINISTRATION

6.1. Description of study vaccines/product

The candidate RTS,S/AS01$_E$ vaccine has been developed by GSK Biologicals.

The Quality Control Standards and Requirements for the candidate vaccine are described in separate Quality Assurance documents (e.g. release protocols, certificate of analysis) and the required approvals have been obtained.

The vaccines/product are labelled and packed according to applicable regulatory requirements.

Commercial vaccines/product are assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics.

Table 11 Study products

Treatment name	Vaccine/product name	Formulation	Presentation	Volume to be administered	Number of doses
RTS,S/AS01$_E$*	RTS,S	RTS,S=25µg	Lyophilized pellet in a two-dose glass vial	0.5 ml	4
	AS01E	MPL=25µg; QS21=25µg; Liposomes	Liquid solution in a two-dose glass vial		
Yellow fever	WHO prequalified Yellow Fever	17D	Lyophilized with diluent	0.5 ml	1
Measles and Rubella	MR-VAC	Edmonston-Zagreb measles virus=1000CCID$_{50}$; Wistar RA 27/3 rubella virus=1000CCID$_{50}$	Lyophilized with diluent	0.5 ml	1
Vitamin A	Vitamin A	-	Capsules	100000 IU (30 mg RE)	1

IU: international units; MPL : 3-O-desacyl-4'-monophosphoryl lipid A; QS-21 Stimulon®: *Quillaja saponaria* Molina, fraction 21; RE: retinol equivalent
MR-VAC: Live attenuated measles virus and rubella virus vaccine (Serum Institute of India)
* In this study the commercial presentation of RTS,S/AS01$_E$ will be used, i.e. a two-doses glass vial of lyophilized RTS,S antigen (50 µg) to be reconstituted with 1.0 ml of AS01 Adjuvant System (MPL = 50 µg; QS-21 Stimulon® = 50 µg; Liposome). From the reconstituted vaccine vial, 0.5-ml will be withdrawn to administer to each children a dose of 25 µg RTS,S and 25 µg QS-21 Stimulon®, 25 µg MPL and liposome, also called AS01$_E$.

6.2. Storage and handling of study vaccines/product

The study vaccines/product must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to

authorized study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccines/product.

Temperature excursions must be reported in degree Celsius.

Any temperature excursion outside the range of 0.0 to +8.0°C (for +2 to +8°C/+36 to +46°F label storage condition) impacting investigational medicinal products (IMPs) must be reported in the appropriate (electronic) temperature excursion decision form ([e]TDF). The impacted IMPs must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor.

In case of temperature excursion below +2.0°C down to 0.0°C impacting IMP(s) there is no need to report in (e)TDF, but adequate actions must be taken to restore the +2 to +8°C/+36 to +46°F label storage temperature conditions. The impacted IMP(s) may still be administered, but the site should avoid re-occurrence of such temperature excursion. Refer to the Module on Clinical Trial Supplies in the SPM for more details on actions to take.

Non-IMPs that are impacted by a temperature excursion may not be used and must be quarantined at label storage conditions until usage approval has been obtained from/via the local study contact (e.g. Site Monitor). There is no need for reporting via the eTDF.

Refer to the Module on Clinical Trial Supplies in the SPM for details and instructions on the temperature excursion reporting and usage decision process, packaging and accountability of the study vaccines/product.

6.3. Dosage and administration of study vaccines/product

Table 12 Dosage and administration

Type of contact and timepoint	Dose to be administered	Study Group	Treatment name	Route [1]	Site	Side
Visit 2	100000 IU	Coad group	Vitamin A	O	Not applicable	Not applicable
	0.5 ml	Coad group	RTS,S/AS01$_E$	IM	Deltoid	Left
	100000 IU	RTS,S group	Vitamin A	O	Not applicable	Not applicable
	0.5 ml	RTS,S group	RTS,S/AS01$_E$	IM	Deltoid	Left
	100000 IU	Control group	Vitamin A	O	Not applicable	Not applicable
Visit 3	0.5 ml	Coad group	RTS,S/AS01$_E$	IM	Deltoid	Left
	0.5 ml	RTS,S group	RTS,S/AS01$_E$	IM	Deltoid	Left
Visit 4	0.5 ml	Coad group	RTS,S/AS01$_E$	IM	Deltoid	Left
	0.5 ml	Coad group	Yellow fever	IM	Anterolateral thigh	Right
	0.5 ml	Coad group	Measles and Rubella	SC	Anterolateral thigh	Left
	0.5 ml	RTS,S group	RTS,S/AS01$_E$	IM	Deltoid	Left
	0.5 ml	Control group	Yellow fever	IM	Anterolateral thigh	Right
	0.5 ml	Control group	Measles and Rubella	SC	Anterolateral thigh	Left
Visit 6	0.5 ml	RTS,S group	Yellow fever	IM	Anterolateral thigh	Right
	0.5 ml	RTS,S group	Measles and Rubella	SC	Anterolateral thigh	Left
	0.5 ml	Control group	RTS,S/AS01$_E$	IM	Deltoid	Left
Visit 7	0.5 ml	Control group	RTS,S/AS01$_E$	IM	Deltoid	Left
Visit 8	0.5 ml	Control group	RTS,S/AS01$_E$	IM	Deltoid	Left
Visit 10	0.5 ml	Coad group	RTS,S/AS01$_E$	IM	Deltoid	Left
	0.5 ml	RTS,S group	RTS,S/AS01$_E$	IM	Deltoid	Left
Visit 12	0.5 ml	Control group	RTS,S/AS01$_E$	IM	Deltoid	Left

[1] IM: Intramuscular; O: Oral; SC: Subcutaneous

The subjects will be observed closely for at least 60 minutes following the administration of the vaccines, with appropriate medical treatment readily available in case of anaphylaxis.

6.3.1. RTS,S/AS01$_E$ (0.5 ml dose)

The commercial presentation will be a two-doses glass vial of lyophilized RTS,S antigen to be reconstituted with a two-doses glass vial of AS01$_E$ Adjuvant System. The final product for administration will be prepared by reconstitution of the lyophilized antigen with the liquid adjuvant to deliver two doses (1.0 ml). A single dose consists of 0.5 ml of RTS,S/AS01$_E$ final preparation. All vials of vaccine provided in this study are intended for single use only.

Disinfect top of vaccine vial (pellet) and adjuvant vial with alcohol swabs and let dry. Withdraw the contents of the adjuvant vial in a syringe and inject adjuvant into the vial of lyophilized antigen. The pellet is then dissolved by gently shaking the vial. Wait for one minute to ensure complete dissolution of vial contents before withdrawing one dose of RTS,S/AS01$_E$ (0.5 ml). The reconstituted vaccine should be administered by slow IM

injection, using a fresh 25G needle with length of one inch (25 mm), in the left deltoid. Vaccine should be injected within four hours of reconstitution (storage at +2°C to +8°C).

6.3.2. Combined measles and rubella vaccine (*MR-VAC*) (0.5 ml dose)

The combined measles and rubella vaccine will be used according to manufacturer instructions and the Summary of Product Characteristics. The vaccine will be administered as a SC injection into the left anterolateral thigh.

6.3.3. Licensed WHO prequalified yellow fever vaccine (0.5 ml dose)

The YF vaccine will be used according to manufacturer instructions and the Summary of Product Characteristics. The vaccine will be administered as an IM injection into the right anterolateral thigh.

