Clinical Study Protocol

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

Primary Study vaccines	• GlaxoSmithKline (GSK) Biologicals' candidate *Plasmodium falciparum* malaria vaccine RTS,S/AS01$_E$ (SB257049).
Other Study vaccines	• Purified Vero cell culture rabies vaccine (Sanofi Pasteur). • GSK Biologicals' DTPwHepB/Hib vaccine: Tritanrix HepB™/Hib. • GSK Biologicals' oral polio vaccine: Polio Sabin™. • Meningococcal C conjugate vaccine: Menjugate™ (Novartis).
eTrack study number and Abbreviated Title	200599 (MALARIA-076)
Date of protocol	Final Version 1: 15 July 2013
Date of protocol amendment	Amendment 1 Final: 18 February 2014 Amendment 2 Final: 15 April 2015
Title	Extension to study MALARIA-055 PRI (110021) for evaluation of long-term efficacy, safety and immunogenicity of GSK Biologicals'candidate malaria vaccine (SB257049) in infants and children in Africa
Detailed Title	An open extension to the phase III, multi-center study MALARIA-055 PRI (110021) to evaluate long-term efficacy, safety and immunogenicity of the RTS,S/AS01$_E$ candidate vaccine against malaria disease caused by *Plasmodium falciparum* in infants and children in Africa
Co-ordinating author	PPD (Scientific Writer, Keyrus Biopharma consultant for GSK Biologicals)

eTrack study number and Abbreviated Title	200599 (MALARIA-076)
Detailed Title	An open extension to the phase III, multi-center study MALARIA-055 PRI (110021) to evaluate long-term efficacy, safety and immunogenicity of the RTS,S/AS01$_E$ candidate vaccine against malaria disease caused by *Plasmodium falciparum* in infants and children in Africa
Contributing authors	• PPD (Clinical Research and Development Lead) • PPD (Lead Statistician) • PPD (Study Delivery Manager) • PPD (Study Delivery Manager, SynteractHCR consultant for GSK Biologicals) • PPD ***(Study Delivery Manager)*** • PPD ***(Local Delivery Lead)*** • PPD (Study Delivery Lead, Novellas Healthcare consultant for GSK Biologicals) • PPD (Clinical Regulatory Affairs representative) • PPD (Clinical Immunology representative) • PPD (Clinical Safety representative) • PPD (Safety and Pharmacovigilance) • PPD ***(Project Data Manager)*** • PPD (Study Data Manager) • PPD (Vice President, Clinical Development Malaria, TB & Adjuvant support) • PPD (Director, Biometrics)

(Amended 15 April 2015)

GSK Biologicals' Protocol DS v 14.0

Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	200599 (MALARIA-076)
Date of protocol amendment	Amendment 2 Final: 15 April 2015
Detailed Title	An open extension to the phase III, multi-center study MALARIA-055 PRI (110021) to evaluate long-term efficacy, safety and immunogenicity of the RTS,S/AS01$_E$ candidate vaccine against malaria disease caused by *Plasmodium falciparum* in infants and children in Africa
Sponsor signatory	Didier Lapierre (Vice President, Clinical Development Malaria, TB & Adjuvant support)
Signature	
Date	

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Protocol Amendment 2 Rationale

Amendment number: Amendment 2
Rationale/background for changes: In order to maximize and harmonize the clinical information available during the gap period the following information will be documented retrospectively and prospectively in the eCRF: • Results of clinical diagnoses of malaria. • Rapid diagnostic test (RDT). • Blood slides read to guide treatment at the time of presentation. In Appendix E, text describing "Determination of parasitemia" was removed because "Determination of *Plasmodium falciparum* asexual parasite density" is detailed in Appendix C.

Protocol Amendment 2 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 vaccine(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	200599 (MALARIA-076)
Date of protocol amendment	Amendment 2 Final: 15 April 2015
Detailed Title	An open extension to the phase III, multi-center study MALARIA-055 PRI (110021) to evaluate long-term efficacy, safety and immunogenicity of the RTS,S/AS01$_E$ candidate vaccine against malaria disease caused by *Plasmodium falciparum* in infants and children in 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 9.3.2.

SYNOPSIS

Detailed Title	An open extension to the phase III, multi-center study MALARIA-055 PRI (110021) to evaluate long-term efficacy, safety and immunogenicity of the RTS,S/AS01$_E$ candidate vaccine against malaria disease caused by *Plasmodium falciparum* in infants and children in Africa
Indication	Primary immunization against malaria disease caused by *Plasmodium falciparum* in infants and children.
Rationale for the study and study design	It is possible that vaccination with RTS,S/AS01$_E$ in infancy and early childhood may affect the rate of acquisition of natural immunity to malaria and there is a concern that vaccinees would have enhanced susceptibility to malaria relative to unvaccinated children of the same age. We intend to conduct long-term surveillance for malaria disease in participants to randomized controlled trial of RTS,S/AS01$_E$. We will describe the patterns of clinical and severe forms in the long-term under different conditions of transmission. In total we will provide in children aged 5-17 months at first vaccination, approximately 7 years of follow-up post-Dose 1 (mean: 85 months; range: 77-91 months), and in infants aged 6-12 weeks at first vaccination, 6 years of follow-up post-Dose 1 (mean: 77 months; range: 68-84 months).
Objectives	**Primary** • To describe the incidence of severe malaria in the long-term over a 3-year period (from January 2014 to December 2016) of follow-up pooled across transmission settings, in both age categories. – In children enrolled in the 5-17 months age category, starting on average 4 years post primary vaccination. – In children enrolled in the 6-12 weeks age category, starting on average 3.5 years post primary vaccination. **Secondary efficacy objectives** *In each age category (i.e. 5-17 months and 6-12 weeks) over 3 years of follow-up (from January 2014 to December 2016):* • To describe the incidence of clinical malaria in recipients of the RTS,S/AS01$_E$ candidate malaria vaccine and in controls. • To describe the incidence of hospitalization due to

malaria in recipients of the RTS,S/AS01$_E$ candidate malaria vaccine and in controls.

- To describe the prevalence of malaria infection at annual cross sectional timepoints in recipients of the RTS,S/AS01$_E$ candidate malaria vaccine and in controls.
- To describe the hemoglobin level and the prevalence of anemia at annual cross sectional timepoints in recipients of the RTS,S/AS01$_E$ candidate malaria vaccine and in controls.

In each age category since the start of the primary study (MALARIA-055 PRI [110021]) until December 2016:

- To describe the incidence of severe malaria in recipients of the RTS,S/AS01$_E$ candidate malaria vaccine and in controls.
- To describe the incidence of clinical malaria in recipients of the RTS,S/AS01$_E$ candidate malaria vaccine and in controls.
- To describe the incidence of hospitalization due to malaria in recipients of the RTS,S/AS01$_E$ candidate malaria vaccine and in controls.

Secondary safety objective

- To describe the incidence of the following reported serious adverse events (SAEs): fatalities, related SAEs (related to vaccine administration in the primary study MALARIA-055 PRI [110021] and to study participation), malaria hospitalization, potential Immune-Mediated Disease (pIMDs), and meningitis from January 2014 to December 2016.

Secondary immunogenicity objective

- To describe anti-circumsporozoite protein of *Plasmodium falciparum* (anti-CS) antibodies response over the 3-year follow-up period, in each age category.

Study design

- Experimental design: extension to the phase III, randomized, controlled, multi-centric study MALARIA-055 PRI (110021) that comprised 3 parallel groups
- Duration of the study: approximately 3 years
  - Epoch 001: starting at Visit 39, including and ending at Visit 41 (December 2014).
  - Epoch 002: starting at Visit 42, including and ending

at Visit 43 (December 2015).

– Epoch 003: starting at Visit 44, including and ending at Visit 45 (December 2016).

- Study groups: same study groups as in the primary study MALARIA-055 PRI (110021). Subjects enrolled in each of the 2 age categories (5-17 months and 6-12 weeks at first vaccination) were randomized in 3 study groups:
  – R3C: infants/children randomized to receive 3 doses of RTS,S/AS01$_E$ on a 0-, 1-, 2-month schedule with a dose of comparator vaccine at Month 20 during the primary study MALARIA-055 PRI (110021).
  – R3R: infants/children randomized to receive 3 doses of RTS,S/AS01$_E$ on a 0-, 1-, 2-month schedule with an RTS,S/AS01$_E$ booster dose at Month 20 during the primary study MALARIA-055 PRI (110021).
  – C3C: infants/children randomized to receive 3 doses of a comparator vaccine on a 0-, 1-, 2-month schedule with a dose of comparator vaccine at Month 20 during the primary study MALARIA-055 PRI (110021).

Synopsis Table 1 Study groups and epochs foreseen in the study

Study groups	Estimated number of subjects	Age (Min/Max)	Epochs		
			Epoch 001	Epoch 002	Epoch 003
R3C	600	6 weeks - 12 weeks*	x	x	x
	600	5 months -17 months*	x	x	x
R3R	600	6 weeks - 12 weeks*	x	x	x
	600	5 months -17 months*	x	x	x
C3C	600	6 weeks - 12 weeks*	x	x	x
	600	5 months -17 months*	x	x	x

R3C: RTS,S/AS01$_E$: primary schedule without booster
R3R: RTS,S/AS01$_E$: primary schedule with booster
C3C: controls
* Age at first vaccination in the primary study MALARIA-055 PRI (110021).

- Control: active comparator administered in the primary study MALARIA-055 PRI (110021; rabies vaccine in the 5-17 months age category and Meningococcal C conjugate vaccine in the 6-12 weeks age category).
- Vaccination schedule: not applicable, all vaccinations were performed in the primary study MALARIA-055 PRI (110021).
- Treatment allocation: follow-up of a randomized study (Randomization performed in the primary study MALARIA-055 PRI will be kept for this extension.

Subjects will remain in the same group as the one of the primary study MALARIA-055 PRI [110021]).

- Blinding: open

Synopsis Table 2 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	open
Epoch 002	open
Epoch 003	open

- Sampling schedule: blood samples will be taken at annual intervals during the extension (maximum 3 blood samples).
- Type of study: extension of other protocol(s) (MALARIA-055 PRI [110021]). Data of the MALARIA-076 study will be analyzed with those of the primary study MALARIA-055 PRI [110021]). Endpoints of the MALARIA-076 study are pooled with those of the primary study.
- Data collection: electronic Case Report Form (eCRF).

Case definition

Clinical malaria

Synopsis Table 3 Case definition for clinical malaria

1° definition	*Plasmodium falciparum* asexual parasitemia > 5000 parasites/μL **AND** presence of fever (axillary temperature ≥ 37.5°C) at the time of presentation **AND** occurring in a child who is unwell and brought for treatment to a healthcare facility **OR** A case of malaria meeting the primary case definition of severe malaria (refer to Synopsis Table 4)
2° definition 1	*Plasmodium falciparum* asexual parasitemia > 0 **AND** presence of fever (axillary temperature ≥ 37.5°C) at the time of presentation or history of fever within 24 hours of presentation **AND** occurring in a child who is unwell and brought for treatment to a healthcare facility
2° definition 2	*Plasmodium falciparum* asexual parasitemia > 500 parasites/μL **AND** presence of fever (axillary temperature ≥ 37.5°C) at the time of presentation **AND** occurring in a child who is unwell and brought for treatment to a healthcare facility
2° definition 3	*Plasmodium falciparum* asexual parasitemia > 20 000 parasites/μL **AND** presence of fever (axillary temperature ≥ 37.5°C) at the time of presentation **AND** occurring in a child who is unwell and brought for treatment to a healthcare facility

Severe malaria

Severe malaria will be diagnosed based on symptoms and signs occurring at presentation or developing during admission according to the case definitions below.

Synopsis Table 4 Primary case definition for severe malaria

Plasmodium falciparum asexual parasitemia > 5000 parasites/μL	
AND with one or more marker of disease severity:	- Prostration. - Respiratory distress. - Blantyre score ≤ 2. - Seizures 2 or more. - Hypoglycemia < 2.2 mmol/L. - Acidosis BE ≤ -10.0 mmol/L. - Lactate ≥ 5.0 mmol/L. - Anemia < 5.0 g/dL.
AND without diagnosis of co-morbidity:	- Radiographically proven pneumonia. - Meningitis on cerebrospinal fluid (CSF) examination. - Positive blood culture. - Gastroenteritis with dehydration.

Prostration is defined as, in an acutely sick child, the inability to perform previously-acquired motor function: in a child previously able to stand, inability to stand; in a child previously able to sit, inability to sit and in a very young child, inability to suck.
Respiratory distress is defined as lower chest wall indrawing or abnormally deep breathing.
2 or more seizures occurring in the total time period including 24 h prior to admission to the emergency room and the hospitalization.
Radiographically proven pneumonia is a consolidation or pleural effusion as defined by World Health Organization [WHO; 2001a] on a chest x-ray (CXR) taken within 72 h of admission.
Meningitis on CSF examination is defined as white cells ≥ 50 x 10^6/L or positive culture of compatible organism or latex agglutination positive for *Haemophilus influenzae* type b, pneumococci or meningococci [Berkley, 2001].
Positive blood culture as defined by WHO [WHO, 1999] on a blood culture taken within 72 h of admission.
Gastroenteritis with dehydration is defined as a history of 3 or more loose or watery stools in previous 24 h and an observed watery stool with decreased skin turgor (> 2 seconds for skin to return following skin pinch).

Secondary case definitions of severe malaria are given below.

Synopsis Table 5 Secondary case definition for severe malaria

2° definition 1	*Plasmodium falciparum* asexual parasitemia > 5000 parasites/μL
"with co-morbidity"	**AND** with one or more marker(s) of disease severity
2° definition 2	*Plasmodium falciparum* asexual parasitemia > 0
"without a density threshold"	**AND** with one or more marker(s) of disease severity
	AND without diagnosis of a co-morbidity

Malaria hospitalization

Synopsis Table 6 Case definitions for malaria hospitalization

Definition 1	A medical hospitalization with confirmed *Plasmodium falciparum* asexual parasitemia > 5000 parasites/μL (excludes planned admissions for medical investigation/care or elective surgery and trauma)
Definition 2	A hospitalization for which, in the judgment of the principal investigator, *Plasmodium falciparum* infection was the sole or a major contributing factor to the presentation

Prevalent anemia

Synopsis Table 7 Case definitions of prevalent anemia

Prevalent severe anemia	A documented hemoglobin < 5.0 g/dL identified at an annual visit
Prevalent moderate anemia	A documented hemoglobin < 8.0 g/dL identified at an annual visit

Prevalent parasitemia

Synopsis Table 8 Case definitions for prevalent parasitemia

Prevalent parasitemia	A documented *Plasmodium falciparum* asexual parasite density > 0 identified at an annual visit

Number of subjects Approximately 3000 to 4000 children who were vaccinated during the primary study MALARIA-055 PRI (110021) will be enrolled in the MALARIA-076 study.

Endpoints

Primary

- The occurrence of severe malaria meeting the primary case definition analyzed over the time period starting January 2014 until the end of the 3-year follow-up period (Visit 45).

