Protocol Amendment 3

Study ID: 204889

Official Title of Study: Efficacy, Safety and Immunogenicity Study of GSK Biologicals' Candidate Malaria Vaccine (SB257049) Evaluating Schedules With or With-out Fractional Doses, Early Dose 4 and Yearly Doses, in Children 5-17 Months of Age

NCTID: NCT03276962

Date of Document: 14 November 2019

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

Primary study vaccine/product and number	• GlaxoSmithKline (GSK) Biologicals' candidate *Plasmodium falciparum* malaria vaccine RTS,S/AS01$_E$ (SB257049).
Other study vaccine/product	• Rabies vaccine (Rabipur™)
eTrack study number and abbreviated title	204889 (MALARIA-094)
EudraCT number	2016-000290-20
Date of protocol	Final: 16 February 2016
Date of protocol amendment	Amendment 1 Final: 13 September 2016 Amendment 2 Final: 06 April 2017 ***Amendment 3 Final: 14 November 2019***
Title	Efficacy, safety and immunogenicity study of GSK Biologicals' candidate malaria vaccine (SB257049) evaluating schedules with or without fractional doses, early Dose 4 and yearly doses, in children 5-17 months of age.
Detailed title	Phase IIb randomized, open-label, controlled, multi-center study of the efficacy, safety and immunogenicity of GSK Biologicals' candidate malaria vaccine RTS,S/AS01$_E$ evaluating schedules with or without fractional doses, early Dose 4 and yearly doses, in children 5-17 months of age living in sub-Saharan Africa.
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Contributing authors/ *Reviewers*	• PPD , TCS, ***and*** PPD ***, ICON,*** Study Data Managers, contractors for GSK Biologicals • PPD , Study Delivery Leads • PPD , Vaccine Supply Coordinator • PPD , Biostatistics • PPD Safety Physicians • PPD , Clinical Laboratory Sciences Lead

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Contributing authors/ *Reviewers* (continues)	• PPD, Clinical Laboratory Sciences Study Manager*s* • PPD, Lead Statistician*s* • PPD Clinical Research and Development Leads • PPD, Senior Local Delivery Lead*s* • PPD, Global Patent representative • PPD, Business and Decision Life Sciences, Project Data Managers, contractors for GSK Biologicals • PPD, Project Statistician*s* • PPD, Clinical Regulatory Affairs representative • PPD, Study Delivery Manager • PPD, Clinical Research & Development, R&D Center Belgium and PPD, Clinical & Epidemiology Project Lead, DDW Vaccines, Belgium

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Amended 14 November 2019

Protocol Amendment 3 Sponsor Signatory Approval

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Sponsor signatory	François Roman, Clinical & Epidemiology Project Lead, DDW Vaccines
Signature	_____
Date	_____

Protocol Amendment 3 Rationale

Amendment number: Amendment 3

Rationale/background for changes:

Case definition of severe *P. falciparum* malaria: Per protocol, impaired consciousness was to be evaluated using the Glasgow coma score for children ≥ 2 years and using the Blantyre coma score for children < 2 years (Appendix C: Case definition of severe *P. falciparum* malaria). However, local practice is to use the Blantyre coma score for children. After discussion with the Independent Data Monitoring Committee (IDMC), only the Blantyre coma score is to be used for assessment of impaired consciousness in all age groups in the study.

Per protocol, filter paper blood spots were to be collected for use in the ancillary study, MALARIA-095, to look at vaccine efficacy against clinical and asymptomatic malaria infection using ultra-sensitive molecular amplification and sequencing methodology. However, the MALARIA-095 protocol will use samples only up to Month 32. The MALARIA-094 protocol has been amended to reflect filter paper sampling up until the Month 32 timepoint.

In the assessment of vaccine efficacy against all episodes of malaria (Section 11.7.2), an estimated seven days for drug clearance (half-life) following an episode meeting the case definition under evaluation was to be subtracted from the follow-up time. This has been changed to 14 days to be in line with actual clearance and also to allow for comparison with previous Phase III efficacy data in the same population (MALARIA-055 data).

The anti-CS immunogenicity endpoint for the immunogenicity secondary objective ‘Immune response to the CS antigen’ was inadvertently omitted between protocol amendment 1 and protocol amendment 2 and has been reinstated.

According to EU regulation, the definition of end of study (EoS) must be included in the clinical protocol, and the study report submitted in a predefined timeframe based on the EoS milestone. Per GSK policies, a summary of the study results have to be publicly disclosed, the reference milestone for which is based on the primary completion date. The definitions for the EoS and primary completion date have been clarified. Details for the disclosure of protocol information and study results have been updated (Section 12.5).