6.3.4. Vitamin A (100000 IU dose)

The Vitamin A will be used according to manufacturer instructions and the Summary of Product Characteristics. Vitamin A will be administered orally.

6.4. Replacement of unusable vaccine/product doses

In addition to the vaccine/product doses provided for the planned number of subjects (including over-randomization when applicable), at least 10% additional vaccine/product doses will be supplied to replace those that are unusable.

6.5. Contraindications to subsequent vaccination

The following events constitute absolute contraindications to further administration of study vaccines. If any of these events occur during the study, the subject must not receive additional doses of vaccines but may continue other study procedures at the discretion of the investigator (see Section 8.4).

- Anaphylaxis following the administration of vaccines.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Failure to thrive.
- Any other findings that the investigator feels would increase the risk of having an adverse outcome from participation in the trial.
- Administration of a dose of measles, rubella or YF vaccines outside of this study protocol.

The following events constitute contraindications to administration of study vaccines at that point in time; if any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the

protocol (see Section 5.5), or the subject may be withdrawn at the discretion of the investigator (see Section 8.4).

- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as temperature ≥ 37.5°C/99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C/100.4°F for rectal route. The preferred route for recording temperature in this study will be axillary.
  - Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever can be administered all vaccines/.
- A lesion that would prevent injection.
- Administration of a vaccine not foreseen by the study protocol within seven days of any dose of RTS,S/AS01$_E$, YF vaccine and the combined measles and rubella vaccine.

6.6. Warnings and precautions

Refer to the approved product label/package insert.

6.7. Concomitant medications/products and concomitant vaccinations

At each study visit/contact, the investigator should question the subject's parent(s)/LAR(s) about any medications/products taken and vaccinations received by the subject.

6.7.1. Recording of concomitant medications/products and concomitant vaccinations

The following concomitant medication(s)/product(s)/vaccine(s) must be recorded in the eCRF.

- Anti-inflammatory, analgesics, anti-pyretic, and systemic antibiotics administered starting 30 days before and following each dose of study vaccine.
- Any concomitant vaccination administered in the period starting seven days before the first dose of study vaccine and ending at Visit 5 (Month 4).
- Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

  E.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring (fever is defined as temperature ≥ 37.5°C/99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C/100.4°F for rectal route).
- Any concomitant medications/products/vaccines listed in Section 6.7.2.
- Any concomitant medication/product/vaccine relevant to a SAE* or administered at any time during the study period for the treatment of a SAE*.

* SAEs that are required to be reported per protocol.

- Any concomitant medications/products/vaccines relevant to a SAE/pIMD to be reported as per protocol or administered at any time during the study period for the treatment of a SAE/pIMD. In addition, concomitant medications relevant to SAEs and pIMD need to be recorded on the expedited Adverse Event report.

6.7.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from ATP analyses

The use of the following concomitant medications/products/vaccines will not require withdrawal of the subject from the study but may determine a subject's evaluability in the ATP analysis. See Section 10.5 for cohorts to be analyzed.

- Use of a drug or vaccine that is not approved for that indication (by one of the following regulatory authorities: FDA or European Union member state or WHO [with respect to prequalification]) other than the study vaccines during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days) during the study period. For corticosteroids, this will mean prednisone ≥ 0.5 mg/kg/day or equivalent. Inhaled and topical steroids are allowed.
- A vaccine not foreseen by the study protocol administered during the period starting from seven days before each dose of vaccine(s) and ending 42 days after.*

  * In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic or polio control) is organized by the public health authorities, outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its Summary of Product Characteristics or Prescribing Information and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.
- Immunoglobulins and/or any blood products administered during the study period.
- Administration of a dose of measles, rubella or YF vaccines from seven days before the first dose of study vaccine and ending at the first birthday of the subject.

6.8. Capture of cases of measles and rubella (Amended: 09 August 2016)

At each study visit subsequent to the first vaccination, it must be verified if the subject has experienced or is experiencing measles or rubella. If it is the case, the condition(s) must be recorded in the eCRF.

During the course of the study, any clinical presentation compatible with measles, rubella or YF will be captured as AE or SAE as appropriate and confirmatory serology tests should be performed to identify cases of vaccine failure.

7. HEALTH ECONOMICS

Not applicable.

8. SAFETY

The investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an AE or SAE as provided in this protocol.

Each subject's parent(s)/LAR(s) will be instructed to contact the investigator immediately should they/the subject manifest any signs or symptoms they perceive as serious.

8.1. Safety definitions

8.1.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE include:

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational vaccine(s)/product(s) administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational vaccine(s)/product(s) or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with vaccine administration.
- Significant failure of expected pharmacological or biological action.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

AEs to be recorded as endpoints (solicited AEs) are described in Section 8.1.3. All other AEs will be recorded as UNSOLICITED AEs.

Examples of an AE DO NOT include:

- Medical or surgical procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE/SAE.
- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pre-existing conditions or signs and/or symptoms present in a subject prior to the first study vaccination. These events will be recorded in the medical history section of the eCRF.

8.1.2. Definition of a serious adverse event

A SAE is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

   Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c. Requires hospitalization or prolongation of existing hospitalization,

   Note: In general, hospitalization signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalization are also considered AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

   Hospitalization for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

d. Results in disability/incapacity, OR

   Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other

outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

In this study, the following AEs of specific interest (pIMDs, meningitis and seizure within 30 or 42 days of vaccination) will be reported as SAEs (see also Section 8.1.5).

8.1.3. Solicited adverse events

8.1.3.1. Solicited local (injection-site) adverse events

The following local (injection-site) AEs will be solicited:

Table 13 Solicited local adverse events

Pain at injection site
Redness* at injection site
Swelling at injection site

* In case the principal investigator or designate is unable to determine the extent of redness on darkly pigmented skin, it will be reported as uninterpretable in the eCRF

8.1.3.2. Solicited general adverse events

The following general AEs will be solicited:

Table 14 Solicited general adverse events

Drowsiness
Fever
Irritability/Fussiness
Loss of appetite
Measles/rubella-like rash*

* To be confirmed by physician

Note: Temperature will be recorded daily. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded in the eCRF.

8.1.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

In absence of diagnosis, abnormal laboratory findings (e.g. clinical chemistry, hematology, urinalysis) or other abnormal assessments that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE (refer to Sections 8.1.1 and 8.1.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.1.5. Adverse events of specific interest

All adverse events of specific interest described below will be reported as SAEs.

8.1.5.1. Potential immune-mediated diseases

pIMDs are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology. AEs that need to be recorded and reported as pIMDs include those listed in Table 15. pIMD will be reported as SAEs.

However, the investigator will exercise his/her medical and scientific judgment in deciding whether other diseases have an autoimmune origin (i.e. pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD.