Secondary efficacy endpoints

- The occurrence of clinical malaria meeting the primary and secondary case definitions analyzed over the time period starting January 2014 until the end of the 3-year follow-up period (Visit 45).
- The occurrence of malaria hospitalization meeting each of the case definitions analyzed over the time period starting January 2014 until the end of the 3-year follow-up period (Visit 45).

- The prevalence of parasitemia at 3 annual timepoints (Visit 41, 43 and 45), in both age categories (6-12 weeks and 5-17 months).
- The prevalence of anemia at 3 annual timepoints (Visit 41, 43 and 45), in both age categories (6-12 weeks and 5-17 months).
- The level of hemoglobin at 3 annual timepoints (Visit 41, 43 and 45), in both age categories (6-12 weeks and 5-17 months).
- The occurrence of severe malaria meeting the primary and secondary case definitions analyzed over the time period starting at the beginning of the primary study (MALARIA-055 PRI [110021]; Visit 2) until the end of the follow-up period (Visit 45), in both age categories (6-12 weeks and 5-17 months).
- The occurrence of clinical malaria meeting the primary and secondary case definitions analyzed over the time period starting at the beginning of the primary study (MALARIA-055 PRI [110021]; Visit 2) until the end of the follow-up period (Visit 45), in both age categories (6-12 weeks and 5-17 months).
- The occurrence of malaria hospitalization meeting all case definitions analyzed over the time period starting at the beginning of the primary study (MALARIA-055 PRI [110021]; Visit 2) until the end of the follow-up period (Visit 45), in both age categories (6-12 weeks and 5-17 months).

Secondary safety endpoint

- The occurrence of the following reported SAEs: fatalities, related SAEs (related to vaccine administration in the primary study MALARIA-055 PRI [110021] and to study participation), malaria hospitalization, pIMDs, and meningitis over the time period starting January 2014 until the end of the 3-year follow-up period (Visit 45).

Secondary immunogenicity endpoint

- The annual anti-CS antibody titers (Visit 41, 43 and 45) for children of both age categories (6-12 weeks and 5-17 months).

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LIST OF ABBREVIATIONS

AE:	Adverse event
$AS01_E$:	GSK's proprietary liposome-based Adjuvant System containing MPL and QS21
ATP:	According-to-Protocol
BS:	Blood Sampling
C3C:	Infants/Children randomized to receive 3 doses of a comparator vaccine on a 0-, 1-, 2-month schedule with a dose of comparator vaccine at Month 20 in study MALARIA-055 PRI
CI:	Confidence Interval
CS:	Circumsporozoite protein of *Plasmodium falciparum*
CSF:	Cerebrospinal Fluid
CXR:	Chest X-Ray
eCRF:	electronic Case Report Form
ELISA:	Enzyme-Linked Immunosorbent Assay
EPI:	Expanded Program on Immunization
FWV:	Field Worker Visit
GCP:	Good Clinical Practice
GMT:	Geometric Mean Titers
GSK:	GlaxoSmithKline
HR:	Hazard Ratio
ICF:	Informed Consent Form
ICH:	International Conference on Harmonization
IEC:	Independent Ethics Committee
IR:	Incidence Ratio
IRB:	Institutional Review Board
IRS:	Indoor Residual Spraying

ITT:	Intention-to-Treat
LAR:	Legally Acceptable Representative
LP:	Lumbar Puncture
MedDRA:	Medical Dictionary for Regulatory Activities
MF:	Microscope Factor
MPL:	3-O-desacyl-4'-monophosphoryl lipid A
pIMD:	Potential Immune-Mediated Disease
PT:	Preferred Terms
QS21 (*Quillaja saponaria* 21):	A triterpene glycoside purified from the bark of the soap bark tree, *Quillaja saponaria*
RBC:	Red Blood Cells
RDE:	Remote Data Entry
RDT:	***Rapid diagnostic test***
R3R:	Infants/Children randomized to receive 3 doses of RTS,S/AS01$_E$ on a 0-, 1-, 2-month schedule with an RTS,S/AS01$_E$ booster dose at Month 20 in study MALARIA-055 PRI
R3C:	Infants/Children randomized to receive 3 doses of RTS,S/AS01$_E$ on a 0-, 1-, 2-month schedule with a dose of comparator vaccine at Month 20 in study MALARIA-055 PRI
RR:	Risk Ratio
RTS:	Hybrid protein comprising S (hepatitis B surface antigen) and CS portions
RTS,S:	Particulate antigen, containing both RTS and S (hepatitis B surface antigen) proteins
RTS,S/AS:	GSK Biologicals' candidate *Plasmodium falciparum* malaria vaccine adjuvanted with GSK Biologicals' proprietary Adjuvant Systems
SAE:	Serious Adverse Event
SDV:	Source Document Verification
SPM:	Study Procedures Manual

VE:	Vaccine Efficacy
WBC:	White Blood Cells
WHO:	World Health Organization

(Amended 15 April 2015)

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.
Immunological correlate of protection:	The defined humoral antibody 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.
Passive case detection:	The passive case detection is the detection of malaria disease by self-presentation to health facility in the study area. If there is a history of fever within 24 hours or axillary temperature is ≥ 37.5°C at presentation then a blood slide is taken and examined for parasitemia.
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. Note: Any change that falls under the definition of a protocol amendment (e.g. a change that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.
Randomization:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Serious Adverse Event:	A serious adverse event 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, blood dyscrasias or convulsions that do not result in hospitalization.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Sub-cohort:	A group of subjects for whom specific study procedures are planned as compared to other subjects.
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.
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.

1. INTRODUCTION

1.1. Background

GlaxoSmithKline (GSK) Biologicals is developing the RTS,S/AS01 vaccine for prevention of malaria disease in children 6 to 12 weeks of age in co-administration with Expanded Program on Immunization (EPI) vaccines and in children 5 to 17 months of age. Phase III evaluation of the vaccine is ongoing.

Study MALARIA-055 PRI (110021) is a phase III, randomized, controlled, double-blind study conducted in 11 centers in 7 African countries with a range of malaria transmission intensities to support licensure. Approximately 9000 children 5 – 17 months of age and 6000 infants 6 - 12 weeks have been enrolled. This study has reported the co-primary endpoints of efficacy to one year of follow-up post-Dose 3. In children 5–17 months of age at first vaccination, the vaccine efficacy (VE) was 55.8% (97.5% confidence interval [CI]: 50.6 to 60.4) and in infants aged 6-12 weeks in EPI co-administration VE was 31.3% (97.5% CI: 23.6 to 38.3). All children enrolled in MALARIA-055 PRI are under continuous surveillance for efficacy, immunogenicity and safety until December 2013.

In parallel to the phase III evaluation, long-term follow-up of a phase II study was ongoing. This study examined children 5 to 17 months of age who were randomized to receive RTS,S/AS01$_E$ or control (MALARIA-059 [112902]). These children have now been followed for more than 5 years. Clinical malaria incidence in the 5th year of follow-up was 1.4-fold higher in the vaccinees (95% CI: 0.97-2.04, p = 0.07) than in the control group. The number of cases averted over the 5-year follow-up period was approximately 55/100 children vaccinated. In the control group the incidence was 0.7 to 1 cases per child per year. This corresponds to a moderate to high transmission setting and it is an unexpected finding that incidence is rising in the controls in sequential years as the children age. These data suggested a waning efficacy over time up to 4 years and then in the 5th year an apparent reversal of disease incidence [Olotu, 2013].

This reversal of incidence may be due to a slower buildup of natural immunity to malaria in the vaccine recipients compared to controls. Theoretically, children who receive an intervention, may not develop natural immunity through exposure to infection. As a consequence when the intervention is withdrawn the intervention recipients have less immunity than children of the same age in the population. The delay in acquisition of natural immunity may also induce a clinical risk which may be specific to the age; in infants and young children severe malaria anemia is predominant, whereas in older children and adolescents it is cerebral malaria.

The heightened susceptibility is theoretically more likely to occur when:

- The intervention is given early in life before natural immunity has been induced.
- The intervention is highly efficacious preventing natural exposure.
- The intervention is removed or efficacy wanes abruptly.

This has been demonstrated experimentally when a group of Mozambican children were randomized to receive highly effective malaria chemoprophylaxis during the first year of life. During the period of chemoprophylaxis there was a marked reduction in the incidence of disease, but in the subsequent 2 years these children were at higher risk compared to the comparator group who received no intervention. By 4 years of age, rates were similar in both groups and over the complete time period there was a slight benefit of the intervention [Aponte, 2007].

Results from the MALARIA-059 (112902) study, a long-term follow-up in 450 Kenyan children, are suggestive of greater susceptibility to clinical malaria in the vaccine recipients occurring 5 years after vaccination in a moderate to high transmission area. However, no increase in the incidence of severe malaria has been observed with the available safety data. In order to get additional data on the question of enhanced susceptibility to malaria disease following a primary vaccination series, GSK proposes to extend the follow-up of MALARIA-055 PRI for an additional 3 years from January 2014 to December 2016 at multiple study sites.

Please refer to the current Investigator Brochure for information regarding the pre-clinical and clinical studies, the epidemiological information and the potential risks and benefits of GSK Biologicals' candidate *Plasmodium falciparum* malaria vaccine RTS,S/AS01$_E$ (SB257049).

1.2. Rationale for the study and study design

Extending the ongoing study MALARIA-055 PRI (110021) is the fastest and most robust way to have additional data on the question of enhanced susceptibility to malaria disease following a primary vaccination series. Given the strong benefit shown over one year of follow-up, any new study is likely to be unable to have an unvaccinated control group. Therefore this is a unique opportunity to obtain important long-term data relative to a control group. This study design will also allow evaluating in parallel whether giving a booster 18 months after the primary series changes the long-term experience.

Extending for an additional 3 years will permit to get sufficient follow-up time in both age categories (children aged 5–17 months and infants aged 6-12 weeks at first vaccination) to detect changes in malaria susceptibility as it has been previously observed in a long-term follow-up phase II study (i.e. MALARIA-059 [112902]).

In total we will provide in children aged 5-17 months at first vaccination approximately 7 years of follow-up post-Dose 1 (mean: 85 months; range: 77-91 months), and in infants aged 6-12 weeks at first vaccination, 6 years of follow-up post-Dose 1 (mean: 77 months; range: 68-84 months).

2. OBJECTIVES

2.1. Primary objective

- To describe the incidence of severe malaria in the long-term over a 3-year period (from January 2014 to December 2016) of follow-up pooled across transmission settings, in both age categories.
  - In children enrolled in the 5-17 months age category, starting on average 4 years post primary vaccination.
  - In children enrolled in the 6-12 weeks age category, starting on average 3.5 years post primary vaccination.

Refer to Section 11.1 for the definition of the primary endpoints.

2.2. Secondary objectives

2.2.1. Efficacy objectives

In each age category (i.e. 5-17 months and 6-12 weeks) over 3 years of follow-up (from January 2014 to December 2016)::

- To describe the incidence of clinical malaria in recipients of the RTS,S/AS01$_E$ candidate malaria vaccine and in controls.
- To describe the incidence of hospitalization due to malaria in recipients of the RTS,S/AS01$_E$ candidate malaria vaccine and in controls.
- To describe the prevalence of malaria infection at annual cross sectional timepoints in recipients of the RTS,S/AS01$_E$ candidate malaria vaccine and in controls.
- To describe the hemoglobin level and the prevalence of anemia at annual cross sectional timepoints in recipients of the RTS,S/AS01$_E$ candidate malaria vaccine and in controls.

In each age category since the start of the primary study (MALARIA-055 PRI [110021]) until December 2016:

- To describe the incidence of severe malaria in recipients of the RTS,S/AS01$_E$ candidate malaria vaccine and in controls.
- To describe the incidence of clinical malaria in recipients of the RTS,S/AS01$_E$ candidate malaria vaccine and in controls.
- To describe the incidence of hospitalization due to malaria in recipients of the RTS,S/AS01$_E$ candidate malaria vaccine and in controls.

2.2.2. Safety objective

- To describe the incidence of the following reported serious adverse events (SAEs): fatalities, related SAEs (related to vaccine administration in the primary study MALARIA-055 PRI [110021] and to study participation), malaria hospitalization, potential Immune-Mediated Disease (pIMDs), and meningitis from January 2014 to December 2016.

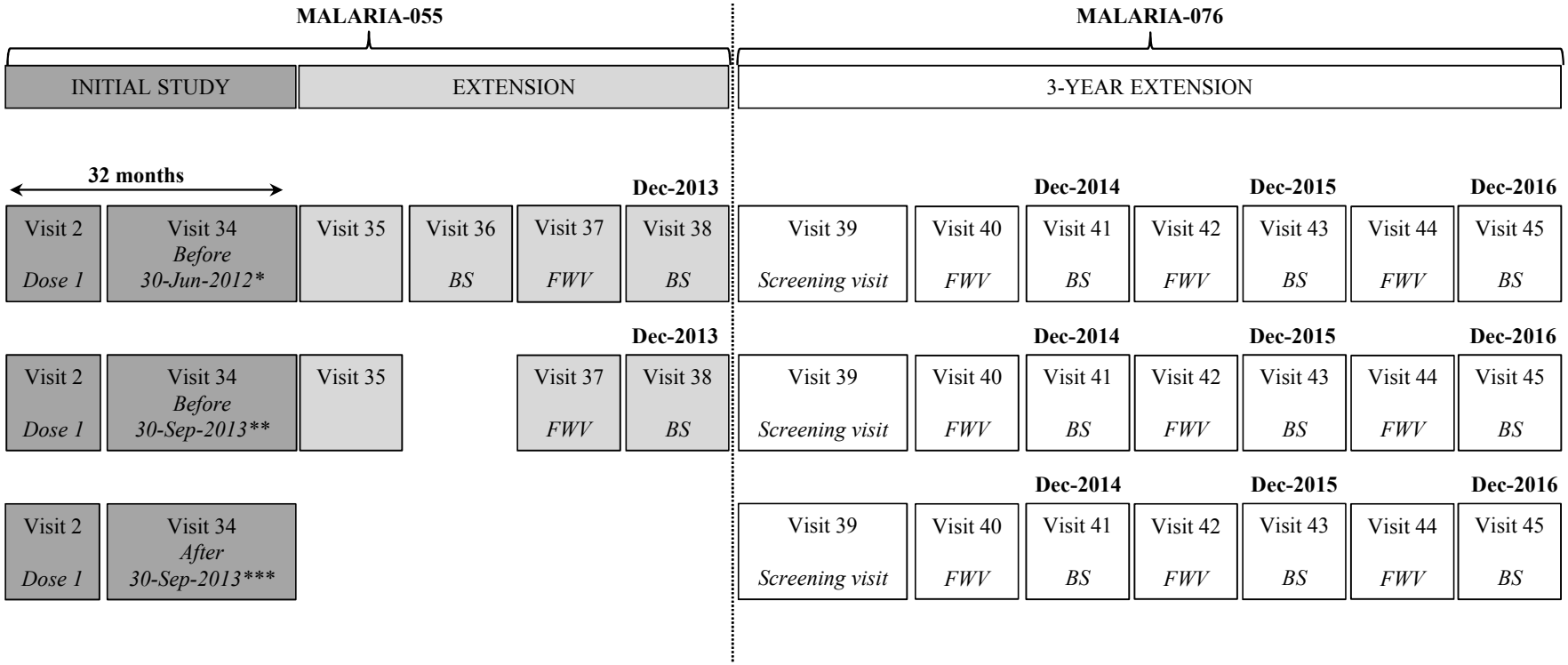
2.2.3. Immunogenicity objective

- To describe anti-circumsporozoite protein of *Plasmodium falciparum* (anti-CS) antibodies response over the 3-year follow-up period, in each age category.