APPENDIX D Safety Laboratory Testing: CLS South Africa: the number of tests that can be performed by polymerase chain reaction (PCR) on cerebrospinal fluid (CSF) and serum samples has increased. The Appendix has been amended to show the breadth of analyses available.

Protocol Amendment 3 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 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 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 (LAR).
- 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, 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.

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Investigator name	_____
Signature	_____
Date	_____
	_____

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

Phase IIb randomized, open-label, controlled, multi-center study of the efficacy, safety and immunogenicity of GSK Biologicals' candidate malaria vaccine RTS,S/AS01$_E$ evaluating schedules with or without fractional doses, early Dose 4 and yearly doses, in children 5-17 months of age living in sub-Saharan Africa.

Indication

Primary immunization against malaria disease caused by *Plasmodium falciparum (P. falciparum)* in children.

Rationale for the study and study design

Rationale for the study

GSK Biologicals and PATH are committed to develop a malaria vaccine for reduction of malaria disease burden in children and contribution to the malaria elimination goal. Characterization of an optimal dosing regimen and boosting schedules will be critical.

The results of the efficacy study MALARIA-055 PRI, including the long term follow-up data and efficacy of the fourth dose administered 18 months after the third dose, and the preliminary results of MALARIA-071 were reviewed by the European Medicines Agency (EMA) during the assessment of the initial Application of the RTS,S/AS01$_E$ candidate vaccine. The EMA asked the company to address the following points in ongoing or future studies: 1) the timing of the fourth dose and evaluation of the safety and efficacy of an early fourth dose; 2) the efficacy and safety of multiple yearly doses and whether the vaccine predisposes to some degree of hyporesponsiveness to sequential doses; and 3) the plans to further investigate the potential utility of a delayed and fractionated third dose schedule in the target age range.

The current study is designed to address these points in the pediatric population. It aims to:

- Establish proof of concept (POC) for a fractional (Fx) dose schedule under conditions of natural exposure.
- Establish the role of third dose spacing in a fractional dose schedule.
- Describe the effect of an earlier full fourth dose at Month 14.
- Describe the effect of multiple fractional or full yearly doses.

Rationale for the study design

A recent controlled human malaria infection (CHMI) study (MALARIA-071) demonstrated superior protection against malaria infection associated with the use of a fractional third dose in a 0, 1, 7-month schedule with a vaccine efficacy against infection of 86.7% (95% CI: 66.8; 94.6; p<0.0001) versus 62.5% (95% CI: 29.4; 80.1; p=0.0009) in the standard 0, 1, 2-month schedule. The incremental efficacy of the 0, 1, 7-month schedule over the 0, 1, 2-month schedule was 64.4% (95% CI: -7.9; 88.3; p=0.0741) [Regules, 2016]. The current study intends to establish POC for a fractional dose schedule under conditions of natural exposure. The study will be conducted in children 5-17 months old at first vaccination living in areas of mid to high malaria transmission, in line with the age group recommended by the World Health Organization (WHO) [WHO, 2016]. Infants 6-12 weeks old will not be included in this POC study to avoid interference of co-administration with the standard Expanded Program on Immunization (EPI) vaccines.

Results from this study will be critical in informing future possibilities for the development of vaccine-based strategies which, in combination with other interventions, may contribute to the malaria elimination agenda.

The study proposed herein will include five study groups. One group (R012-20) will receive the standard schedule consisting of RTS,S/AS01$_E$ full dose given at Month 0, Month 1, Month 2 and a fourth dose at Month 20. This corresponds to the schedule that received a positive scientific opinion from EMA. The four other groups will receive alternative schedules as follow:

- Group R012-14-mD will receive RTS,S/AS01$_E$ full dose at Month 0, Month 1, Month 2, an early fourth dose at Month 14 and yearly full doses at Month 26 and Month 38.
- Group Fx012-14-mFxD will receive RTS,S/AS01$_E$ full dose at Month 0 and Month 1, RTS,S/AS01$_E$ fractional dose (1/5th dose) at Month 2 and yearly fractional doses at Month 14, Month 26, Month 38.
- Group Fx017-mFxD will receive RTS,S/AS01$_E$ full dose at Month 0 and Month 1, RTS,S/AS01$_E$ delayed fractional third dose (1/5th dose) at Month 7 and yearly fractional doses at Month 20 and Month 32.
- Control group: will receive three doses of rabies vaccine at Month 0, Month 1 and Month 2.