Table 15 List of potential immune-mediated diseases

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• Cranial nerve disorders, including paralyses/paresis (e.g. Bell's palsy) • Optic neuritis • Multiple sclerosis • Transverse myelitis • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants • Acute disseminated encephalomyelitis, including site specific variants: e.g. non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome • Immune-mediated peripheral neuropathies and plexopathies, (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy). • Narcolepsy	• Systemic lupus erythematosus and associated conditions • Systemic scleroderma (Systemic sclerosis), including diffuse systemic form and CREST syndrome Idiopathic inflammatory myopathies, including dermatomyositis • Polymyositis • Antisynthetase syndrome • Rheumatoid arthritis, and associated conditions including juvenile chronic arthritis and Still's disease • Polymyalgia rheumatica • Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis • Psoriatic arthropathy • Relapsing polychondritis • Mixed connective tissue disorder	• Psoriasis • Vitiligo • Erythema nodosum • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis) • Alopecia areata • Lichen planus • Sweet's syndrome • Localised Scleroderma (Morphoea)

Vasculitides	Blood disorders	Others
• Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis. • Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome (allergic granulomatous angiitis), Buerger's disease (thromboangiitis obliterans), necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis.	• Autoimmune hemolytic anemia • Autoimmune thrombocytopenia • Antiphospholipid syndrome • Pernicious anemia • Autoimmune aplastic anaemia • Autoimmune neutropenia • Autoimmune pancytopenia	• Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) • Ocular autoimmune diseases (including autoimmune uveitis and autoimmune retinopathy) • Autoimmune myocarditis/cardiomyopathySarcoidosis • Stevens-Johnson syndrome • Sjögren's syndrome • Idiopathic pulmonary fibrosis • Goodpasture syndrome • Raynaud's phenomenon

Liver disorders	Gastrointestinal disorders	Endocrine disorders
• Autoimmune hepatitis • Primary biliary cirrhosis • Primary sclerosing cholangitis • Autoimmune cholangitis	• Inflammatory Bowel disease, including Crohn's disease, ulcerative colitis, microscopic colitis, ulcerative proctitis • Celiac disease • Autoimmune pancreatitis	• Autoimmune thyroiditis (including Hashimoto thyroiditis) • Grave's or Basedow's disease • Diabetes mellitus type I • Addison's disease • Polyglandular autoimmune syndrome • Autoimmune hypophysitis

When there is enough evidence to make any of the above diagnoses, the AE must be reported as a pIMD. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as SAEs but not as pIMDs until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

In order to facilitate the documentation of pIMDs in the eCRF, a pIMD standard questionnaire and a list of preferred terms and preferred terms codes corresponding to the above diagnoses will be available to investigators at study start.

8.1.5.2. Seizures within 30 or 42 days of vaccination (Amended: 09 August 2016)

All seizures occurring within 30 days of vaccination for vaccine doses administered at 6 and 7.5 months of age (Visits 2 and 3) and within 42 days for vaccine doses administered at 9 months of age (Visit 4) will be reported as SAEs and in ***specific eCRF screens***. Key information pertaining to seizures occurring within seven days of vaccination for vaccine doses administered at 6 and 7.5 months of age (Visits 2 and 3) and within 14 days for vaccine doses administered at 9 months of age (Visit 4) will be documented in the eCRF [refer to Bonhoeffer, 2004].

8.1.5.3. Meningitis (Amended: 09 August 2016)

For the further evaluation of the safety signal of meningitis all the cases occurring during the study will be reported as SAE and medical documentation of the events will be reported in ***specific eCRF screens***. Cerebrospinal fluid will be frozen for future testing for infectious agents if applicable (this procedure is fully described in the SPM).

8.2. Detecting and recording adverse events and serious adverse events

8.2.1. Time period for detecting and recording adverse events and serious adverse events

In the Coad and the RTS,S group, all AEs starting after the first vaccine administration (Visit 2) until 42 days following administration of study vaccine at 9 months of age (Visit 4) and AEs starting within 30 days following administration of study vaccine at 27 months of age (Visit 10) must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

In the Control group, all AEs starting after the Vitamin A administration (Visit 2) until 42 days following administration of study vaccine at 9 months of age (Visit 4), AEs starting from the day of the first dose of RTS,S/AS01$_E$ (Visit 6) until 30 days after Visit 8 and from the day of the booster dose of RTS,S/AS01$_E$ administered at 30 months of age (Visit 12) until 30 days after the booster dose must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The time period for collecting and recording SAEs will begin at the first receipt of study vaccine and will end 12 months following administration of the last dose of study vaccine (Month 33 for Coad and RTS,S groups and Month 36 for the Control group) for each subject. See Section 8.3 for instructions on reporting of SAEs.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the first receipt of study vaccine.

In addition to the above-mentioned reporting requirements and in order to fulfill international reporting obligations, SAEs that are related to study participation (i.e. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged from the study.

The time period for collecting and recording of AEs of specific interest will begin at the first receipt of study vaccine and will end 12 months following administration of the last the dose of study vaccine (Month 33 for Coad and RTS,S groups and Month 36 for the Control group). See section 8.3 for instructions on reporting of AEs of specific interest.

An overview of the protocol-required reporting periods for AEs and SAEs is given in Table 16.

Table 16 Reporting periods for adverse events and serious adverse events (Amended: 09 August 2016)

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.

8.2.2. Post-Study adverse events and serious adverse events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 16. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational vaccines/product, the investigator will promptly notify the Study Contact for Reporting SAEs.

8.2.3. Evaluation of adverse events and serious adverse events

8.2.3.1. Active questioning to detect adverse events and serious adverse events

As a consistent method of collecting AEs, the subject's parent(s)/LAR(s) should be asked a non-leading question such as:

'*Has your child acted differently or felt different in any way since receiving the vaccine or since the last visit?*'

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE on the in the eCRF. The investigator is not allowed to send photocopies of the subject's medical records to GSK Biologicals instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

8.2.3.2. Assessment of adverse events

8.2.3.2.1. Assessment of intensity

The intensity of the following solicited AEs will be assessed as described:

Table 17 Intensity scales for solicited symptoms in infants

Infants		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Minor reaction to touch
	2	Moderate: Cries/protests on touch
	3	Severe: Cries when limb is moved/spontaneously painful
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in °C/°F
Irritability/Fussiness	0	Behavior as usual
	1	Mild: Crying more than usual/no effect on normal activity
	2	Moderate: Crying more than usual/interferes with normal activity
	3	Severe: Crying that cannot be comforted/prevents normal activity
Drowsiness	0	Behavior as usual
	1	Mild: Drowsiness easily tolerated
	2	Moderate: Drowsiness that interferes with normal activity
	3	Severe: Drowsiness that prevents normal activity
Loss of appetite	0	Appetite as usual
	1	Mild: Eating less than usual/no effect on normal activity
	2	Moderate: Eating less than usual/interferes with normal activity
	3	Severe: Not eating at all
Measles/rubella-like rash	0	No lesion
	1	1-50 lesions
	2	51-150 lesions
	3	>150 lesions

*Fever is defined as temperature ≥ 37.5°C / 99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C / 100.4°F for rectal route. The preferred route for recording temperature in this study will be axillary.

The maximum intensity of local injection site redness/swelling/fever will be scored at GSK Biologicals as follows:

0 : None
1 : < 5 mm
2 : 5 to 20 mm
3 : > 20 mm

The maximum intensity of fever will be scored at GSK Biologicals as follows (the preferred route for recording temperature in this study will be axillary):

0 : < 37.5°C
1 : 37.5 – 38.0°C
2 : > 38 – 39.0°C
3 : > 39.0°C

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the investigator's clinical judgment.