Refer to Section 11.2 for the definition of the secondary endpoints.

3. STUDY DESIGN OVERVIEW

Figure 1 Study design overview



* Subjects that had their last contact in the primary trial phase (Visit 34) BEFORE (and including) 30-Jun-2012, had 3 clinic visits and one field workers visit in the extension part of MALARIA-055 PRI.
** Subjects that had their last contact in the primary trial phase (Visit 34) BETWEEN 01-Jul-2012 and 30-Sep-2013 had 2 clinic visits and one field workers visit in the extension part of MALARIA-055 PRI.
*** Subjects that had their last contact in the primary trial phase (Visit 34) AFTER 30-Sep-2013 were not enrolled in the extension part of MALARIA-055 PRI.
BS: blood sampling; FWV: Field Worker Visit.

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 6.5), are essential and required for study conduct.

- Experimental design: extension to the phase III, randomized, controlled, multi-centric study MALARIA-055 PRI (110021) that comprised 3 parallel groups
- Duration of the study: approximately 3 years
  - Epoch 001: starting at Visit 39, including and ending at Visit 41 (December 2014).
  - Epoch 002: starting at Visit 42, including and ending at Visit 43 (December 2015).
  - Epoch 003: starting at Visit 44, including and ending at Visit 45 (December 2016).
- Study groups: same study groups as in the primary study MALARIA-055 PRI (110021). Subjects enrolled in each of the 2 age categories (5-17 months and 6-12 weeks at first vaccination) were randomized in 3 study groups:
  - R3C: infants/children randomized to receive 3 doses of RTS,S/AS01$_E$ on a 0-, 1-, 2-month schedule with a dose of comparator vaccine at Month 20 during the primary study MALARIA-055 PRI (110021).
  - R3R: infants/children randomized to receive 3 doses of RTS,S/AS01$_E$ on a 0-, 1-, 2-month schedule with an RTS,S/AS01$_E$ booster dose at Month 20 during the primary study MALARIA-055 PRI (110021).
  - C3C: infants/children randomized to receive 3 doses of a comparator vaccine on a 0-, 1-, 2-month schedule with a dose of comparator vaccine at Month 20 during the primary study MALARIA-055 PRI (110021).

Table 1 Study groups and epochs foreseen in the study

Study groups	Estimated number of subjects	Age (Min/Max)	Epochs		
			Epoch 001	Epoch 002	Epoch 003
R3C	600	6 weeks - 12 weeks*	x	x	x
	600	5 months -17 months*	x	x	x
R3R	600	6 weeks - 12 weeks*	x	x	x
	600	5 months -17 months*	x	x	x
C3C	600	6 weeks - 12 weeks*	x	x	x
	600	5 months -17 months*	x	x	x

R3C: RTS,S/AS01$_E$: primary schedule without booster
R3R: RTS,S/AS01$_E$: primary schedule with booster
C3C: controls
* Age at first vaccination in the primary study MALARIA-055 PRI (110021).

- Control: active comparator administered in the primary study MALARIA-055 PRI (110021) (rabies vaccine in the 5-17 months age category and Meningococcal C conjugate vaccine in the 6-12 weeks age category).

- Vaccination schedule: not applicable, all vaccinations were performed in the primary study MALARIA-055 PRI (110021).
- Treatment allocation: follow-up of a randomized study (Randomization performed in the primary study MALARIA-055 PRI [110021] will be kept for this extension. Subjects will remain in the same group as the one of the primary study MALARIA-055 PRI [110021]).
- Blinding: open

Table 2 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	open
Epoch 002	open
Epoch 003	open

- Sampling schedule: blood samples will be taken at annual intervals during the extension (maximum 3 blood samples).
- Type of study: extension of other protocol(s) (MALARIA-055 PRI [110021]). Data of the MALARIA-076 study will be analyzed with those of the primary study MALARIA-055 PRI [110021]). Endpoints of the MALARIA-076 study are pooled with those of the primary study.
- Data collection: electronic Case Report Form (eCRF).

4. CASE DEFINITION

4.1. Clinical malaria

Table 3 Case definition for clinical malaria

1° definition	*Plasmodium falciparum* asexual parasitemia > 5000 parasites/μL **AND** presence of fever (axillary temperature ≥ 37.5°C) at the time of presentation **AND** occurring in a child who is unwell and brought for treatment to a healthcare facility **OR** A case of malaria meeting the primary case definition of severe malaria (refer to Table 4)
2° definition 1	*Plasmodium falciparum* asexual parasitemia > 0 **AND** presence of fever (axillary temperature ≥ 37.5°C) at the time of presentation or history of fever within 24 hours of presentation **AND** occurring in a child who is unwell and brought for treatment to a healthcare facility
2° definition 2	*Plasmodium falciparum* asexual parasitemia > 500 parasites/μL **AND** presence of fever (axillary temperature ≥ 37.5°C) at the time of presentation **AND** occurring in a child who is unwell and brought for treatment to a healthcare facility
2° definition 3	*Plasmodium falciparum* asexual parasitemia > 20 000 parasites/μL **AND** presence of fever (axillary temperature ≥ 37.5°C) at the time of presentation **AND** occurring in a child who is unwell and brought for treatment to a healthcare facility

4.2. Severe malaria

Severe malaria will be diagnosed based on symptoms and signs occurring at presentation or developing during admission according to the case definitions in Table 4.

Table 4 Primary case definition for severe malaria

Plasmodium falciparum asexual parasitemia > 5000 parasites/μL	
AND with one or more marker of disease severity:	- Prostration. - Respiratory distress. - Blantyre score ≤ 2. - Seizures 2 or more. - Hypoglycemia < 2.2 mmol/L. - Acidosis BE ≤ -10.0 mmol/L. - Lactate ≥ 5.0 mmol/L. - Anemia < 5.0 g/dL
AND without diagnosis of co-morbidity:	- Radiographically proven pneumonia. - Meningitis on cerebrospinal fluid (CSF) examination. - Positive blood culture - Gastroenteritis with dehydration.

Prostration is defined as, in an acutely sick child, the inability to perform previously-acquired motor function: in a child previously able to stand, inability to stand; in a child previously able to sit, inability to sit and in a very young child, inability to suck.
Respiratory distress is defined as lower chest wall indrawing or abnormally deep breathing.
2 or more seizures occurring in the total time period including 24 h prior to admission to the emergency room and the hospitalization.
Radiographically proven pneumonia is a consolidation or pleural effusion as defined by World Health Organization [WHO; 2001a] on a chest x-ray (CXR) taken within 72 h of admission (see APPENDIX D).
Meningitis on CSF examination is defined as white cells $\geq 50 \times 10^6$/L or positive culture of compatible organism or latex agglutination positive for *Haemophilus influenzae* type b, pneumococci or meningococci [Berkley, 2001].
Positive blood culture as defined by WHO [WHO, 1999] on a blood culture taken within 72 h of admission.
Gastroenteritis with dehydration is defined as a history of 3 or more loose or watery stools in previous 24 h and an observed watery stool with decreased skin turgor (> 2 seconds for skin to return following skin pinch).

Secondary case definitions of severe malaria are given in Table 5.

Table 5 Secondary case definition for severe malaria

2° definition 1 "with co-morbidity"	*Plasmodium falciparum* asexual parasitemia > 5000 parasites/μL **AND** with one or more marker(s) of disease severity
2° definition 2 "without a density threshold"	*Plasmodium falciparum* asexual parasitemia > 0 **AND** with one or more marker(s) of disease severity **AND** without diagnosis of a co-morbidity

4.3. Malaria hospitalization

Table 6 Case definitions for malaria hospitalization

Definition 1	A medical hospitalization with confirmed *Plasmodium falciparum* asexual parasitemia > 5000 parasites/μL (excludes planned admissions for medical investigation/care or elective surgery and trauma)
Definition 2	A hospitalization for which, in the judgment of the principal investigator, *Plasmodium falciparum* infection was the sole or a major contributing factor to the presentation

4.4. Prevalent anemia

Table 7 Case definitions of prevalent anemia

Prevalent severe anemia	A documented hemoglobin < 5.0 g/dL identified at an annual visit
Prevalent moderate anemia	A documented hemoglobin < 8.0 g/dL identified at an annual visit

4.5. Prevalent parasitemia

Table 8 Case definitions for prevalent parasitemia

Prevalent parasitemia	A documented *Plasmodium falciparum* asexual parasite density > 0 identified at an annual visit

5. STUDY COHORT

5.1. Number of subjects/centers

This study will be conducted at multiple centers in malaria-endemic countries of sub-Saharan Africa. Approximately 3000 to 4000 children who were vaccinated during the primary study MALARIA-055 PRI (110021) will be enrolled in the present study. Refer to Section 11.3 for the determination of sample size.

In the primary study (MALARIA-055 PRI [110021]), the first 200 subjects in each age category at each site had multiple blood samples to assess the immunological vaccine response. Subjects who previously belonged to the immunogenicity sub-cohort in the primary study and who consented to participate in this extension study will be again part of the immunogenicity sub-cohort in the present study.

Table 9 Sub-cohorts

Sub-cohort name	Description	Estimated number of subjects
Immunogenicity	Blood sample for immunological vaccine response (anti-CS antibodies)	1200*

* The immunogenicity sub-cohort will comprise subjects that were included in the immunogenicity sub-cohort of the primary study (MALARIA-055 PRI [110021]) and who were enrolled in this extension study. There will be a maximum of 200 subjects from each age category in each site in the immunogenicity sub-cohort. Assuming 4 sites and a 25% dropout rate of the primary study (MALARIA-055 PRI [110021]).

5.2. Overview of the recruitment plan

In the participating sites, the parent(s)/ Legally Acceptable Representative(s) (LAR[s]) of the subjects who fulfill inclusion/exclusion criteria described in Section 5.3, will be contacted for this extension study.

- If subjects' parent(s)/LAR(s) agree to let their child participate in the MALARIA-076 study, they will need to sign an Informed Consent Form (ICF) before or at the start of the screening visit of the MALARIA-076 (Visit 39) and their child will be enrolled in this study. Once the child is enrolled in this study, a retrospective collection of efficacy and safety data will be performed as stated in Section 6.6.10.
- For subjects who will not be enrolled in the study, the following reasons for non-participation will be collected:
  - Parent(s)/LAR(s) do not agree to let their child participate in the MALARIA-076 study.

- Subjects are lost to follow-up.
- Subject died before the start of MALARIA-076. In addition, these subjects' parent(s)/LAR(s) will be asked if for the purpose of safety monitoring of the vaccine, they allow reporting of the event leading to the death of their child in the MALARIA-076 database. If the parent(s)/LAR(s) agree, they will be asked to sign an ICF.

5.3. 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)/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).
- Subjects who were enrolled and who received at least one vaccine dose in the primary study MALARIA-055 PRI (110021) and who did not withdraw consent (except those who moved away from the area) during the primary study MALARIA-055 PRI (110021).
- Written informed consent obtained from the parent(s)/LAR(s) of the subject.

5.4. 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 any investigational or non-registered product (drug or vaccine) or planned use during the study period.

6. CONDUCT OF THE STUDY

6.1. 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 International Conference on Harmonization (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 informed consent, 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 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.

6.2. Subject identification and randomization of treatment

6.2.1. Subject identification

Subject identification numbers will be the same as the ones assigned in the primary study MALARIA-055 PRI (110021). Study subjects will receive study identification cards with their picture and subject number.

6.2.2. Allocation of subjects to assay subsets

Serum samples taken at annual clinic visit (see Section 6.5) will be tested for anti-CS antibody on an immunogenicity sub-cohort (see Table 9). The immunogenicity sub-cohort will comprise subjects that were included in the immunogenicity sub-cohort of the primary study (MALARIA-055 PRI [110021]) and who were enrolled in this extension study. There will be a maximum of 200 subjects from each age category in each site in the immunogenicity sub-cohort.

6.3. Method of blinding

This study is an open-label study.

6.4. General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (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.

6.5. Outline of study procedures

Table 10 List of study procedures

Epoch	*Epoch 001*			*Epoch 002*		*Epoch 003*	
Type of contact	**Screening Visit (Visit 39)**	**Visit 40[1]**	**Visit 41**	**Visit 42[1]**	**Visit 43**	**Visit 44[1]**	**Visit 45**
Timepoints	**Day 0**	**Within 30 days before Year 1**	**Year 1**	**Within 30 days before Year 2**	**Year 2**	**Within 30 days before Year 3**	**Year 3**
Recording reasons for non-participation	●						
Informed consent[2]	●						
Issuing identification card	O						
Check identification card		O	O	O	O	O	O
Check inclusion/exclusion criteria	●						
Collect demographic data[3]	●						
Physical examination	O		O		O		O
Anthropometry[4]	●		●		●		●
Screening conclusion	●						
Documentation of bednets and indoor residual spraying[5]		●		●		●	
Retrospective collection of safety and efficacy data since the last contact of the primary study (MALARIA-055)	●						
Surveillance for clinical malaria and severe malaria[10]			●[6]		●[6]		●[6]
Surveillance for safety: recording of SAEs[7,11]			●[6]		●[6]		●[6]
Blood sampling for anti-CS antibodies measurement (approximately 0.5 mL)[8]			●		●		●
Blood sampling for parasite density measurement[9] and hemoglobin level (approximately ***0.5*** mL)			●		●		●
Interim analysis			O		O		
Final analysis							O
Study Conclusion							●

[1] Field worker visits

[2] ICF to be signed by all subjects' parents/LARs who consent to let their child participate in this study and by subjects' parents/LARs who consent to allow reporting of the event leading to the death of their child before the start of MALARIA-076 in the MALARIA-076 database.

[3] Demographic data include age and gender

[4] Anthropometry consists of height, weight and mid upper arm circumference

[5] Use of bednets and indoor residual spraying will be checked between 1 and 30 days before the annual visits (see APPENDIX A).

[6] Retrospective collection since the last visit.

[7] SAEs: fatalities, related SAEs (related to vaccine administration in the primary study MALARIA-055 PRI [110021] and to study participation), malaria hospitalization, pIMDs, and meningitis (see Section 9).

[8] Only for subjects that were included in the immunogenicity sub-cohort of the primary study (MALARIA-055 PRI [110021]) and who were enrolled in this extension study. There will be a maximum of 200 subjects from each age category in each site in the immunogenicity sub-cohort.

[9] A volume of 16 μL is required for this test.