Rationale for the inclusion of a control group

This study plans to evaluate malaria occurrence in subjects vaccinated with RTS,S/AS01$_E$ according to various schedules and in subjects vaccinated with a non-malaria comparator vaccine (rabies vaccine). While partial protection provided by RTS,S/AS01$_E$ in the age range of subjects which will be enrolled in this study has been demonstrated, the use of a non-malaria comparator vaccine is deemed acceptable, in line with relevant published references about the use of placebo in vaccine trials [Rid, 2014; WHO, 2013].

It is deemed unacceptable to use a placebo control when study participants are exposed to unacceptable levels of risk from delaying administration of a safe and effective vaccine that is accessible through the public health system of the country in which the study is planned. However, the Nuffield Council on Bioethics guidelines state that the use of placebos may be acceptable if participants are not deprived of a treatment they would have otherwise received, but are provided at a minimum with the standard of care that is the best available in the country's public health system. CIOMS (Council for International Organizations of Medical Sciences), ICH (International Committee on Harmonization) and UNAIDS (Joint United Nations Programme on HIV/AIDS) guidelines stipulate that researchers must take steps to minimize any risks associated with the use of controls. The protocol should explain clearly the scientific justification for using a placebo-controlled design, and specifically address whether (1) the study question cannot be answered with an active-controlled study design; and (2) the risks of delaying an existing efficacious vaccine are adequately minimized or mitigated; and (3) the use of a placebo control is justified by the potential public health value of the research; and (4) the research is responsive to local health needs.

In accordance with these recommendations, the use of a non-malaria comparator vaccine in this study is deemed acceptable as:

1. **Local availability.** Local regulatory recommendation for RTS,S/AS01$_E$ use has not been granted. If granted, it is anticipated that availability in the local health system will take some time to deploy. It is therefore not the case that study subjects would be deprived from a locally available effective prevention tool.

2. **Risk mitigation.** Subjects will have access to the best locally available malaria prevention and treatment options. All screened subjects will be provided with an insecticide-treated bednet (ITN), and malaria diagnosis and treatment will be ensured. The investigator will make every effort to ensure that preventive measures as provided by the government are adhered to and under circumstances where this is not possible discussions with the sponsor need to take place. It is anticipated that subjects will benefit from participation in the study in terms of facilitated access to care and relatively intense health monitoring. Reduced levels of morbidity related to participation in a RTS,S/AS01$_E$ study has been documented [Hamel, 2014].

3. **Study design justification.** Without a control group, the following scientific questions could not be answered with scientific integrity:

   – Comparison of malaria incidence between different time periods.

     Without a control group, the direct comparison of post-RTS,S/AS01$_E$ vaccination malaria incidence between two different study periods (example: assessment of post-Dose 3 protection in the 0, 1, 2-month and 0, 1, 7-month schedules, evaluation of optimal timing of the fourth dose, waning of efficacy) would carry a risk of bias associated with seasonal variations in malaria incidence.

   – Evaluation of strain-specificity of protection.
     A genetic characterization of malaria infections is planned as an ancillary study (using samples collected in the present study) with the aim to determine whether vaccine efficacy varies according to the parasite strain. This requires comparison of parasite genetics in the vaccinated groups with the Control group.

4. **Public health need.** RTS,S/AS01$_E$ has been shown to prevent malaria with a moderate level of efficacy [The RTS,S Clinical Trials Partnership, 2015]. The development of a malaria vaccine with higher efficacy remains an important public health need [Malaria Vaccine Technology Roadmap, 2013]. Finding the immunization schedule able to provide the highest protection is very relevant to local public health needs.

To be noted, the study subjects in the Control group will get the benefit of receiving a rabies vaccine as comparator vaccine,

also advocated as a valuable preventive health intervention by the WHO [WHO, 2007].

Rationale for the use of a rabies vaccine as a comparator vaccine

Subjects randomized to the Control group will receive three doses of a cell culture rabies vaccine on a 0, 1, 2-month schedule. In humans, rabies is almost invariably fatal once clinical signs occur. Bites by rabid domestic dogs cause 99% of human rabies deaths globally. More than 3.3 billion people live in regions where rabies is enzootic. Approximately 55 000 people die from rabies each year, the vast majority of these deaths occurring in Asia and Africa [WHO, 2007]. Estimates of risks of infection with rabies in Africa are available from the WHO [WHO, 2015].

The efficacy of cell culture-derived rabies vaccines including human diploid cells vaccine (HDCV), purified Vero cell ***rabies*** vaccine (PVRV), purified chick embryo cells vaccine (PCECV), purified hamster kidney cells vaccine (PHKCV) and purified duck embryo cells vaccine (PDEV) has been demonstrated [WHO, 2010]. In this study, a PCECV (*Rabipur*) will be used as comparator vaccine.