The intensity should be assigned to one of the following categories:

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities (in a young child, such an AE would, for example, prevent attendance at day-care center and would cause the parent(s)/LAR(s) to seek medical advice.)

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.1.2.

8.2.3.2.2. Assessment of causality

The investigator is obligated to assess the relationship between investigational vaccine and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational vaccine will be considered and investigated. The investigator will also consult the IB or Prescribing Information for marketed products to determine his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the Expedited Adverse Events Report to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information and update the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple vaccines/products, it may not be possible to determine the causal relationship of general AEs to the individual vaccine/product administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines/products.

All solicited local (injection site) reactions will be considered causally related to vaccination. Causality of all other AEs should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE may have been caused by the investigational vaccine?

YES	:	There is a reasonable possibility that the vaccines contributed to the AE.
NO	:	There is no reasonable possibility that the AE is causally related to the administration of the study vaccines. There are other, more likely causes and administration of the study vaccines is not suspected to have contributed to the AE.

If an event meets the criteria to be determined as 'serious' (see Section 8.1.2), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccines, if applicable.
- Erroneous administration.
- Other cause (specify).

8.2.3.3. Assessment of outcomes

The investigator will assess the outcome of all unsolicited AEs (including SAEs) recorded during the study as:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

8.2.3.4. Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject's parent(s)/LAR(s) will be asked if the subject received medical attention defined as

hospitalization, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF.

8.3. Reporting of serious adverse events and other events

8.3.1. Prompt reporting of serious adverse events and other events to GSK Biologicals

SAEs that occur in the time period defined in Section 8.2 will be reported promptly to GSK within the timeframes described in Table 18, once the investigator determines that the event meets the protocol definition of a SAE.

AEs of specific interest (pIMDs, meningitis and seizure within 30 or 42 days of vaccination) that occur in the time period defined in Section 8.2 will be reported promptly to GSK within the timeframes described in Table 18, once the investigator determines that the event meets the protocol definition of an AEs of specific interest (pIMDs, meningitis and seizure within 30 or 42 days of vaccination).

Table 18 Timeframes for submitting serious adverse event and other events reports to GSK Biologicals

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
AEs of specific interest**	24 hours*‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report

* Timeframe allowed after receipt or awareness of the information.
** 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.
‡ The investigator will be required to confirm review of the SAE/AEs of specific interest causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE/AEs of specific interest.

8.3.2. Contact information for reporting serious adverse events and AEs of specific interest

Study Contact for Reporting SAEs and AEs of specific interest*
Refer to the local study contact information document.
Back-up Study Contact for Reporting SAEs and AEs of specific interest*
24/24 hour and 7/7 day availability: **GSK Biologicals Clinical Safety & Pharmacovigilance** Outside US & Canada sites: Fax: +PPD Email address: PPD

* 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.

8.3.3. Completion and transmission of SAE reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event. Even if the investigator does not have all information regarding a SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report. The investigator will be required to confirm the review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

8.3.3.1. Back-up system in case the electronic reporting system does not work

If the electronic reporting system does not work, the investigator (or designate) must complete, then date and sign a paper Expedited Adverse Events Report and fax it to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours.

This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow. As soon as the electronic reporting system is working again, the investigator (or designate) must complete the electronic Expedited Adverse Events Report within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic SAE reporting system.

8.3.4. Reporting of AEs of specific interest to GSK Biologicals (Amended: 09 August 2016)

Once an AE of specific interest (pIMDs, meningitis and seizure within 30 or 42 days of vaccination) is diagnosed in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS after he/she becomes aware of the diagnosis. The report allows to specify that the event is a pIMD. The report will always be completed as thoroughly as possible with all available details of the event, in accordance with the ***pIMD*** standard questionnaire provided. Even if the investigator does not have all information regarding an AEs of specific interest, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report. The investigator will be required to confirm the review of the AEs of specific interest causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the AEs of specific interest.

Refer to Section 8.3.3.1 for back-up system in case the electronic reporting system does not work.

8.3.5. Updating of SAE and AEs of specific interest information after removal of write access to the subject's eCRF

When additional SAE or AEs of specific interest information is received after removal of the write access to the subject's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 18.

8.3.6. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.3.1. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to the investigational vaccines and unexpected. The purpose of the report is to fulfill specific regulatory and GCP requirements, regarding the product under investigation.

8.4. Follow-up of adverse events and serious adverse events

8.4.1. Follow-up of adverse events and serious adverse events

8.4.1.1. Follow-up during the study

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide additional relevant information on the subject's condition to GSK Biologicals (within 24 hours for SAEs; refer to Table 18).

All SAEs and AEs of specific interest (pIMDs, meningitis and seizure within 30 or 42 days of vaccination) documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end of the study.

All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 30 days after the last vaccination.

8.4.1.2. Follow-up after the subject is discharged from the study

The investigator will follow subjects:

- with SAEs, AEs of specific interest or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilized, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.

If the investigator receives additional relevant information on a previously reported SAE, he/she will provide this information to GSK Biologicals using a paper/ electronic Expedited Adverse Events Report and/or pregnancy report as applicable.

GSK Biologicals may request that the investigator performs or arranges the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognized follow-up period, GSK Biologicals will be provided with any available post-mortem findings, including histopathology.

8.5. Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the subject's eCRF (refer to Section 6.7).

8.6. Subject card

Subjects' parent(s)/LAR(s) must be provided with the address and telephone number of the main contact for information about the clinical study.

The investigator (or designate) must therefore provide a "subject card" to each subject's parent(s)/LAR(s). In an emergency situation this card serves to inform the responsible attending physician that the subject is in a clinical study and that relevant information may be obtained by contacting the investigator.

Subjects' parent(s)/LAR(s) must be instructed to keep subject cards in their possession at all times.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject who returns for the concluding visit/is available for the concluding contact foreseen in the protocol is considered to have completed the study.

9.2. Subject withdrawal

Withdrawals will not be replaced.

9.2.1. Subject withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study refers to any subject who did not come back for the concluding visit/was not available for the concluding contact foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject is considered a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Investigators will make an attempt (phone and visit contacts) to contact those subjects who do not return for scheduled visits or follow-up.

Information relative to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by the subject's parent(s)/LAR(s), or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Non-serious adverse event.
- Protocol violation (specify).
- Consent withdrawal, not due to an adverse event*.
- Moved from the study area.
- Lost to follow-up.

- Other (specify).

*In case a subject is withdrawn from the study because the subject's parent(s)/LAR(s) has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject/subject's parent(s)/LAR(s), in the eCRF.

Subjects who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of a SAE/AE until resolution of the event (see Section 8.4.1.2).

9.2.2. Subject withdrawal from investigational vaccine

A 'withdrawal' from the investigational vaccine refers to any subject who does not receive the complete treatment, i.e. when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the investigational vaccine may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol.

Information relative to premature discontinuation of the investigational vaccine will be documented on the Vaccine Administration screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination/treatment was made by the subject's parent(s)/LAR(s), or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Non-serious adverse event.
- Other (specify).

9.3. Extension study

At the end of the study (study conclusion visit/contact), the investigator will ask subject's parent(s)/LAR(s) if they are interested to allow the subject to participate in a booster study/long-term study. If a subject's parent(s)/LAR(s) is/are not interested in participating in the booster study/long-term study the reason for refusal will be documented in the subject's eCRF.