[10] Note that passive surveillance for clinical and severe malaria is ongoing throughout the study (see Section 6.6.11)

[11] Note that passive surveillance for safety is ongoing throughout the study (see Section 6.6.12)

● 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 11 Intervals between study visits

Interval	Timing of visit[1]	Allowed interval[2]
Screening Visit (Visit 39)[3]	Study start at the center	Not applicable
Visit 40 (Field Worker Visit)[4]	November 2014	October 2014 to December 2014
Visit 41 (Annual Visit)	December 2014	November 2014 to January 2015
Visit 42 (Field Worker Visit)[4]	November 2015	October 2015 to December 2015
Visit 43 (Annual Visit)	December 2015	November 2015 to January 2016
Visit 44 (Field Worker Visit)[4]	November 2016	October 2016 to December 2016
Visit 45 (Annual Visit)	December 2016	November 2016 to January 2017

[1] Whenever possible the investigator should arrange study visits within this interval.
[2] Subjects will not be eligible for inclusion in the According-to-Protocol (ATP) population for analysis of immunogenicity if they make the study visit outside this interval.
[3] Visit 39 should be performed as soon as the center is initiated. However, if the timing of Visit 39 is delayed beyond the allowed interval for Visit 40 or Visit 41, then those visits will be skipped.
[4] Field Worker Visits should be conducted between 1 and 30 days before Annual Visits.

6.6. Detailed description of study procedures

6.6.1. Recording reasons for non-participation

For subjects who will not be enrolled in the study, the following reasons for non-participation will be collected:

- Parent(s)/LAR(s) do not agree to let their child participate in the MALARIA-076 study.
- Subjects are lost to follow-up.
- Subject died between the end of the primary study (MALARIA-055 PRI [110021]) and the beginning of MALARIA-076 (see Section 5.2).

6.6.2. 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 6.1 for the requirements on how to obtain informed consent.

6.6.3. Check inclusion and exclusion criteria

Check all inclusion and exclusion criteria as described in Sections 5.3 and 5.4 before enrolment.

6.6.4. Collect demographic data

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

6.6.5. Physical examination

Perform physical examination of the subject, if deemed necessary by the investigator (at the screening visit [Visit 39] and at annual clinic visits [Visits 41, 43 and 45]).

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

6.6.6. Anthropometry

Perform anthropometric measurements of the subject (height, weight and mid upper arm circumference) at the screening visit (Visit 39) and at annual clinic visits (Visits 41, 43 and 45). Collected information needs to be recorded in the eCRF.

The methodologies used for height, weight and mid upper arm circumference 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.

6.6.7. Issuing subject identification card

At the screening visit (Visit 39), take a picture of the subject 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 (Visit 40 to 45), check this identification card.

6.6.8. Screening conclusion

Screening conclusion will be completed in the eCRF for all subjects who participate to this extension study.

6.6.9. Documentation of bednets and indoor residual spraying

Bednets usage and indoor residual spraying (IRS) will be assessed during field worker visits (Visits 40, 42 and 44) at subjects' house between 1 and 30 days before the annual visits.

The parent(s)/LAR(s) will be asked if the house has been sprayed with a residual insecticide and if so when (yes/no). In addition it will be asked if the child sleeps under a bednet and whether or not the net is impregnated with insecticide.

The response to these questions will be documented in the eCRF.

These procedures are fully described in APPENDIX A.

6.6.10. Retrospective collection of efficacy and safety data

During Visit 39, all subjects for whom the parents/LARs gave their consent to let their child participate in this study, will have a retrospective collection of efficacy data (cases of clinical, severe or malaria hospitalization) and safety data (SAEs: fatalities, related SAEs [related to vaccine administration in the primary study MALARIA-055 PRI and to study participation], malaria hospitalization, pIMD, and meningitis) since their last contact in the primary study MALARIA-055 PRI (110021). Retrospective data will be collected, for example by questioning subject's parents/LARs and by reviewing available medical records. Collected information needs to be recorded in the eCRF.

For subjects who will not be enrolled in the study, because they died before the start of MALARIA-076, subjects' parent(s)/LAR(s) will be asked if they consent to allow reporting of the event leading to the death of their child in the MALARIA-076 database. If the parent(s)/LAR(s) agree, they will be asked to sign an ICF. This event will be reported as SAE in the MALARIA-076 database ***and any available information captured in the inpatient module of the eCRF or any other specific section as applicable.***

(Amended 15 April 2015)

6.6.11. Surveillance for efficacy

Retrospective data since the previous visit will be collected by questioning subject's parents/LARs and by reviewing available medical record during annual clinic visit (Visits 41, 43, and 45). Collected information needs to be recorded in the eCRF. ***For clarity, if available the following data will be collected: history of fever, temperature, parasite density, treatment administered, any clinical diagnoses of malaria, rapid diagnostic test (RDT) and blood slides read to guide treatment at the time of presentation will be captured.***

Passive surveillance for clinical malaria

All subjects presenting to health facilities in the study area will be evaluated as potential cases of clinical malaria. A blood sample for the evaluation of malaria parasites will be taken for all children who are reported to have had a fever within 24 hours of presentation or have a measured axillary temperature of ≥ 37.5°C.

Data points that will be captured in the eCRF for all cases of suspected clinical malaria are: history of fever; temperature; parasite density; treatment administered. ***To supplement this information, any clinical diagnoses of malaria, RDT and blood slides read to guide treatment at the time of presentation will be captured.***

Note that the data on all subjects investigated for malaria will be captured in the eCRF regardless of whether the case was confirmed.

Passive surveillance for severe malaria

All subjects presenting for admission through the outpatient and emergency departments of hospitals in the study areas will be evaluated as potential cases of severe malaria following an algorithm (see APPENDIX B).

During the hospitalization, the subject's course will be monitored to capture the signs and blood parameters indicative of severe malaria. If the subject's condition changes from admission and he/she meets one of the criteria for additional investigations, these will be performed.

Harmonization of case evaluation across centers will be assured by training of clinicians in the assessment of clinical signs and the standardization of equipment and processes used for laboratory investigations. On all admissions, data will be captured to support the endpoints of this study. ***In addition RDT and blood slides read to guide treatment at the time of presentation will be captured.***

Note that measurement of creatinine and total bilirubin were not specified per algorithm. If performed for case management these will be captured in the eCRF.

Prevalent parasitemia and anemia

Evaluation of prevalent parasitemia (see APPENDIX C) and prevalent anemia will be performed annually (see also Section 6.6.13.2, for the sampling method).

All slides will be made in duplicate and stored locally in the clinical center. For each slide, the parasite density will be determined, independently by two readers and in the case of non-concordance a third read will be carried out (see APPENDIX C).

Children who are symptomatic will be assessed by a clinician and managed as appropriate. Collected information needs to be recorded in the eCRF.

(Amended 15 April 2015)

6.6.12. Passive surveillance for safety

Retrospective data since the previous visit will be collected by questioning subject's parents/LARs and by reviewing available medical record during annual clinic visit (Visits 41, 43, and 45). Collected information needs to be recorded in the eCRF.

The following SAEs: fatalities, related SAEs (related to vaccine administration in the primary study MALARIA-055 PRI [110021] and to study participation), malaria hospitalization, pIMDs, and meningitis will be collected for all subjects presenting to health facilities in the study area and through annual clinic visits.

Verbal autopsy will be performed on all cases of mortality occurring outside hospital and where it adds value to ascribe the cause of a fatal event. The questionnaire used will be based on the INDEPTH standard and adapted to be locally appropriate [WHO, 2007]. For children who died before study start and whose parents consent, the death will be

reported as an SAE. If there is uncertainty of cause of death based on the review of available medical records, a verbal autopsy should be performed.

Refer to Section 9.2 for procedures for the investigator to record SAEs and pIMDs. Refer to Section 9.3 for guidelines on how to submit SAE and pIMD 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.

6.6.13. Sampling

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

6.6.13.1. Blood sampling for surveillance of immunogenicity

Blood samples will be taken during annual clinic visits (Visits 41, 43 and 45).

A volume of at least 0.5 mL of whole blood (to provide at least 200 µL of serum) for anti-CS antibodies measurement should be drawn from all subjects who were previously included in the immunogenicity sub-cohort in the primary study MALARIA-055 PRI (110021). 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.

6.6.13.2. Blood sampling for prevalent parasitemia and anemia

Blood samples will be taken during annual clinic visits (Visits 41, 43 and 45).

A volume of at least 0.5 mL of whole blood for parasite density (16 µL needed for this test) and haemoglobin level measurement should be drawn from all subjects.

For prevalent parasitemia one out of two blood slide reading methods which were approved by GSK Biologicals and collaborating partners and contributors should be used.

The first method counts parasites relative to a concomitantly measured white blood cell count [Greenwood, 1991] and the second method counts parasites relative to a fixed measured blood volume [Planche, 2001]. These two methodologies are well established and used as gold-standards in the field. Slides are always taken in duplicate.

These procedures are fully described in the APPENDIX C.

6.6.14. Study conclusion

The investigator will:

- review collected data to ensure accuracy and completeness.
- complete the Study Conclusion screen in the eCRF.

6.7. 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).

Under the following circumstances, additional testing on the samples may be performed by GSK Biologicals outside the scope of this protocol:

- Collected samples may be used in other assays, for test improvement or development of analytical methods related to the study vaccine(s) and its constituents or the disease under study.
- Collected samples may be used for purposes related to the quality assurance of data generated linked to the study vaccine(s) or the disease under study, such as for maintenance of assays described in this protocol and comparison between analytical methods and/or laboratories.

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).

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.

6.7.1. 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 11.4 for the definition of study cohorts/ data sets 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.

6.7.2. Biological samples

The different biological samples collected in the study, the quantity needed, the unit and the timepoints are described in Table 12.

Table 12 Biological samples

Sample type	Quantity	Unit	Timepoint	Sub-cohort Name*
Blood for anti-CS antibodies	0.5	ml	Visit 41 Visit 43 Visit 45	Immunogenicity sub-cohort
Blood sampling for parasite density and hemoglobin level	0.5	ml	Visit 41 Visit 43 Visit 45	All subjects

* Refer to Section 5.1 for sub-cohort description

6.7.3. Laboratory assays

Please refer to APPENDIX E for a detailed description of the assays performed in the study. Please refer to APPENDIX F 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 13).

Table 13 Humoral Immunity (Antibody determination)

System	Component	Method	Kit / Manufacturer	Unit	Cut-off	Laboratory
Serum	Plasmodium falciparum.Circumsporozoite Protein.R32LR Ab.IgG	ELISA	NA	EU/ml	0.5	CEVAC*

* Centre for Vaccinology, Ghent University, Belgium (Refer to APPENDIX F for the laboratory address).
CS = Circumsporozoite protein of *Plasmodium falciparum;* ELISA: enzyme-linked immunosorbent assay; EU/mL: ELISA units per milliliter; NA: not applicable.

6.7.4. Biological samples evaluation

6.7.4.1. Immunological read-outs

The plan for immunogenicity testing on samples obtained is shown in Table 14.

Table 14 Immunological read-outs

Blood sampling timepoint		Estimated No. subjects	Component
Type of contact and timepoint	Sampling timepoint		
Visit 41	Year 1	1200	anti-CS antibodies
Visit 43	Year 2	1200	anti-CS antibodies
Visit 45	Year 3	1200	anti-CS antibodies

6.7.4.2. Parasitemia and anemia

The plan for parasitemia and anemia testing on samples obtained is shown in Table 15.

Table 15 Parasitology and hemoglobin read-outs

Blood sampling timepoint		Estimated No. subjects	Component
Type of contact and timepoint	Sampling timepoint		
Visit 41	Year 1	3600	Parasite density
			Hemoglobin
Visit 43	Year 2	3600	Parasite density
			Hemoglobin
Visit 45	Year 3	3600	Parasite density
			Hemoglobin

Additionally, blood samples for parasitology will be taken at each presentation to a health facility with a febrile illness (documented or history of fever; refer to Section 6.6.11).

6.7.5. Immunological correlates of protection

No generally accepted immunological correlate of protection has been demonstrated so far for the antigen (CS) used in the candidate vaccine.

7. STUDY VACCINE(S) AND ADMINISTRATION

This section is not applicable since no vaccine is administered in this study. Vaccines were administered in the study MALARIA-055 PRI (110021) and the current study is a long-term follow-up of the MALARIA-055 PRI study.

8. HEALTH ECONOMICS

Not applicable.

9. SAFETY

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

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

9.1. Safety definitions

9.1.1. 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.
- 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).

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.

9.1.2. Definition of a serious adverse event

A serious adverse event 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 fulfills 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.

   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.

9.1.3. Clinical laboratory parameters and other abnormal assessments qualifying as 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 SAE if they meet the definition of an SAE (refer to Section 9.1.2). 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 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.

9.1.4. Adverse events of specific interest

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

9.1.4.1. 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 16.

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 16 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, myeloradiculomyelitis • 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 • Scleroderma, including diffuse systemic form and CREST syndrome • Systemic sclerosis • Dermatomyositis • Polymyositis • Antisynthetase syndrome • Rheumatoid arthritis, • Juvenile chronic arthritis, (including Still's disease) • Polymyalgia rheumatic • 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) • Cutaneous lupus erythematosus • Alopecia areata • Lichen planus • Sweet's syndrome • Morphoea

Liver disorders	Gastrointestinal disorders	Metabolic diseases
• Autoimmune hepatitis • Primary biliary cirrhosis • Primary sclerosing cholangitis • Autoimmune cholangitis	• Crohn's disease • Ulcerative colitis • Ulcerative proctitis • Celiac disease	• Autoimmune thyroiditis (including Hashimoto thyroiditis) • Grave's or Basedow's disease • Diabetes mellitus type I • Addison's disease

Vasculitides	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 glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) • Uveitis • Autoimmune myocarditis/cardiomyopathy • Sarcoidosis • Stevens-johnson syndrome • Sjögren's syndrome • Idiopathic pulmonary fibrosis • Goodpasture syndrome • Raynaud's phenomenon

When there is enough evidence to make any of the above diagnoses, the event must be reported as a pIMD. Regardless of it being considered an AE or an SAE, it should be reported per the SAE reporting rules.

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

9.1.4.2. *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 appropriate targeted follow-up forms included in the eCRF.

9.2. Detecting and recording serious adverse events

SAEs that will be reported under this protocol are: those that are fatal, those that are related to vaccine administration in the primary study MALARIA-055 PRI (110021), those that are related to study participation, malaria hospitalization, pIMDs, and meningitis. SAEs will be captured at the health facilities in the study area or by direct questioning at the Annual Visits (Visits 41, 43 and 45).

9.2.1. Time period for detecting and recording serious adverse events

The time period for collecting and recording SAEs will begin at the first study visit (i.e. Visit 39) and will end at the last study visit (i.e. Visit 45) for each subject. See Section 9.3 for instructions on reporting of SAEs.

In addition, at Visit 39, a retrospective collection of SAEs (fatalities, related SAEs, malaria hospitalization, pIMDs, and meningitis) since the last study contact of the primary study (MALARIA-055 PRI [110021]) will be performed.

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 pIMDs will begin at the first study visit (i.e. Visit 39) and will end at the last study visit (i.e. Visit 45). See section 9.3 for instructions on reporting of pIMDs.

An overview of the protocol-required reporting periods for SAEs (fatalities, related SAEs, malaria hospitalization, pIMDs, and meningitis) is given in Table 17.