9.4. Screen and baseline failures

Screening failures are defined as subjects who are withdrawn from the study after giving informed consent, but who do not meet the inclusion and exclusion criteria. Reason for screening failure will be collected.

10. STATISTICAL METHODS

10.1. Primary endpoints

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

10.2. Secondary endpoints

Immunogenicity

- Antibody response to the candidate vaccine RTS,S/AS01$_E$ (RTS,S group and Coad group):
  - Anti-CS antibody titers and seropositivity at Day 0 and at one month post Dose 3 of RTS,S/AS01$_E$ (Month 4).
  - Anti-HBs antibody titers and seroprotection 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 titer below 150 mIU/ml and a post-vaccination titer $\geq$ 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 titers and seropositivity ($\geq$ 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 titer below 4 IU/ml and a post-vaccination titer $\geq$ 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 titers and seropositivity ($\geq$ 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 titers 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 administrations.
  - 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).

10.3. 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.

10.4. Determination of sample size

For the primary endpoint, with 205 evaluable subjects per group the study has at least 90% power to rule out a minimum 2-fold decrease in anti-CS GMTs in the Coad group versus the RTS,S group with a 2-sided 5% alpha level and an assumed anti-CS log standard deviation of ≤ 0.9 (see Table 19).

For the secondary endpoints, the power to demonstrate non-inferiority in terms of anti-YF, anti-Ru and anti-Me with 205 evaluable subjects per group is presented in Table 19. Non-inferiority is defined as the UL of the 95% CI on the difference (Control group minus Coad group) in response <10%.

In order to account for drop-outs and subjects non-evaluable for immunogenicity endpoints (approximately 12%), 233 subjects per group will be enrolled for a total of 699 subjects.

Table 19 Sample size and power

Antibody	Endpoint	Non-inferiority limit	Reference in control	Power
Anti-CS	GMT ratio (RTS,S group / Coad group)	2-fold decrease	log SD ≤ 0.9	90%
Anti-Ru	Seroconversion	10%	90%*	90%
Anti-YF	Seropositivity	10%	95%**	99%
Anti-Me	Seroconversion	10%	90%**	90%

Power of a non-inferiority test on seroconversion/positivity or means, 2-sided alpha 0.05, N=205 (Pass 2005).
* Adapted from Rubella vaccines: WHO position paper [WHO, 2011].
** [GlaxoSmithKline Biologicals Clinical Study Report Amendment 1 - 106369 (MALARIA-050)].

10.5. Cohorts for analyses

10.5.1. Total vaccinated cohort

The total vaccinated cohort (TVC) will include all subjects who received treatment (i.e. receiving at least one dose of study vaccine or Vitamin A). The TVC analysis will be performed per treatment actually administered.

10.5.2. According-to-protocol cohort for analysis of immunogenicity (ATP immunogenicity)

The ATP cohort 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.

10.6. Derived and transformed data

- A subject seropositive for anti-CS antibody will be a subject whose antibody titer will be greater than or equal to the cut-off value (anti-CS ≥ 0.5 EU/ml).

- Seroprotection rate for anti-HBs antibody is defined as the percentage of subjects with antibody titers greater than or equal to an established cut-off (anti-HBs ≥ 10 mIU/ml).
- Seroconversion rates for anti-Me is defined as children with an anti-Me pre-vaccination titer below 150 mIU/ml and a post-vaccination titer ≥ 150 mIU/ml.
- Seroconversion rates for anti-Ru is defined as children with an anti-Ru pre-vaccination titer below 4 IU/ml and a post-vaccination titer ≥ 4 IU/ml.
- A subject seropositive for anti-YF antibody will be a subject whose antibody titer 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 GMT calculations will be performed by taking the anti-log of the mean of the log transformations (base 10). Antibody titers below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMT calculation. All available immunogenicity data will be analyzed. Missing data will not be imputed.

10.7. Analysis of demographics

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

The mean age at first vaccination (in months) (plus range and standard deviation) of the vaccinated subjects, as a whole, and per group, will be calculated.

10.8. Analysis of immunogenicity

The primary analysis will be based on the ATP cohort 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 titers ≥ 0.5 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 titers will be summarized by GMT with 95% CI. Antibody titers 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 titers will be summarized by GMT with 95% CI. Anti-HBs titers 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 titers will be summarized by GMT with 95% CI. Anti-Ru and anti-Me titers 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 titers will be summarized by GMT with 95% CI. Anti-YF titers 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.

10.9. Analysis of safety

The primary analysis will be based on the TVC.

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 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.

The proportion of subjects reporting an SAE (all, fatal, related) occurring within 30 days (day of vaccination and 29 subsequent days) after each dose of study vaccines, 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 15 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.

10.10. Interpretation of analyses

Except for analyses on objectives with a pre-defined success criterion (see Section 2), comparative analyses will be descriptive with the aim to characterize the difference in immunogenicity and safety between groups.

10.11. Conduct of analyses

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

10.11.1. Sequence of analyses

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.

All analyses will be conducted on data as clean as possible.

10.11.2. Statistical considerations for interim analyses

No interim analyses are planned.

11. ADMINISTRATIVE MATTERS

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality and publications must be fulfilled.

11.1. electronic Case Report Form instructions

A validated GSK defined electronic data collection tool will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

11.2. Study Monitoring by GSK Biologicals

GSK will monitor the study to verify that, amongst others, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform an eCRF review and a Source Document Verification (SDV). By SDV we understand verifying eCRF entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the eCRF. This document should be completed and signed by the site monitor and investigator and should be filed in the monitor's and investigator's study file. Any data item for which the eCRF will serve as the source must be identified, agreed and documented in the source documentation agreement form.

For eCRF, the monitor freezes completed and approved screens at each visit.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

11.3. Record retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible, when needed (e.g. audit or inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g. microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for making these reproductions.

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP, any institutional requirements, applicable laws or regulations, or GSK standards/procedures.

The investigator/institution must notify GSK of any changes in the archival arrangements, including, but not limited to archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

11.4. Quality assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

11.5. Posting of information on publicly available clinical trial registers and publication policy

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

Summaries of the results of GSK interventional studies (phase I-IV) are posted on publicly available results registers within 6 months of the primary completion date for studies of authorized vaccines and 18 months for studies of non-authorized vaccines.

GSK also aims to publish the results of these studies in the searchable, peer reviewed scientific literature. Manuscripts are submitted for publication within 24 months of the last subject's last visit. At the time of publication, this protocol will be fully disclosed.

11.6. Provision of study results to investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK Biologicals will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

12. COUNTRY SPECIFIC REQUIREMENTS

Not applicable.

13. REFERENCES

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APPENDIX A LABORATORY ASSAYS

Blood for analysis of humoral immune response will be obtained at timepoints listed in Table 8. After centrifugation, serum samples should be kept at -20°C/-4°F until shipment.

Antibody titers against the CS repeat region

Antibody levels against *P. falciparum* CS-repeat region will be measured at CEVAC by a standard ELISA methodology using plate adsorbed recombinant R32LR antigen, as described by Clement [Clement, 2012]. Anti-CS antibody titers will be determined relative to a standard reference antibody as a control according to standard operating procedures from the laboratory. The cut-off for the assay is 0.5 EU/ml. Results will be reported in EU/ml.