Table 17 Reporting periods for serious adverse events

Event	From Visit 39* to Visit 45
Fatalities	
Related SAEs	
Malaria hospitalization	
pIMDs	
Meningitis	

* A retrospective collection of safety data (SAEs: fatalities, related SAEs [related to vaccine administration in the primary study MALARIA-055 PRI and to study participation], malaria hospitalization, pIMD, and meningitis) since the last contact in the primary study MALARIA-055 PRI (110021) will be performed at Visit 39.

Additional, safety data could also be collected as required to support the further evaluation of a safety signal.

9.2.2. Post-Study serious adverse events

A post-study SAE is defined as any event that occurs outside of the SAE reporting period defined in Table 17. Investigators are not obligated to actively seek 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 vaccine/product, the investigator will promptly notify the Study Contact for Reporting SAEs.

9.2.3. Evaluation of serious adverse events

9.2.3.1. Active questioning to detect serious adverse events

As a consistent method of collecting SAEs, the subject or 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 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 SAE 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 SAE and not the individual signs/symptoms.

9.2.3.2. Assessment of adverse events

9.2.3.2.1. Assessment of intensity

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 school/kindergarten/a day-care center and would cause the parent(s)/LAR(s) to seek medical advice.

Grade 3 is a category used for rating the intensity of an event; 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 9.1.2.

9.2.3.2.2. Assessment of causality

The definitions for 'NO' and 'YES' have been written in such a way that all events that have been attributed a 'NO' can be pooled with events which in the primary vaccination study were determined to be 'not related' or 'unlikely to be related' to vaccination. Those events that are attributed a 'YES' can be pooled with those events that in the past were determined to have a 'suspected' or 'probable' relationship to vaccination in the primary vaccination study.

The investigator is obligated to assess the relationship between investigational vaccine/product and the occurrence of each 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/product will be considered and investigated. The investigator will also consult the IB 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 SAE 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, it may not be possible to determine the causal relationship of SAEs to the individual vaccines administered. The investigator should, therefore, assess whether the SAE could be causally related to vaccination rather than to the individual vaccines.

Causality of SAEs should be assessed by the investigator using the following question:

Is there a reasonable possibility that the SAE may have been caused by the investigational vaccine/product?

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

If an event meets the criteria to be determined as ‘serious’ (see Section 9.1.2), 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 vaccine(s), if applicable.
- Erroneous administration.
- Other cause (specify).

9.2.3.3. 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).

9.2.3.4. 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 in the eCRF.

9.3. Reporting of serious adverse events and other events

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

SAEs that occur in the time period defined in Section 9.2 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.

pIMDs that occur in the time period defined in Section 9.2 will be reported promptly to GSK within the timeframes described in Table 18, once the investigator becomes aware of the pIMD.

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
Fatalities	24 hours*	electronic SAE report	24 hours*	electronic SAE report
Related SAEs**	24 hours*	electronic SAE report	24 hours*	electronic SAE report
Malaria hospitalization	24 hours*	electronic SAE report	24 hours*	electronic SAE report
pIMDs	24 hours*	electronic SAE report	24 hours*	electronic SAE report
Meningitis	24 hours*	electronic SAE report	24 hours*	electronic SAE report

* Timeframe allowed after receipt or awareness of the information.
** Related to vaccine administration in the primary study MALARIA-055 PRI (110021) and to study participation.

9.3.2. Contact information for reporting serious adverse events and other events to GSK Biologicals

Back-up Study Contact for Reporting SAEs
24/24 hour and 7/7 day availability: GSK Biologicals Clinical Safety & Pharmacovigilance Fax: +PPD or +PPD

9.3.3. 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 SAE report WITHIN 24 HOURS. The SAE 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.

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

If the electronic SAE reporting system does not work, the investigator (or designate) must complete, then date and sign a paper SAE report and fax it to the GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours.

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

9.3.4. Reporting of pIMDs to GSK Biologicals

Once onset of a new pIMD or exacerbation of a pre-existing pIMD is diagnosed (serious or non-serious) in a study subject, the investigator (or designate) must complete the information in the electronic SAE report WITHIN 24 HOURS after he/she becomes aware of the diagnosis. A field on the SAE report allows to specify that the event is a pIMD and whether it is serious or non-serious. The SAE 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 a pIMD, 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.

Refer to Section 9.3.3.1 for back-up system in case the electronic SAE reporting system does not work.

9.3.5. Updating of SAE and pIMD information after freezing of the subject's eCRF

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

9.3.6. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 9.3.1. 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 vaccine/product and unexpected. The purpose of the report is to fulfill specific regulatory and GCP requirements, regarding the product under investigation.

9.4. Follow-up of serious adverse events

9.4.1. Follow-up of serious adverse events

9.4.1.1. Follow-up during the study

After the initial 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 pIMDs (serious or non-serious) 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.

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

The investigator will follow subjects with SAEs, pIMDs, or subjects withdrawn from the study as a result of an SAE, 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 SAE 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 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.

9.5. Treatment of serious adverse events

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

9.6. 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.

10. SUBJECT COMPLETION AND WITHDRAWAL

10.1. 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.

10.2. Subject withdrawal

Withdrawals will not be replaced.

10.2.1. 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 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) or 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 he/she/the subject's parent(s) has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject, in the CRF.

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 9.4.1.2).

10.3. 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. The following information will be collected for screening failures:

- Informed consent.

- Inclusion/exclusion criteria.
- Demographic data.
- SAEs related to study participation, to concomitant use of GSK products or any fatal SAEs.
- Screening conclusion.

11. STATISTICAL METHODS

11.1. Primary endpoint

- The occurrence of severe malaria meeting the primary case definition analyzed over the time period starting January 2014 until the end of the 3-year follow-up period (Visit 45).

11.2. Secondary endpoints

11.2.1. Efficacy endpoints

- The occurrence of clinical malaria meeting the primary and secondary case definitions analyzed over the time period starting January 2014 until the end of the 3-year follow-up period (Visit 45).
- The occurrence of malaria hospitalization meeting each of the case definitions analyzed over the time period starting January 2014 until the end of the 3-year follow-up period (Visit 45).
- The prevalence of parasitemia at 3 annual timepoints (Visit 41, 43 and 45), in both age categories (6-12 weeks and 5-17 months).
- The prevalence of anemia at 3 annual timepoints (Visit 41, 43 and 45), in both age categories (6-12 weeks and 5-17 months).
- The level of hemoglobin at 3 annual timepoints (Visit 41, 43 and 45), in both age categories (6-12 weeks and 5-17 months).
- The occurrence of severe malaria meeting the primary and secondary case definitions analyzed over the time period starting at the beginning of the primary study (MALARIA-055 PRI [110021]; Visit 2) until the end of the follow-up period (Visit 45), in both age categories (6-12 weeks and 5-17 months).
- The occurrence of clinical malaria meeting the primary and secondary case definitions analyzed over the time period starting at the beginning of the primary study (MALARIA-055 PRI [110021]; Visit 2) until the end of the follow-up period (Visit 45), in both age categories (6-12 weeks and 5-17 months).
- The occurrence of malaria hospitalization meeting all case definitions analyzed over the time period starting at the beginning of the primary study (MALARIA-055 PRI

[110021]; Visit 2) until the end of the follow-up period (Visit 45), in both age categories (6-12 weeks and 5-17 months).

11.2.2. Safety endpoint

- The occurrence of the following reported SAEs: fatalities, related SAEs (related to vaccine administration in the primary study MALARIA-055 PRI [110021] and to study participation), malaria hospitalization, pIMDs, and meningitis over the time period starting January 2014 until the end of the 3-year follow-up period (Visit 45).

11.2.3. Immunogenicity endpoint

- The annual anti-CS antibody titers (Visit 41, 43 and 45) for children of both age categories (6-12 weeks and 5-17 months).

11.3. Power of the trial

The incidence of severe malaria and clinical malaria following a primary RTS,S/AS01$_E$ vaccination given in 2 different age categories, with or without booster, across different transmission settings will be described. If 600 subjects per group in each category are enrolled with an attack rate of 24 episodes over 3 years in controls (4% over 3 years [or 1.3% per year]) of severe malaria this sample size will allow to detect a 2-fold increase in the incidence of severe malaria between the recipients of primary vaccination only (R3C versus C3C) or primary vaccination + booster (R3R versus C3C) over the 3-year additional follow-up, with 80% power.

The projected attack rates of severe malaria have been calculated using attack rates over the first year of observation and the transmission intensity at each center and projected according to the expected variations over time and by transmission intensity as described by Carneiro [Carneiro, 2010].

11.4. Study populations

11.4.1. Modified Intention-to-Treat (ITT) population

The modified Intention-to-Treat (ITT) population will include all subjects that consented to the trial. The analyses on the modified ITT population will be performed per treatment assignment.

11.4.2. According-to-Protocol population for efficacy

The According-to-Protocol (ATP) population for efficacy will include all subjects included in the ITT who were in the ATP population for efficacy of the primary study (MALARIA-055 PRI) and who have follow-up data available in the current study.

11.4.3. According-to-Protocol population for immunogenicity

The ATP population for immunogenicity will include all subjects who were in the ATP population for immunogenicity of the primary study (MALARIA-055 PRI) and that attended all annual follow-up visits within specified intervals.

11.5. Derived and transformed data

The cut-off of the anti-CS assay is ≥ 0.5 EU/mL (see Section 6.7.3). The Geometric Mean Titer (GMT) calculations are 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.

11.6. Analysis of demographics

For both age categories (6-12 weeks and 5-17 months), demographic characteristics (age and gender) will be tabulated per study group.

For both age categories, the distribution of subjects enrolled among the study sites will be tabulated as a whole and per study group.

11.7. Analysis of malaria disease incidence

All analyses will be performed on the ATP population for efficacy and modified ITT population.

VE will be calculated on the entire follow-up period. Incidence comparison, using the same formula and analytic methodology will be calculated for time period breakdown.

Disease incidence will be estimated over the following time-period:

i. Over the 3-year extension period.

ii. Over the complete time at risk (including primary study [MALARIA-055 PRI] and follow-up).

iii. By yearly and 6-monthly breakdown periods covering the 3-year period.

11.7.1. Clinical malaria

For both age categories (6-12 weeks and 5-17 months), VE/ incidence comparison against all episodes of clinical malaria will be estimated as 1-incidence ratio (IR; total number of events/follow-up time in the RTS,S/AS01$_E$ groups [R3R/R3C] over the total number of events/follow-up time in the control group [C3C]) calculated by negative binomial regression allowing for interdependence between episodes within the same subject (mixed model with over-dispersion parameter estimated from the random effect) and will be presented together with 95% CI and p-values calculated from this model. Results will be analyzed per site and overall.

For both age categories (6-12 weeks and 5-17 months), VE against first or only episodes of clinical malaria will be estimated as 1-hazard ratio (HR; log survival in the RTS,S/AS01$_E$ groups [R3R/R3C] over log survival in the control group [C3C]) calculated by Cox regression models and will be presented together with 95% CI and p-values (likelihood ratio test). Results will be analyzed per site and overall.

Schoenfeld residuals and models with time-varying covariates will be evaluated on Cox models on first or only episodes and including multiple episodes of clinical malaria for each site and overall.

11.7.2. Severe malaria and malaria hospitalization

For both age categories (6-12 weeks and 5-17 months), severe malaria and malaria hospitalization will be analyzed by the proportion of children affected. VE will be estimated as 1-the risk ratio (RR; proportion of subjects reporting events in the RTS,S/AS01$_E$ groups [R3R/R3C] over the proportion in controls [C3C]) over the entire follow-up period, and will be presented together with 95% CIs and p-values. Results will be analyzed per site and overall.

11.7.3. Vaccine efficacy against prevalent parasitemia and prevalent anemia

For both age categories (6-12 weeks and 5-17 months), VE against prevalent endpoints (parasitemia, moderate and severe anemia) assessed annually will be estimated as 1-RR where RR is the risk ratio (proportion of subjects reporting events in the RTS,S/AS01$_E$ groups [R3R/R3C] over the proportion in controls [C3C]) and will be presented together with 95% CIs and p-values. Results will be analyzed per site and overall. The geometric mean parasite density and arithmetic mean hemoglobin level will be calculated per site and overall. The effect of the group will be evaluated using the t-test.

11.7.4. Vaccine impact

For both age categories (6-12 weeks and 5-17 months), each site and overall, the number of cases of clinical malaria, severe malaria, and malaria hospitalizations averted will be calculated (difference between incidences, expressed per 1000 population vaccinated) for each 6-monthly time period and totaled over the entire follow-up time. Graphical presentations will be generated showing the cumulative number of averted cases over time (breakdown of follow-up period).

To evaluate effect on growth, the height for age, weight for age and mid arm circumference z-scores and absolute height measurements annually will be tabulated for each site and overall and the mean values will be compared between study groups using a t-test.

11.8. Analysis of immunogenicity

All analyses will be performed on the ATP population immunogenicity and modified ITT population.

For both age categories (6-12 weeks and 5-17 months), 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 each blood sampling timepoint. Antibody titers will be summarized by GMT with 95% CI at all timepoints at which serological samples are taken.

11.9. Analysis of safety

The primary analysis will be performed on the modified ITT population.

For both age categories (6-12 weeks and 5-17 months), safety will be evaluated by examining SAEs (fatalities, related SAEs [related to vaccine administration in the primary study MALARIA-055 PRI and to study participation], malaria hospitalization, pIMDs, and meningitis) from study start (MALARIA-076). All safety analyses will be performed separately for both age categories.

The proportion of subjects with SAEs, classified by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term level, will be tabulated by group with exact 95% CI.

11.10. Interpretation of analyses

All analyses will be descriptive with respect to malaria disease incidence, safety and immunogenicity.

11.11. 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.

11.11.1. Sequence of analyses

All analyses (including interim analyses) will be conducted on data as clean as possible.

Two interim analyses of efficacy, immunogenicity and safety data will be performed when all data up to and including the end of Year 1 (i.e. Visit 41) and end of Year 2 (i.e. Visit 43) will be available.

The final analysis of efficacy, immunogenicity and safety data will be performed when all data up to and including the end of the 3-year follow-up (i.e. Visit 45) will be available. Annual study reports will be written after each analyses.

11.11.2. Statistical considerations for interim analyses

Two interim analyses will be performed. As all analyses are descriptive, p-values will be informatory and not confirmatory. No alpha-adjustment will be planned.

12. ADMINISTRATIVE MATTERS

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

12.1. Case Report Form/Remote Data Entry instructions

Remote Data Entry (RDE), a validated computer application, 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.

12.2. 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 a RDE review and a Source Document

Verification (SDV). By SDV we understand verifying RDE 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 RDE. 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 RDE will serve as the source must be identified, agreed and documented in the source documentation agreement form.

For RDE, the monitor will mark 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.

12.3. 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; otherwise, the minimum retention period will default to 15 years.

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.

12.4. 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.

12.5. 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 12 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.

12.6. 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.

13. COUNTRY SPECIFIC REQUIREMENTS

Not applicable.

14. REFERENCES

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APPENDIX A Documentation of bednet usage and indoor residual spraying

Bednet usage and IRS will be assessed at three home visits (field worker visits) at Visit 40, 42 and 44.

- **Bednets**

The parent(s)/LAR(s) will be asked if the child sleeps under a bednet and whether or not the net is impregnated with insecticide. The child's bednet will be inspected and the integrity of the net (i.e. whether or not the net has holes) documented. Net usage will be classified in the eCRF according to the following choices:

1: No bednet
2: Impregnated bednet with no hole large enough to admit three fingers
3: Impregnated bednet with at least one hole large enough to admit three fingers
4: Untreated bednet with no hole large enough to admit three fingers
5: Untreated bednet with at least one hole large enough to admit three fingers

- **Indoor residual spraying**

The parent(s)/LAR(s) will be asked if the house has been sprayed with a IRS and if so when.

The question asked at Visit 40, 42 and 44 will be

'Has indoor residual spraying been performed since last visit?'

The response to these questions (yes/no) will be documented in the eCRF.

The investigator will endeavor to find out what chemical was used from the malaria control programs in the study area and if the information is available, the investigator will record it in the eCRF.

APPENDIX B Assessment of a potential case of severe malaria

Algorithm for the evaluation of a hospital admission as a potential case of severe malaria

For all acute hospital admissions (i.e. except planned admissions for medical investigation/care or elective surgery and trauma admissions), an eCRF module will be filled in and a blood sample will be taken for evaluation of:

- Malaria parasite density.
- Blood culture.
- Hemoglobin.
- Blood glucose, lactate and base excess determination.

Lumbar Puncture (LP) is indicated by:

- Seizure except simple febrile seizure (simple febrile seizure is defined as associated with fever, lasts for 5 minutes or less, generalized as opposed to focal, not followed by transient or persistent neurological abnormalities, occurring in a child ≥ 6 months of age, with full recovery within 1 hour).
- Level of consciousness < 5 (or in children ≤ 9 months of age level < 4 [in association with best motor response of 1]).
- Prostration in child < 3 year of age.
- Meningism stiff neck/bulging fontanelle.
- Clinician's judgment: note that this list is not an exhaustive list of indications for lumbar puncture in clinical practice.

NB: LP can be delayed until child is stable.

Chest X-ray (CXR) is indicated by:

- Tachypnea (≥ 50 breaths per minute in a child < 1 year and ≥ 40 breaths per minute in a child ≥ 1 year) [Berkley, 2003].
- Lower chest wall indrawing.
- Abnormally deep breathing.
- Clinician's judgment: note that this list is not an exhaustive list of indications for CXR in clinical practice.

Methodologies for the assessment of clinical signs

Level of consciousness (Blantyre Score)

Conscious level will be scored using the Blantyre coma scale [Molyneux, 1989] (see Table 19). To obtain the coma score, add the scores for each section; the maximum coma score is 5, the minimum is 0.

Table 19 Coma scale for young children

	Score
Best motor response	
Localizes painful stimulus*	2
Withdraws limb from painful stimulus†	1
No response or inappropriate response	0
Best verbal response	
Cries appropriately with painful stimulus* or, if verbal, speaks appropriately	2
Moan or abnormal cry with painful stimulus or inappropriate speech	1
No vocal response to painful stimulus	0
Eye movement	
Watches or follows (e.g. mother's face)	1
Fails to watch or follow	0

* Pressure with blunt end of pencil on sternum or supraorbital ridge
† Pressure with horizontal pencil on nailbed of finger or toe

Guidance on the application of the scale is given by WHO [WHO, 2000a]. 'Testing should begin with a minimal stimulus which should be increased only to a point where a clear response is obtained. A localizing response must be distinguished from a brisk flexion response which brings the hand into coincidental proximity to the stimulus. The interpretation of 'verbal cry' is difficult, some children are stoical and the appropriateness of verbal response needs to be considered in the light of other responses and the age of the child. It is best to test orientation by asking the mother to move her face across the child's field of vision as the child may be less interested in looking at a strangers'face.

The coma score will be assessed at presentation. If it is depressed, it will be re-assessed after initial resuscitation; approximately one hour after correction of hypoglycemia and control of fits. This value will be recorded in the eCRF (if anticonvulsants were given prior to the assessment this will be documented in the eCRF). The intention is to avoid diagnosing cerebral malaria in a child with post-ictal coma [WHO, 2000a]. A child with persistent seizure activity despite optimal therapy should have the coma scale recorded 1 hour after the treatment is optimized.

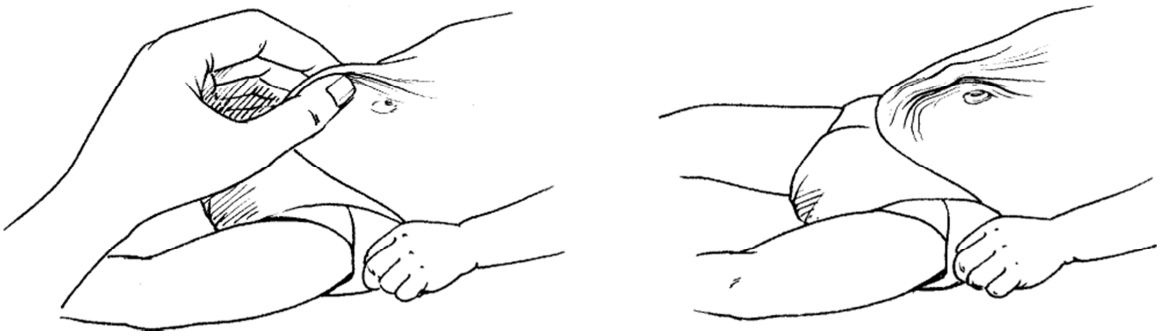
A normal coma score in a child of > 9 months of age is 5. In children ≤ 9 months of age, because localization of pain is difficult to assess, a normal coma score is 4 (in association with a best motor response of 1).

Skin Turgor

Dehydration will be assessed by skin pinch test. The standard procedures are:

- Locate the area on the child's abdomen halfway between the umbilicus and the side of the abdomen. The hand should be placed so that when the skin is pinched, the fold of skin will be in a line up and down the child's body and not across the child's body.
- Pinch the skin using the thumb and first finger. It is important to firmly pick up all of the layers of skin and the tissue under them for one second and then release it.
- When released, the skin pinch goes back either very slowly (longer than 2 seconds), or slowly (skin stays up even for a brief instant), or immediately. In a child with marasmus (severe malnutrition), the skin may go back slowly even if the child is not dehydrated. In an overweight child, or a child with edema, the skin may go back immediately even if the child is dehydrated. [WHO, 2000b; WHO, 2001b; WHO, 2005] (see Figure 2).

Figure 2 Diagnosis of dehydration



Left: pinching the child's abdomen to test for decreased skin turgor Right: Slow return of skin pinch in severe dehydration [WHO, 2005].

Prostration

Prostration will be defined as, in an acutely sick child, the inability to perform previously-acquired motor function: in a child previously able to stand, inability to stand; in a child previously able to sit, inability to sit and in a very young child, inability to suck.

Guidance on the assessment of prostration is given by the WHO [WHO, 2000a].

'Prostration must always be recorded directly and not based on history. Many children who are pyrexial and feel unwell prefer to lie or be carried but are capable of sitting if gently encouraged to do so.'

Respiratory signs

Respiratory signs will be assessed in line with the guidance on the assessment of respiratory signs by WHO [WHO, 2005].

'Respiratory signs should be looked for while the child is calm; (usually before the child is disturbed by hands on clinical examination). Ask the mother or caretaker to cautiously reveal part of the chest to look for lower chest wall indrawing or to count the respiratory rate. If a child is distressed or crying, it might need to be left for a brief time with its mother in order to settle, or the mother could be ask to breastfeed, before key signs such as respiratory rate can be measured. Then proceed to signs which require touching the child but are little disturbing.'

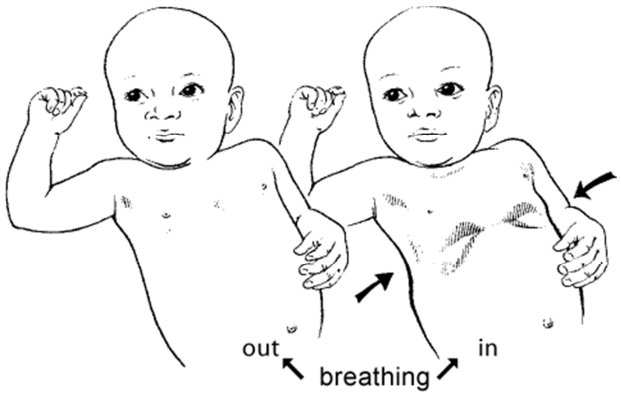
- **Rate:** The respiratory rate will be counted over one full minute while the child is calm [WHO, 2005].

- **Lower chest wall indrawing:** Lower chest wall indrawing will be defined as the inward movement of the bony structure of the chest wall with inspiration [WHO, 2001b] (see Figure 3).

  Note: chest indrawing should only be considered present if it is consistently present in a calm child. Agitation, a blocked nose or breastfeeding can all cause temporary chest indrawing [WHO, 2001b].

  Note: lower chest wall indrawing occurs when the lower chest wall goes in when the child breathes in; if only the soft tissue between the ribs or above the clavicle goes in when the child breathes, this is not lower chest wall indrawing [WHO, 2005].

Figure 3 Lower chest wall indrawing



With inspiration, the lower chest wall moves in [WHO, 2005]

- **Acidotic or Kussmaul respiration:** Abnormally deep breathing will be defined as breathing that is deep and labored while the chest is clear [WHO, 2005]. The key component is increased inspiratory and expiratory excursion of the chest [WHO, 2000a].

APPENDIX C Determination of *Plasmodium falciparum* asexual parasite density

Slide reading methodology

Two blood slide reading methods for the determination of *Plasmodium falciparum* asexual parasitemia density were approved by GSK Biologicals and collaborating partners and contributors.

The first method counts parasites relative to a concomitantly measured white blood cell count [Greenwood, 1991] and the second method counts parasites relative to a fixed measured blood volume [Planche, 2001]. These two methodologies are well established and used as gold-standards in the field. Slides are always taken in duplicate.

A positive parasitemia identified on any thick blood film must always be identified to species. This will be done on thin blood film except in case of low parasitemia. This section relates only to the determination of *Plasmodium falciparum* parasite density results.

Method 1: Counting against known blood cell concentration

This method follows the principles described by Greenwood and Armstrong [Greenwood, 1991].

- A contemporaneous measure of white and red blood cell count is determined and used in parasite density calculation.
- 6 μL of blood for the thick smear and 2 μL of blood for the thin smear are put on the same slide with a standard template. All slides are prepared in duplicate.
- **Negative result:** 100 fields on the thick blood smear free of parasites are to be read before a slide is declared negative.
- **Positive result:**
  - ***High parasitemia***: If 100 parasites or more are seen on the first field of the thick smear, the parasites are counted on the thin film. Red blood cells (RBC) and parasitized RBC are counted on the thin film until a minimum of 20 parasitized RBC are counted. If 20 parasitized RBC are counted before all the parasitized RBC in a field are counted, finish counting all parasitized RBCs and non-parasitized RBC in that field.
  - ***Medium parasitemia***: If less than 100 parasites are seen on the first field of the thick smear, parasites are counted up to when 200 white blood cells (WBC) are counted, on the thick smear. If 200 WBC are counted before finishing a field, finish counting all parasites and WBC in that field.
  - ***Low parasitemia***: If less than 10 parasites are counted per 200 WBC on the thick smear, the parasite counting is extended up to when 500 WBC have been

counted. If 500 WBC are counted before finishing a field, finish counting all parasites and WBC in that field.

Method 2: Counting against known blood volume

This method follows the principles described by Planche et al. [Planche, 2001].

- 10 µL of blood are spread with a pipette on an area of 1x1.8 cm, using a template on which the slide is set.
- **Negative result:** 100 fields free of parasites are to be read before a slide is declared negative.
- **Positive result**:
  - If there are 1 to 9 parasites per field, 100 fields are counted.
  - If there are 10 to 99 parasites per field, 10 fields are counted.
  - If there are 100 to 999 parasites per field, 1 field is counted.
- The parasitemia count will be calculated on the basis of the following formula:

Parasites/µL = parasites/field x Microscope Factor (MF)

- The Microscope Factor (MF) is the assumed blood volume per microscope high power field. To calculate the MF:
  - Make a thick blood film with 10 µL of blood.
  - Calculate the mean number of WBC per high power field, after counting WBC across 10 fields. (X)
  - Count the number of WBC in 10 µL of blood using a computerized blood analyzer. (Y)
  - The microscope factor is calculated as follows:

$$MF = Y / X$$

X = Mean WBC number per high power field (microscopy)

Y = WBC in 10 µL of blood (automated analyzer)

- For each microscope, this predetermination of the MF is done once.

Criteria for concordance for double reading of slides

All slides are read twice, by two independent readers to quantify the *Plasmodium falciparum* parasite density. A third independent reader will examine the slides if the following discrepancies are observed between the first two readings:

A. The result from one reader is negative and the one from the other reader is positive.

B. For high and medium parasitemia (parasitemia > 400 parasites/μL), the higher count divided by the lower count is > 2.

C. For low parasitemia (parasitemia ≤ 400 parasites/μL), the highest reading density is more than one log10 higher than the lowest reading.

If parasitemia result is high or medium and one is low, i.e. one is > 400/μL and the other is ≤ 400/μL, parasitemia, criteria (C) will be applied.

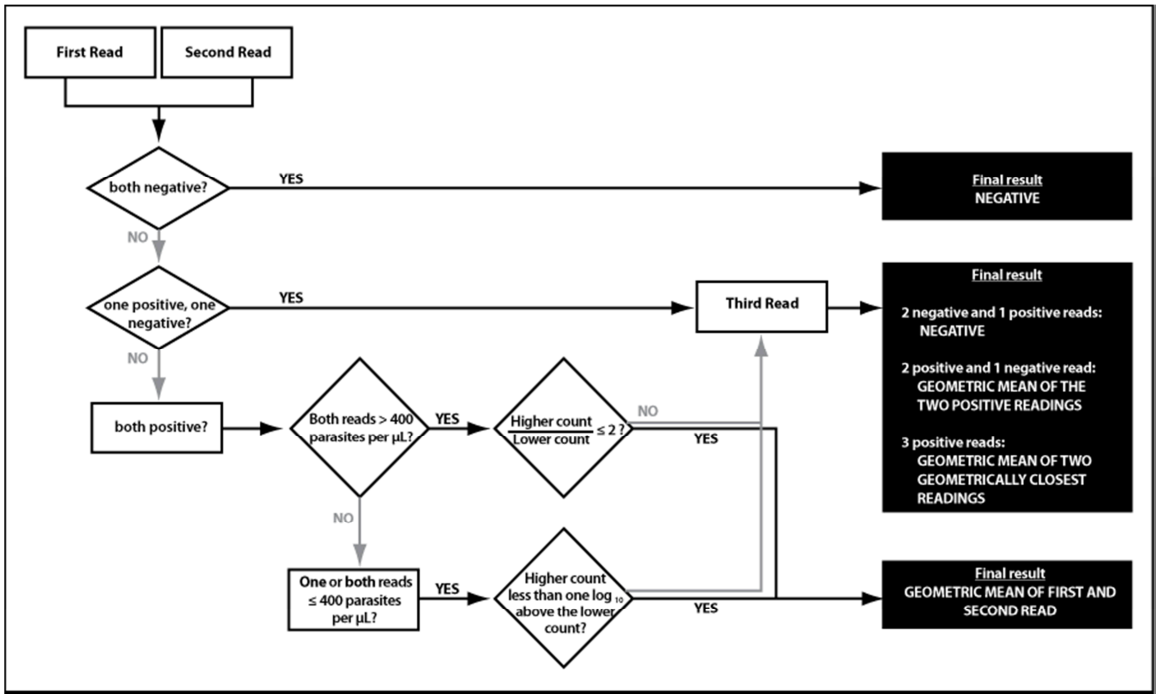
Determination of final result

If there are two concordant results, the final result is the geometric mean of the two readings.