Antibody titers against the HB antigen

Anti-HBs antibody titers will be determined using commercially available CLIA kits ADVIA® Centaur anti-HBs2 manufactured by Siemens Healthcare. The cut-off for the assay is 6.2 mIU/ml. Results will be reported in mIU/ml.

Antibody titers against the catalase antigen

Anti-catalase antibody concentrations will be determined using in house ELISA. The cut-off for the assay is 65 ng/ml. Results will be reported in ng/ml.

Antibody titers against the measles antigen

Anti-measles antibody titers will be determined using commercially available ELISA kits Enzygnost™ manufactured by Dade Behring. The cut-off for the assay is 150 mIU/ml. Results will be reported in mIU/ml.

Antibody titers against the rubella antigen

Anti-rubella antibody titers will be determined using commercially available ELISA kits Enzygnost™ manufactured by Dade Behring. The cut-off for the assay is 4 IU/ml. Results will be reported in IU/ml.

Antibody titers against the YF antigen

Antibody levels against YF will be measured by a neutralization assay [Osei-Kwasi, 2001]. The cut-off for the assay is 10 ED50. Results will be reported in ED50.

SAFETY LABORATORY TESTING: CLS South Africa (Amended 09 August 2016)

Cerebrospinal fluid (CSF) for meningitis testing

The recommended method for evaluation of meningitis will be through CSF analysis. The minimum acceptable volume for CSF should be 500 µl.

All CSF samples for suspected meningitis cases will be sent to CLS South Africa for CSF polymerase chain reaction (PCR) testing for selected common aetiological pathogens of meningitis as listed below.

- ***CSF: PCR testing***

	TEST
Bacteria	*Haemophilus influenzae*
	Streptococcus pneumoniae
	Neisseria meningitidis
	Salmonella enterica
	Mytobacterium tuberculosis
Viruses	*Adenovirus*
	Cytomegalovirus
	Enterovirus
	Epstein Bar virus
	Herpes simplex virus 1 & 2
	HHV 6
	Rabies
	Mumps virus
Parasite	*Plasmodium spp*

The following additional tests are available at CLS South Africa and can be requested by the treating clinician if required.

- ***CSF: Other possible PCR testing***

	TEST
Bacteria	*Borrelia burgdorferi**
	*Brucella spp.**
	*Coxiella burnetii**
	*Ehrlichia spp**
	*Leptospira spp**
	*Rickettsia spp **
Viruses	*Chikungunya**
	*Crimean-Congo haemorrhagic fever virus**
	*Dengue virus**
	*Flavivirus genus**
	*Hepatitis A virus**
	*Hepatitis B virus **
	*JC virus **
	*Measles virus **
	*Rift valley fever virus**
	*Sindbis virus**
	*Rubella virus**
	*Varicella zoster virus**
	*West Nile virus**
Parasite	*Toxoplasmosis*

**These tests are performed in a multiplex PCR.*

An additional blood sample of approximately 5 ml whole blood may be taken at the discretion of the treating clinician to aid in the diagnosis of meningitis through serum PCR or serum serology. The following tests will be available at CLS South Africa, if not available locally.

- ***Serum: PCR***

	TEST
Viruses	*Cytomegalovirus*
	Enterovirus
	Haemophilus Influenza
	Varicella
Parasite	*Toxoplasmosis*

- ***Serum: Serology***

	TEST
Bacteria	*Beta haemolytic streptococcus*
	Mycoplasma pneumoniae
	Streptococcus pneumoniae
Viruses	*CMV IgG & IgM*
	Epstein-Barr virus
	HSV IgG
	HSV IgM
	Measles IgG/IgM
	Mumps IgG/IgM
	Rabies IgG/IgM
	VZV IgG/IgM
Parasites	*Cryptococcus*

Analysis of potential Immune-Mediated Diseases (pIMDs)

The medical and scientific judgement of the investigator is required in deciding whether other disorders not mentioned in the list of pIMDs have enough evidence of an autoimmune origin.

A volume of approximately 5 ml of whole blood will be required for testing. A list of potential serum autoimmune tests that can be performed at CLS South Africa is provided below.

- ***Serum: Autoimmune tests***

TEST
*Anti-insulin autoantibodies (IA2)**
Anti-glutamic acid decarboxylase autoantibodies (anti-GAD65)
Anti-Tyrosine phosphatase-like IA2 antibodies
Anti-islet cell antibodies
Anti-smooth muscle antibodies (ASMA)
Anti-liver-kidney microsomal antibodies (anti-LKM)
Anti-soluble liver antigens (anti-SLA)
Anti-mitochondrial antibodies (AMA)
Anti-nuclear antibodies (ANA)
Anti-double stranded DNA (anti-dsDNA)
Rheumatoid factor (RF)
Anti-Glomerular Basement Membrane antibodies (anti-GBM)
Anti-neutrophil cytoplasmic autoantibodies (ANCAs)
Anti-streptolysin O / Anti-DNAse
Serum C3, C4 complement
Anti-cyclic citrullinated peptide antibodies (anti-CCP)
Anti-skin basement membrane protein
IgA endomysial antibodies
Anticardiolipin (ELISA) IgM, IgG
Anti-beta 2 glycoprotein I
Anti-prothrombin

Measles/Rubella confirmatory testing

Confirmatory testing for measles and rubella may be required for suspected cases. A volume of approximately 5 ml of whole blood will be required for confirmatory serology to be sent to CLS South Africa.

APPENDIX B CLINICAL LABORATORIES

Table 20 GSK Biologicals' laboratories (Amended: 09 August 2016)

Laboratory	Address
GSK Biologicals ***Clinical Laboratory Sciences***, Rixensart	Biospecimen Reception - B7/44 Rue de l'Institut, 89 - B-1330 Rixensart - Belgium
GSK Biologicals ***Clinical Laboratory Sciences***, Wavre-Nord Noir Epine	Avenue Fleming, 20 - B-1300 Wavre - Belgium

Table 21 Outsourced laboratories

Laboratory	Address
Focus Diagnostics, Inc.	5785 Corporate Avenue Cypress, CA 90630 USA
CEVAC - University of Gent	De Pintelaan, 185 Gent Belgium
NEOMED-LABS Inc	***525 Cartier blvd West-Laval- Quebec Canada- H7V 3S8***
Clinical Laboratory Sciences (CLS South Africa)	***4th Floor Spencer Lister Building Corner of Hospital and de Korte Streets Braamfontein Johannesburg 2000, South Africa***

APPENDIX C AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals SA Vaccines R &D **Protocol Amendment 1**	
eTrack study number and Abbreviated Title	200596 (MALARIA-073)
Amendment number:	Amendment 1
Amendment date:	09 August 2016
Co-ordinating author:	PPD Scientific Writer

Rationale/background for changes:
The protocol was amended for the following reasons:

- The volumes of whole blood collected from subjects were considered insufficient. To ensure that an adequate blood volume is obtained for the analysis, the volumes of whole blood to be collected specified in the protocol were increased to take into account the dead volume due to aliquoting, and also to enable repeat testing of samples in case of invalid results.
- It has been clarified that confirmatory testing for any subject showing clinical presentations compatible with yellow fever, rubella or measles will be performed only to identify cases of vaccine failure.
- Clarification about the eCRF pages required to be filled in for pIMDs and seizures was provided.
- The names and address of the laboratories performing the biological assays and study personnel at GSK were updated. Details of the safety lab tests were also added.
- The Ghana FDA requested that screening and vaccination should not be performed on the same day, so the screening will be performed up until one day before vaccination (Day -28 to Day -1).

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

Contributing authors: The list of contributing authors was updated.

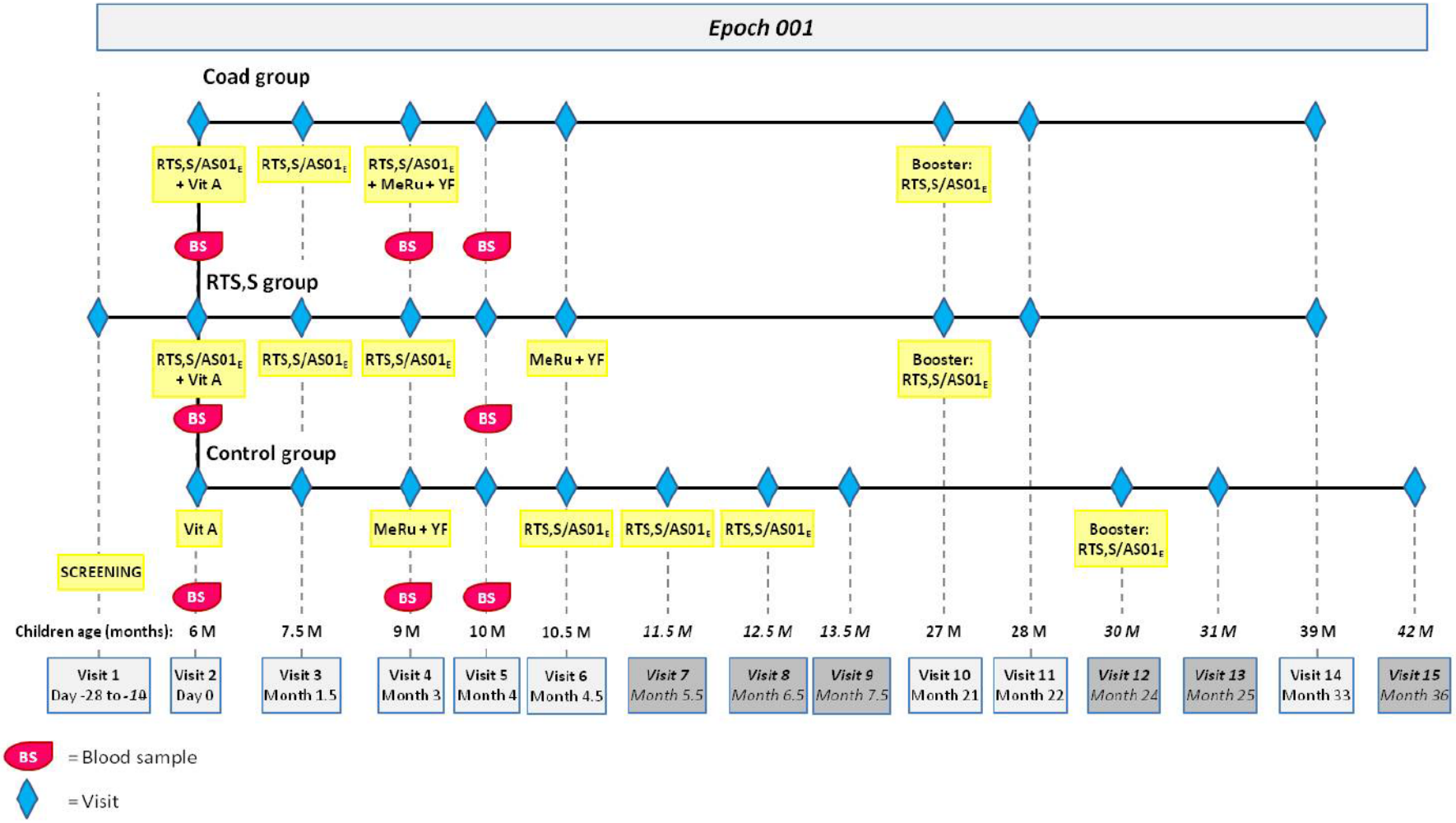
- PPD (Study Delivery Leads~~; Novellas Healthcare contractor for GSK Biologicals~~)
- PPD (Clinical ***Readout Team Leader*** ~~Immunology representative~~***)***
- PPD ***(Clinical Laboratory Sciences Senior Lab Study Manager)***
- PPD (Study Data Managers; TCS contractor for GSK Biologicals)
- PPD (Project Data Managers)

- PPD *(Clinical Research and Development Lead)*

List of abbreviations: The list was updated:

CLS:	***Clinical Laboratory Sciences***
~~GVCL:~~	~~Global Vaccine Clinical Laboratories~~

Figure 1: Study Design: The figure was updated.



Tables 4, 5 and 6: List of study procedures

The following changes were made:

Type of contact	Visit 1 (Screening)*
Timepoints	Day -28 to ~~0~~*-1*

† Confirmatory serology tests should be performed to identify ~~pre-exposure which may lead to elimination from According-to-Protocol (ATP) or~~ cases of vaccine failure.

Table 7: Intervals between study visits

The following changes were made:

Study visit	Timing of visit[a]	Allowed interval[b]
Visit 1 (Screening)[c]	~~0~~*1*-28 days before Visit 2	-

~~[c] Visit 1 (Screening visit) can occur on the same day as Visit 2 (Day 0).~~

Section 5.6.12.1: Blood sampling for anti-HBs and anti-CS immune response assessments

A volume of at least ~~1.0~~*1.2* ml of whole blood (to provide at least ~~50~~ ***500*** µl of serum for anti-CS and ~~at least 250 µl of serum for~~ anti-HBs) should be drawn from all subjects from the **Coad group** and the **RTS,S group** for each analysis of humoral immune response at each pre-defined timepoint.

Section 5.6.12.2: Blood sampling for anti-catalase immune response assessments

A volume of at least ~~500~~ ***600*** µl of whole blood (to provide at least ~~150~~ ***250*** µl of serum) should be drawn from all subjects from the **Coad** and the **Control groups** for analysis of anti-catalase immune response at each pre-defined timepoint.

Section 5.6.12.3: Blood sampling for anti-Me and anti-Ru immune response assessments

A volume of at least ~~500 µl~~***600 µl*** of whole blood (to provide at least ***250*** µl of serum for anti-Me and anti-Ru) should be drawn from all subjects from the **Coad group** and the **Control group** for each analysis of humoral immune response at each pre-defined timepoint.

Section 5.6.12.4: Blood sampling for anti-YF immune response assessments

A volume of at least ***600*** ~~750~~µl of whole blood (to provide at least 250 µl of serum for anti-YF) should be drawn from all subjects from the **Coad group** and the **Control group** for each analysis of humoral immune response at each pre-defined timepoint.