If the first two readings are discordant, then the final result follows the following principles:

- For cases of positive/negative discrepancy (A), the majority decision following the reading by the third reader is adopted. If the decision is positive, the final result is the geometrical mean of the two positives.
- For cases of three positive readings (B and C), the final result is the geometric mean of the two geometrically closest readings (see Figure 4).

Figure 4 Determination of final result



Identification of *Plasmodium* species

Positive parasitemia identified on any thick blood film must always be identified to species. This will be done on thin blood film except in case of low parasitemia. Only *Plasmodium falciparum* results will be accounted for in the efficacy analyses.

APPENDIX D Interpretation of chest x-rays

All x-rays will be classified for quality and findings according to the scales in Table 20 and Table 21. For more details about these definitions, please refer to [WHO, 2001a]. Note that for 'uninterpretable' chest x-rays, no further reading will be made.

Table 20 Classification of quality of chest x-rays

Uninterpretable:	an image is classified as "uninterpretable" if the features of the image are not interpretable without additional images. No further reading should be made for such images.
Suboptimal:	an image is classified as "suboptimal" if the features allow interpretation of primary end-point but not of other infiltrates or findings. No entries should be made for other infiltrates for such images
Adequate:	an image is classified as "adequate" if the features allow confident interpretation of end-point as well as other infiltrates

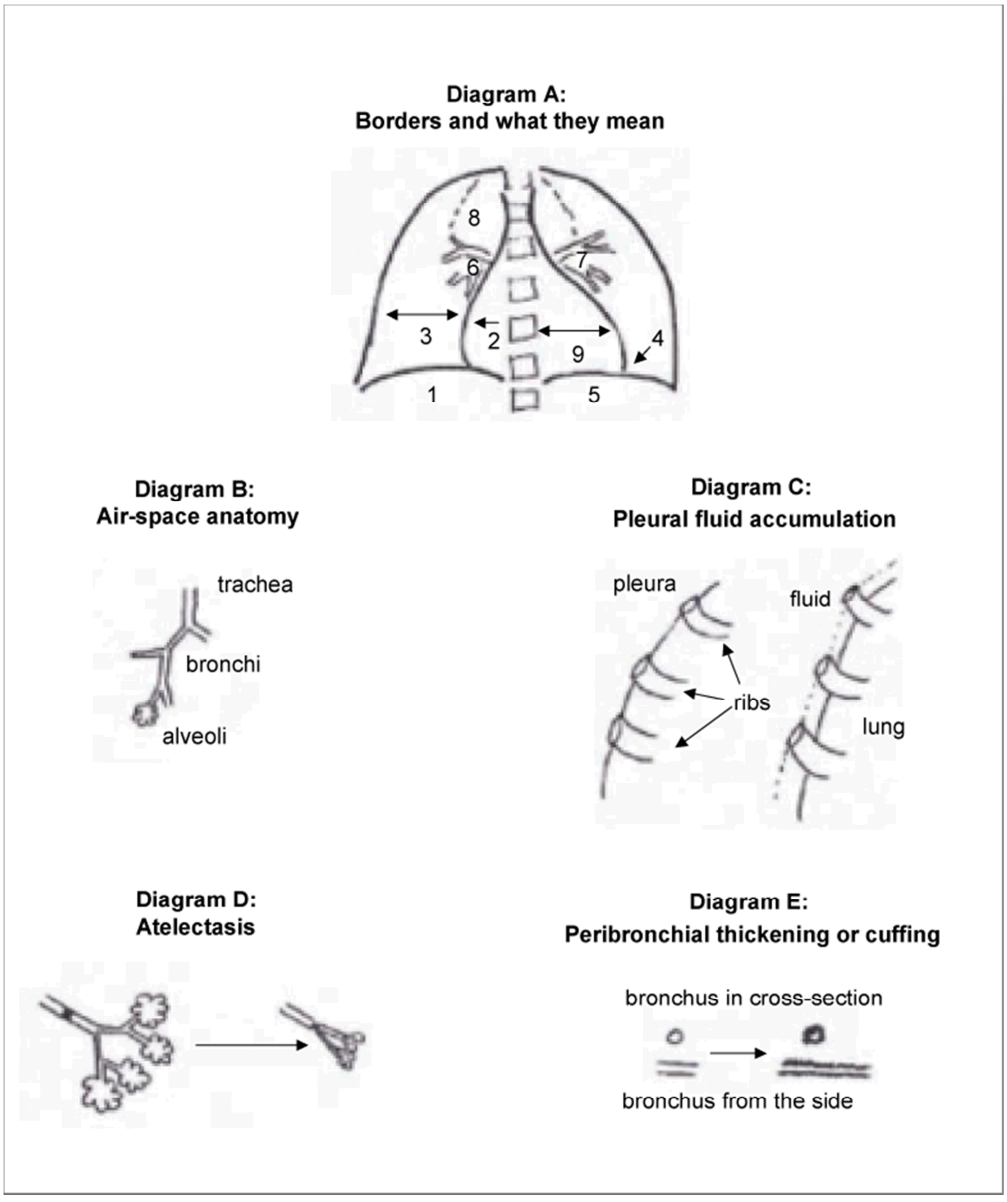
Table 21 Classification of findings of chest x-rays

Consolidation or pleural effusion	where consolidation is defined as a dense opacity that may be a fluffy consolidation of a portion or whole of a lobe or of the entire lung, often containing air bronchograms* and where pleural effusion is defined if it occurs in the lateral pleural space (and not just in the minor or oblique fissure) and is spatially associated with a pulmonary parenchymal infiltrate (including other infiltrate) or if the effusion obliterates enough of the hemithorax to obscure an opacity * atelectasis of an entire lobe that produces a dense opacity and a positive silhouette sign with the mediastinal border will be considered to be an endpoint consolidation
Other infiltrate	linear and patchy densities (interstitial infiltrate) in a lacy pattern involving both lungs, featuring peribronchial thickening and multiple areas of atelectasis. Lung inflation is normal to increased. It also includes minor patchy infiltrates that are not of sufficient magnitude to constitute primary end-point consolidation, and small areas of atelectasis which in children can be difficult to distinguish from consolidation.
No consolidation, infiltrate or effusion	

Definitions of terms: for the purposes of this study. (See Figure 5, below)

1) **Infiltrate**: any pathologic density in the lung.
2) **Alveoli**: tiny air-filled spaces where oxygen and $C0_2$ are exchanged (see diagram B)
3) **Bronchi**: tubes leading from the trachea to the alveoli
4) **Interstitium**: lung tissue outside the air-containing spaces: includes support tissues, blood vessels, bronchial walls, lymphatics
5) **Alveolar infiltrate**: alveoli filled with fluid (pus, edema, etc.)
6) **Heart and diaphragm borders**: (see diagram A).
7) **Air bronchogram**: branching linear lucent structure representing air still present in bronchi after the alveoli around them have consolidated; not to be confused with peribronchial thickening (an interstitial infiltrate)
8) **Consolidation**: especially dense, often homogeneous, confluent alveolar infiltrate sometimes may encompass an entire lobe or large segment, fluffy, mass-like, cloud-like density, erases heart and diaphragm borders (silhouette sign); often contains air bronchograms
9) **Atelectasis**: volume loss as air is absorbed from lung tissue, usually distal to an airway obstruction (e.g. a mucous plug). The lung tissue collapses like a Japanese fan, leaving a dense streak on the film that radiates outward from the hilum (see diagram D).
10) **Interstitial infiltrate**: includes peribronchial thickening and tiny areas of atelectasis (thought to be typical of viral infection).
11) **Pleural effusion:** fluid collecting in the pleural space around the lung, seen as a dense rim (the same density as the chest-wall muscles) interposed between the lung and the ribs (see diagram C)
12) **Peribronchial thickening or cuffing**: increased density of the walls of the smaller bronchi (away from the immediate hilar area) so that they become visible as circles or parallel lines (see diagram E)

Figure 5 Diagrams to support classification of findings of chest x-rays



1) **Right diaphragm:** erased by a right lower lobe infiltrate.
2) **Right heart (right atrium):** erased by a right middle lobe infiltrate.
3) **Minor fissure:** divides the right upper lobe from the right middle lobe; seen as a line when there is fluid in it; seen as a border when there is infiltrate in the lobe adjacent to it.
4) **Left heart (left ventricle):** erased by an infiltrate in the lingula (homolog of the right middle lobe; actually a part of the left upper lobe).
5) **Left diaphragm:** erased by an infiltrate in the left lower lobe, often behind the heart shadow.
6) & 7) **Right hilum and left hilum:** contain large blood vessels, lymph nodes, and main bronchi; bronchial walls may be normally visible here, but should disappear quickly just outside the immediate hilar area.
8) **Thymus:** bi-lobed semi-lucent structure in the upper mid chest with defined borders, may resemble an upper lobe infiltrate but often shrinks when the child is sick.
9) **Heart:** from the spine to the left heart border should be the same density.

APPENDIX E Laboratory assays

Determination of hemoglobin level

Quantification of hemoglobin level will be made at the investigator's sites according to laboratory standard operating procedures at the timepoints listed in Table 10.

Antibody titers against the CS repeat region

Blood for analysis of humoral immune response will be obtained at timepoints listed in Table 10. After centrifugation, serum samples should be kept at ≤ -20°C until shipment.

Antibody levels against *Plasmodium 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. Results will be reported in EU/mL.

(Amended 15 April 2015)

APPENDIX F Clinical laboratories

Table 22 Outsourced laboratories

Laboratory	Address
Center For Vaccinology (CEVAC) - Ghent University and Hospital	De Pintelaan, 185 Building A - 1st floor 9000 Ghent (Belgium)

APPENDIX G AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment 1**	
eTrack study number and Abbreviated Title	200599 (MALARIA-076)
Amendment number:	Amendment 1
Amendment date:	Amendment 1 Final: 18 February 2014
Co-ordinating author:	PPD (Scientific Writer, Keyrus Biopharma consultant for GSK Biologicals)

Rationale/background for changes:

- Name and function title of contributing authors have been updated on the Title page.
- The procedure for "passive case detection" was corrected.
- Central nervous system infections was removed from the secondary safety objective and only meningitis was kept as meningitis is the safety signal observed in malaria studies. This modification was done in the relevant sections of the protocol. Information on meningitis reporting was added in the section "adverse events of specific interest".
- The blood volume collected for parasite density and hemoglobin level was mistakenly set to 2.0 ml while it should have been 0.5 ml. This has been corrected.
- Clarification of the timing for passive surveillance for clinical malaria and severe malaria as well as for safety was brought to the list of study procedures.
- The timing for the study visits have been clarified in the event that the first study visit (Visit 39) occurs after the allowed interval for the subsequent visits.
- A note regarding the collection of creatinine and total bilirubin was added because disease manifestation of severe malaria at the later age are renal and liver dysfunctions.
- It was clarified that children who died before the study start of MALARIA-076 and whose parents consent will be reported as serious adverse events. If there is uncertainty on the cause of death based on the review of available medical records, a procedure for verbal autopsy should be performed. This was added in the passive surveillance for safety.
- All adverse events of specific interest (i.e. potential immune-mediated disease and meningitis) occurring during this study will be reported as serious adverse events. Clarification was performed in the relevant sections of the protocol.
- Clarification of the serious adverse events to be recorded during the study was brought in Section 9.2.1.

- An adaptation in the wording of the Blantyre coma scale was performed in order to clarify the best verbal response for the age range of the children enrolled in the present study (4 to 9 years).
- Smear and polymerase chain reaction for detection and quantification of parasite were mistakenly mentioned in Appendix E. This was removed as no polymerase chain reaction will be performed in the present study.

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

On the Title page

- PPD (~~Lead Clinical Development Manager~~***Clinical Research and Development Lead***)
- PPD ***(Study Delivery Manager, SynteractHCR consultant for GSK Biologicals)***
- PPD ***(Safety and Pharmacovigilance)***

In Synopsis

Secondary safety objective

- To describe the incidence of the following reported serious adverse events (SAEs): fatalities, related SAEs (related to vaccine administration in the primary study MALARIA-055 PRI [110021] and to study participation), malaria hospitalization, potential Immune-Mediated Disease (pIMDs), ***and*** meningitis, ~~and central nervous system (CNS) infections,~~ from January 2014 to December 2016.

Secondary safety endpoint

- The occurrence of the following reported SAEs: fatalities, related SAEs (related to vaccine administration in the primary study MALARIA-055 PRI [110021] and to study participation), malaria hospitalization, pIMDs, ***and*** meningitis, ~~and CNS infections,~~ over the time period starting January 2014 until the end of the 3-year follow-up period (Visit 45).

In List of abbreviations

~~CNS: Central Nervous System~~

In Glossary of Terms

Passive case detection:	The passive case detection is the detection of malaria disease by self-presentation to health facility in the study area. If there is a history of fever within 24 hours or axillary temperature is ~~≤~~ ***≥*** 37.5°C at presentation then a blood slide is taken and examined for parasitemia.

In Section 2.2.2 Safety objective

- To describe the incidence of the following reported serious adverse events (SAEs): fatalities, related SAEs (related to vaccine administration in the primary study MALARIA-055 PRI [110021] and to study participation), malaria hospitalization, potential Immune-Mediated Disease (pIMDs), ***and*** meningitis, ~~and central nervous system (CNS) infections~~, from January 2014 to December 2016.