Table 8: Biological Samples

Timepoint	Group	Sample type	Quantity	Unit
Visit 2 (Day 0)	Coad group	Blood	~~1.5~~*1.8*	ml
	RTS,S group	Blood	~~1.0~~*1.2*	ml
	Control group	Blood	~~0.5~~*0.6*	ml
Visit 4 (Month 3)	Coad group	Blood	~~0.5~~*0.6*	ml
	Control group	Blood	~~0.5~~*0.6*	ml
Visit 5 (Month 4)	Coad group	Blood	~~2.75~~*3.5*	ml
	RTS,S group	Blood	~~1.0~~*1.2*	ml
	Control group	Blood	~~1.75~~*1.8*	ml

Table 9: Humoral Immunity (Antibody determination)

*GSK Biologicals laboratory refers to the ~~Global Vaccines Clinical Laboratories~~***Clinical Laboratory Sciences** (***CLS~~GVCL~~***) in Rixensart, Belgium; Wavre, Belgium; ~~Laval, Canada~~***NEOMED- LABS Inc, Canada.**

Section 6.8: Capture of cases of measles and rubella

During the course of the study, any clinical presentation compatible with measles, rubella or YF will be captured as AE or SAE as appropriate and confirmatory serology tests should be performed to identify ~~pre-exposure which may lead to elimination from ATP or~~ cases of vaccine failure.

Section 8.1.5.2: Seizures within 30 or 42 days of vaccination

All seizures occurring within 30 days of vaccination for vaccine doses administered at 6 and 7.5 months of age (Visits 2 and 3) and within 42 days for vaccine doses administered at 9 months of age (Visit 4) will be reported as SAEs and in ***specific eCRF screens*** ~~appropriate targeted follow-up forms included in the eCRF~~.

Section 8.1.5.3: Meningitis:

For the further evaluation of the safety signal of meningitis all the cases occurring during the study will be reported as SAE and medical documentation of the events will be reported in ***specific eCRF screens*** ~~appropriate targeted follow-up forms included in the eCRF~~. Cerebrospinal fluid will be frozen for future testing for infectious agents if applicable (this procedure is fully described in the SPM).

Section 8.3.4: Reporting of AEs of specific interest to GSK Biologicals

Once an AEs of specific interest (pIMDs, meningitis and seizure within 30 or 42 days of vaccination) is diagnosed in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS after he/she becomes aware of the diagnosis. The report allows to specify that the event is a pIMD. The report will always be completed as thoroughly as possible with all available details of the event, in accordance with the ***pIMD*** ~~AEs of specific interest~~ standard questionnaire provided.

Table 16: 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 ~~01~~	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]													

Appendix A: Laboratory assays: The following information has been added.

SAFETY LABORATORY TESTING: CLS South Africa

Cerebrospinal fluid (CSF) for meningitis testing

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	Cytomegalovirus
	Enterovirus
	Epstein Bar virus
	Herpes simplex virus 1 & 2
	HHV 6
	Rabies
	Mumps virus
Parasite	*Plasmodium spp*

The following additional tests are available at CLS South Africa and can be requested by the treating clinician if required.

- ***CSF: Other possible PCR testing***

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	*Brucella spp.**
	*Coxiella burnetii**
	*Ehrlichia spp**
	*Leptospira spp**
	*Rickettsia spp **
Viruses	*Chikungunya**
	*Crimean-Congo haemorrhagic fever virus**
	*Dengue virus**
	*Flavivirus genus**
	*Hepatitis A virus**
	*Hepatitis B virus **
	*JC virus **
	*Measles virus **
	*Rift valley fever virus**
	*Sindbis virus**
	*Rubella virus**
	*Varicella zoster virus**
	*West Nile virus**
Parasite	*Toxoplasmosis*

** These tests are performed in a multiplex PCR.*

An additional blood sample of approximately 5 ml whole blood may be taken at the discretion of the treating clinician to aid in the diagnosis of meningitis through serum PCR or serum serology. The following tests will be available at CLS South Africa, if not available locally.

- ***Serum: PCR***

	TEST
Viruses	*Cytomegalovirus*
	Enterovirus
	Haemophilus Influenza
	Varicella
Parasite	*Toxoplasmosis*

- ***Serum: Serology***

	TEST
Bacteria	*Beta haemolytic streptococcus*
	Mycoplasma pneumoniae
	Streptococcus pneumoniae
Viruses	*CMV IgG & IgM*
	Epstein-Barr virus
	HSV IgG
	HSV IgM
	Measles IgG/IgM
	Mumps IgG/IgM
	Rabies IgG/IgM
	VZV IgG/IgM
Parasites	*Cryptococcus*

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*Anti-insulin autoantibodies (IA2)**
Anti-glutamic acid decarboxylase autoantibodies (anti-GAD65)
Anti-Tyrosine phosphatase-like IA2 antibodies
Anti-islet cell antibodies
Anti-smooth muscle antibodies (ASMA)
Anti-liver-kidney microsomal antibodies (anti-LKM)
Anti-soluble liver antigens (anti-SLA)
Anti-mitochondrial antibodies (AMA)
Anti-nuclear antibodies (ANA)
Anti-double stranded DNA (anti-dsDNA)
Rheumatoid factor (RF)
Anti-Glomerular Basement Membrane antibodies (anti-GBM)
Anti-neutrophil cytoplasmic autoantibodies (ANCAs)
Anti-streptolysin O / Anti-DNAse
Serum C3, C4 complement
Anti-cyclic citrullinated peptide antibodies (anti-CCP)
Anti-skin basement membrane protein
IgA endomysial antibodies
Anticardiolipin (ELISA) IgM, IgG
Anti-beta 2 glycoprotein I
Anti-prothrombin

Measles/Rubella confirmatory testing

Confirmatory testing for measles and rubella may be required for suspected cases. A volume of approximately 5 ml of whole blood will be required for confirmatory serology to be sent to CLS South Africa.

Table 20: GSK Biologicals' laboratories

Laboratory	Address
GSK Biologicals ***Clinical Laboratory Sciences*** ~~Global Vaccine Clinical Laboratory~~, Rixensart	Biospecimen Reception - B7/44 Rue de l'Institut, 89 - B-1330 Rixensart - Belgium
~~GSK Biologicals Global Vaccine Clinical Laboratory, North America- Laval~~	~~Biospecimen Reception - Clinical Serology~~ ~~525 Cartier blvd West - Lavala - Quebec - Canada - H7V 3S8~~
GSK Biologicals ***Clinical Laboratory Sciences*** ~~Global Vaccine Clinical Laboratory~~, Wavre-Nord Noir Epine	Avenue Fleming, 20 - B-1300 Wavre - Belgium

Table 21: Outsourced laboratories

Laboratory	Address
Focus Diagnostics, Inc.	5785 Corporate Avenue Cypress, CA 90630 USA
CEVAC - University of Gent	De Pintelaan, 185 Gent Belgium
NEOMED-LABS Inc	***525 Cartier blvd West-Laval- Quebec Canada- H7V 3S8***
Clinical Laboratory Sciences (CLS South Africa)	***4th Floor Spencer Lister Building Corner of Hospital and de Korte Streets Braamfontein Johannesburg 2000, South Africa***

Protocol Sponsor Signatory Approval

eTrack study number and Abbreviated Title	200596 (MALARIA-073)
Date of protocol	Final Version 1: 03 June 2015
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.
Sponsor signatory	Didier Lapierre Vice President, Clinical Development Malaria, TB & Adjuvant support GlaxoSmithKline Biologicals PPD
Signature	PPD
Date	June 9th, 2015

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