In Section 6.5 Outline of study procedures

Table 10 List of study procedures

Epoch	*Epoch 001*			*Epoch 002*		*Epoch 003*	
Type of contact	**Screening Visit (Visit 39)**	**Visit 40[1]**	**Visit 41**	**Visit 42[1]**	**Visit 43**	**Visit 44[1]**	**Visit 45**
Timepoints	**Day 0**	**Within 30 days before Year 1**	**Year 1**	**Within 30 days before Year 2**	**Year 2**	**Within 30 days before Year 3**	**Year 3**
Recording reasons for non-participation	●						
Informed consent[2]	●						
Issuing identification card	O						
Check identification card		O	O	O	O	O	O
Check inclusion/exclusion criteria	●						
Collect demographic data[3]	●						
Physical examination	O		O		O		O
Anthropometry[4]	●		●		●		●
Screening conclusion	●						
Documentation of bednets and indoor residual spraying[5]		●		●		●	
Retrospective collection of safety and efficacy data since the last contact of the primary study (MALARIA-055)	●[6]						
Surveillance for clinical malaria and severe malaria[10]			●[7,6]		●[7,6]		●[7,6]
Surveillance for safety: recording of SAEs[7,11]			●[7,6]		●[7,6]		●[7,6]
Blood sampling for anti-CS antibodies measurement (approximately 0.5 mL)[8]			●		●		●
Blood sampling for parasite density measurement[9] and hemoglobin level (approximately ~~***2.0***~~ ***0.5*** mL)			●		●		●
Interim analysis			O		O		
Final analysis							O
Study Conclusion							●

[1] Field worker visits

[2] ICF to be signed by all subjects' parents/LARs who consent to let their child participate in this study and by subjects' parents/LARs who consent to allow reporting of the event leading to the death of their child before the start of MALARIA-076 in the MALARIA-076 database.
[3] Demographic data include age and gender
[4] Anthropometry consists of height, weight and mid upper arm circumference~~)~~
[5] Use of bednets and indoor residual spraying will be checked between 1 and 30 days before the annual visits (see APPENDIX A).
~~[6] Retrospective collection since the last contact of the primary study (MALARIA-055 PRI).~~
~~[7]~~***[6]*** Retrospective collection since the last visit.
~~[8]~~***[7]*** SAEs: fatalities, related SAEs (related to vaccine administration in the primary study MALARIA-055 PRI [110021] and to study participation), malaria hospitalization, pIMDs, and meningitis ~~and CNS infections~~ (see Section 9).
~~[9]~~***[8]*** Only for subjects that were included in the immunogenicity sub-cohort of the primary study (MALARIA-055 PRI [110021]) and who were enrolled in this extension study. There will be a maximum of 200 subjects from each age category in each site in the immunogenicity sub-cohort.
~~[10]~~***[9]*** A volume of 16 μL is required for this test.
[10] Note that passive surveillance for clinical and severe malaria is ongoing throughout the study (see Section 6.6.11)
[11] Note that passive surveillance for safety is ongoing throughout the study (see Section 6.6.12)
● 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 11 Intervals between study visits

Interval	Timing of visit[1]	Allowed interval[2]
Screening Visit (Visit 39)***[3]***	Study start at the center	~~Earliest October 2013~~ ***Not applicable***
Visit 40 (Field Worker Visit)~~[3]~~***[4]***	November 2014	October 2014 to December 2014
Visit 41 (Annual Visit)	December 2014	November 2014 to January 2015
Visit 42 (Field Worker Visit)~~[3]~~***[4]***	November 2015	October 2015 to December 2015
Visit 43 (Annual Visit)	December 2015	November 2015 to January 2016
Visit 44 (Field Worker Visit)~~[3]~~***[4]***	November 2016	October 2016 to December 2016
Visit 45 (Annual Visit)	December 2016	November 2016 to January 2017

[1] Whenever possible the investigator should arrange study visits within this interval.
[2] Subjects will not be eligible for inclusion in the According-to-Protocol (ATP) population for analysis of immunogenicity if they make the study visit outside this interval.
[3] Visit 39 should be performed as soon as the center is initiated. However, if the timing of Visit 39 is delayed beyond the allowed interval for Visit 40 or Visit 41, then those visits will be skipped.
~~[3]~~***[4]*** Field Worker Visits should be conducted between 1 and 30 days before Annual Visits.

In Section 6.6 Detailed description of study procedures

6.6.9 Documentation of bednets and indoor residual spraying

Bednets usage and indoor residual spraying (IRS) will be assessed during field worker visits ***(Visits 40, 42 and 44)*** at subjects' house between 1 and 30 days before the annual visits ~~(Visits 40, 42 and 44).~~

6.6.10 Retrospective collection of efficacy and safety data

During Visit 39, all subjects for whom the parents/LARs gave their consent to let their child participate in this study, will have a retrospective collection of efficacy data (cases of clinical, severe or malaria hospitalization) and safety data (SAEs: fatalities, related SAEs [related to vaccine administration in the primary study MALARIA-055 PRI and to study participation], malaria hospitalization, pIMD, ***and*** meningitis~~, and CNS infections~~) since their last contact in the primary study MALARIA-055 PRI (110021). Retrospective

data will be collected, for example by questioning subject's parents/LARs and by reviewing available medical records. Collected information needs to be recorded in the eCRF.

For subjects who will not be enrolled in the study, because they died before the start of MALARIA-076, subjects' parent(s)/LAR(s) will be asked if they consent to allow reporting of the event leading to the death of their child in the MALARIA-076 database. If the parent(s)/LAR(s) agree, they will be asked to sign an ICF. ***This event will be reported as SAE in the MALARIA-076 database.***

6.6.11 Surveillance for efficacy
In Passive surveillance for severe malaria

Note that measurement of creatinine and total bilirubin were not specified per algorithm. If performed for case management these will be captured in the eCRF.

6.6.12 Passive surveillance for safety
The following SAEs: fatalities, related SAEs (related to vaccine administration in the primary study MALARIA-055 PRI [110021] and to study participation), malaria hospitalization, pIMDs, and meningitis, ~~and CNS infections~~ will be collected for all subjects presenting to health facilities in the study area and through annual clinic visits.

Verbal autopsy will be performed on all cases of mortality occurring outside hospital ***and where it adds value to ascribe the cause of a fatal event.*** ~~as described in WHO (2007)~~. ***The questionnaire used will be based on the INDEPTH standard and adapted to be locally appropriate [WHO, 2007]. For children who died before study start and whose parents consent, the death will be reported as an SAE. If there is uncertainty of cause of death based on the review of available medical records, a verbal autopsy should be performed.***

6.6.13.2 Blood sampling for prevalent parasitemia and anemia
A volume of at least ~~2.0~~ ***0.5*** mL of whole blood for parasite density (16 µL needed for this test) and haemoglobin level measurement should be drawn from all subjects.

In Section 6.7 Biological samples

Table 12 Biological samples

Sample type	Quantity	Unit	Timepoint	Sub-cohort Name*
Blood for anti-CS antibodies	0.5	ml	Visit 41 Visit 43 Visit 45	Immunogenicity sub-cohort
Blood sampling for parasite density and hemoglobin level	~~2~~ ***0.5***	ml	Visit 41 Visit 43 Visit 45	All subjects

* Refer to Section 5.1 for sub-cohort description

In Section 9 Safety

9.1.3 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~~ 9.1.1 and~~ 9.1.2). 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.

9.1.4 Adverse events of specific interest

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

9.1.4.1 Potential immune-mediated diseases

When there is enough evidence to make any of the above diagnoses, the ~~AE~~***event*** must be reported as a pIMD. ***Regardless of it being considered an AE or an SAE, it should be reported per the SAE reporting rules***. ~~Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs 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.~~

9.1.4.2 ~~CNS infections and CNS inflammations~~ *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 appropriate targeted follow-up forms included in the eCRF.

9.2 Detecting and recording serious adverse events

SAEs that will be reported under this protocol are: those that are fatal, those that are related to vaccine administration in the primary study MALARIA-055 PRI (110021), those that are related to study participation, malaria hospitalization, pIMDs, and meningitis~~, and CNS infections~~. SAEs will be captured at the health facilities in the study area or by direct questioning at the Annual Visits (Visits 41, 43 and 45).

9.2.1 Time period for detecting and recording serious adverse events

In addition, at Visit 39, a retrospective collection of SAEs ***(fatalities, related SAEs, malaria hospitalization, pIMDs, and meningitis)*** since the last study contact of the primary study (MALARIA-055 PRI [110021]) will be performed.

An overview of the protocol-required reporting periods for SAEs (fatalities, related SAEs, malaria hospitalization, pIMDs, and meningitis~~, and CNS infections~~) is given in Table 17.

Table 17 Reporting periods for serious adverse events

Event	From Visit 39* to Visit 45
Fatalities	
Related SAEs	
Malaria hospitalization	
pIMDs	
Meningitis~~, and CNS infections~~	

* A retrospective collection of safety data (SAEs: fatalities, related SAEs [related to vaccine administration in the primary study MALARIA-055 PRI and to study participation], malaria hospitalization, pIMD, ***and*** meningitis~~, and CNS infections~~) since the last contact in the primary study MALARIA-055 PRI (110021) will be performed at Visit 39.

9.3 Reporting of serious adverse events and other events

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
Fatalities	24 hours*	electronic SAE report	24 hours*	electronic SAE report
Related SAEs**	24 hours*	electronic SAE report	24 hours*	electronic SAE report
Malaria hospitalization	24 hours*	electronic SAE report	24 hours*	electronic SAE report
pIMDs	24 hours*	electronic SAE report	24 hours*	electronic SAE report
Meningitis~~, and CNS infections~~	24 hours*	electronic SAE report	24 hours*	electronic SAE report

* Timeframe allowed after receipt or awareness of the information.
** Related to vaccine administration in the primary study MALARIA-055 PRI (110021) and to study participation.

9.4.1.2 Follow-up after the subject is discharged from the study

The investigator will follow subjects with SAEs, pIMDs ~~(serious or non-serious)~~, or subjects withdrawn from the study as a result of an SAE, until the event has resolved, subsided, stabilized, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.

In Section 11 Statistical methods

11.2.2 Safety endpoint

- The occurrence of the following reported SAEs: fatalities, related SAEs (related to vaccine administration in the primary study MALARIA-055 PRI [110021] and to study participation), malaria hospitalization, pIMDs, ***and*** meningitis~~, and CNS infections~~, over the time period starting January 2014 until the end of the 3-year follow-up period (Visit 45).

11.3 Power of the trial

The incidence of severe malaria and clinical malaria following a primary RTS,S/AS01$_E$ vaccination given in 2 different age categories, with or without booster, across different transmission settings will be described. If 600 subjects per group in each category are enrolled with an attack rate of 24 episodes over 3 years in controls (4% over 3 years [or 1.3% per year]) of severe malaria~~. T~~***, t***his sample size will allow to detect a 2-fold increase in the incidence of severe malaria between the recipients of primary vaccination only (R3C versus C3C) or primary vaccination + booster (R3R versus C3C) over the 3-year additional follow-up, with 80% power.

11.9 Analysis of safety

For both age categories (6-12 weeks and 5-17 months), safety will be evaluated by examining SAEs (fatalities, related SAEs [related to vaccine administration in the primary study MALARIA-055 PRI and to study participation], malaria hospitalization, pIMDs, and meningitis, ~~and CNS infections~~) from study start (MALARIA-076). All safety analyses will be performed separately for both age categories.

In APPENDIX B Assessment of a potential case of severe malaria

Table 19 Coma scale for young children

	Score
Best motor response	
Localizes painful stimulus*	2
Withdraws limb from painful stimulus†	1
No response or inappropriate response	0
Best verbal response	
Cries appropriately with painful stimulus* or, if verbal, speaks ***appropriately***	2
Moan or abnormal cry with painful stimulus or ***inappropriate speech***	1
No vocal response to painful stimulus	0
Eye movement	
Watches or follows (e.g. mother's face)	1
Fails to watch or follow	0

* Pressure with blunt end of pencil on sternum or supraorbital ridge

† Pressure with horizontal pencil on nailbed of finger or toe**)**

In APPENDIX E Laboratory assay

Determination of parasitemia and hemoglobin level

~~Blood samples for smear and polymerase chain reaction will be taken at the timepoints listed in Table 10.~~ Detection and quantification of *Plasmodium falciparum* parasitemia and hemoglobin level will be made at the investigator's sites according to laboratory standard operating procedures ***at the timepoints listed in Table 10***.

GlaxoSmithKline Biologicals

Vaccine Value & Health Science (VVHS)

Protocol Amendment 2

eTrack study number and Abbreviated Title	200599 (MALARIA-076)
Amendment number:	Amendment 2
Amendment date:	Amendment 2 Final: 15 April 2015
Co-ordinating author:	PPD (Scientific Writer, Keyrus Biopharma contractor for GSK Biologicals)

Rationale/background for changes:
In order to maximize and harmonize the clinical information available during the gap period the following information will be documented retrospectively and prospectively in the eCRF:

- Results of clinical diagnoses of malaria.
- Rapid diagnostic test (RDT).
- Blood slides read to guide treatment at the time of presentation.

In Appendix E, text describing "Determination of parasitemia" was removed because "Determination of *Plasmodium falciparum* asexual parasite density" is detailed in Appendix C.

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

On the Title page

- PPD ***(Study Delivery Manager)***
- PPD ***(Local Delivery Lead)***
- PPD ***(Project Data Manager)***

In List of abbreviations

RDT: ***Rapid diagnostic test***

In Section 6.6 Detailed description of study procedures

6.6.10 Retrospective collection of efficacy and safety data

For subjects who will not be enrolled in the study, because they died before the start of MALARIA-076, subjects' parent(s)/LAR(s) will be asked if they consent to allow reporting of the event leading to the death of their child in the MALARIA-076 database. If the parent(s)/LAR(s) agree, they will be asked to sign an ICF. This event will be

reported as SAE in the MALARIA-076 database ***and any available information captured in the inpatient module of the eCRF or any other specific section as applicable.***

6.6.11 Surveillance for efficacy

Retrospective data since the previous visit will be collected by questioning subject's parents/LARs and by reviewing available medical record during annual clinic visit (Visits 41, 43, and 45). Collected information needs to be recorded in the eCRF. ***For clarity, if available the following data will be collected: history of fever, temperature, parasite density, treatment administered, any clinical diagnoses of malaria, rapid diagnostic test (RDT) and blood slides read to guide treatment at the time of presentation will be captured.***

Passive surveillance for clinical malaria

Data points that will be captured in the eCRF for all cases of suspected clinical malaria are: history of fever; temperature; parasite density; treatment administered. ***To supplement this information, any clinical diagnoses of malaria, RDT and blood slides read to guide treatment at the time of presentation will be captured.***

Passive surveillance for severe malaria

Harmonization of case evaluation across centers will be assured by training of clinicians in the assessment of clinical signs and the standardization of equipment and processes used for laboratory investigations. On all admissions, data will be captured to support the endpoints of this study. ***In addition RDT and blood slides read to guide treatment at the time of presentation will be captured.***

In APPENDIX E Laboratory assay

Determination of ~~parasitemia and~~ hemoglobin level

~~Detection and q~~***Q***uantification of ~~*Plasmodium falciparum* parasitemia and~~ hemoglobin level will be made at the investigator's sites according to laboratory standard operating procedures at the timepoints listed in Table 10.

Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	200599 (MALARIA-076)
Date of protocol amendment	Amendment 2 Final: 15 April 2015
Detailed Title	An open extension to the phase III, multi-center study MALARIA-055 PRI (110021) to evaluate long-term efficacy, safety and immunogenicity of the RTS,S/AS01$_E$ candidate vaccine against malaria disease caused by *Plasmodium falciparum* in infants and children in Africa
Sponsor signatory	Didier Lapierre (Vice President, Clinical Development Malaria, TB & Adjuvant support)
Signature	PPD
Date	April 16th, 2015

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