PCECV has been widely used for rabies pre-exposure prophylaxis in children. In total, PCECV has been administered to more than 1200 children in clinical studies, from toddlers to those in elementary school, demonstrating safety and immunogenicity. Various schedules of PCECV (2-doses and 3-doses) and administration route (intramuscular and intradermal) were evaluated in children. Intramuscular administration resulted in 3- to 5-fold higher titers than intradermal administration [Malerczyk, 2013]. In studies using pre-exposure prophylaxis in children, all children achieved adequate rabies virus neutralizing antibody (VNA) concentrations by Day 14, i.e., after receiving two doses of vaccine, even before the third dose of vaccine was received. Regardless of the route of administration (intramuscular or intradermal), VNA concentrations reached levels above 0.5 IU/ml [Malerczyk, 2013]. The definition of a target antibody titer varies among laboratories and is influenced by the type of test conducted. WHO specifies a titer of 0.5 IU/ml [WHO, 2007].

Objectives

Primary

- **Efficacy: Incremental efficacy of a schedule with a fractional third dose at Month 2 over the standard schedule**

  To demonstrate the superiority of a 3-dose schedule of GSK Biologicals' malaria vaccine RTS,S/AS01$_E$ with a fractional third dose at Month 2 compared to a standard schedule of RTS,S/AS01$_E$ with three full doses in terms of vaccine efficacy against clinical malaria (primary case definition) over 12 months post-Dose 3.

  Criterion:

  The lower limit of the 95% CI of the incremental vaccine efficacy estimate is above 0.

Secondary

- **Efficacy**
  - To assess the incremental vaccine efficacy against clinical malaria of a schedule with a fractional third dose at Month 2 versus a schedule with 3 full doses (primary and secondary case definitions) over 12 months post-Dose 3.
  - To assess the incremental vaccine efficacy against clinical malaria, over 7 and 12 months post-Dose 3, of a schedule with a fractional third dose at Month 7 versus a schedule with a fractional third dose at Month 2.
  - To assess the incremental vaccine efficacy against clinical malaria, over 7 and 12 months post-Dose 3, of a schedule with a fractional third dose at Month 7 versus a schedule with 3 full doses.
  - To assess the incremental vaccine efficacy against clinical malaria, over 12 months post-Dose 4, post-Dose 5 and post-Dose 6 of a schedule with a fractional third dose at Month 2 and yearly fractional doses versus a schedule with full doses at Month 0, Month 1, Month 2 and yearly full doses.
  - To assess the incremental vaccine efficacy against clinical malaria, over 12 months post-Dose 4, of a schedule with a fractional third dose at Month 7 versus a standard schedule with 4 full doses at 0,1,2,20 months.

- To assess the vaccine efficacy and impact of each RTS,S/AS01$_E$ schedule over the entire study period by measuring the efficacy against clinical malaria at Months 14, 20, 26, 32, 38 and 50.
- To assess the prevalence of *P. falciparum* infections of each RTS,S/AS01$_E$ schedule at cross-sectional visits (monthly from Month 0-20 and every three months thereafter till study end).
- To assess the vaccine efficacy against incident *P. falciparum* infections defined by positive blood slide over the entire study period.

- **Immunogenicity: Immune response to the CS and HBs antigens**
  - To describe the antibody response to the anti-circumsporozoite protein of *P. falciparum* (anti-CS) for each schedule.
  - To describe the antibody response to the hepatitis B surface antigen (anti-HBs) for each schedule.
- **Safety and reactogenicity**
  - To assess the safety of RTS,S/AS01$_E$ for each schedule in terms of serious adverse events (SAEs), unsolicited adverse events (AEs) and AEs of specific interest.
  - To assess the reactogenicity of RTS,S/AS01$_E$ in terms of solicited local and general AEs.
  - To assess the safety of RTS,S/AS01$_E$ in terms of biochemistry (alanine aminotransferase [ALT], creatinine) and hematology (hemoglobin, white blood cells [WBC], platelets) parameters.

Tertiary

- **Immunogenicity**
  - To describe the anti-CS antibody response in terms of avidity.

Of note, blood samples taken in this study may also be used in ancillary studies. More details on ancillary studies are provided in the study design section of this protocol.

Study design

- **Experimental design:** Phase IIB, randomized, open-label, controlled, multi-centric study with five parallel groups.
- **Duration of the study:** Approximately 50 months, with two interim analyses and option for conditional continuation (see next bullet point).
  - Epoch 001: Starting at Visit 1 (Screening) and ending at Visit 17 (Month 13). Note: the data up to Visit 18 (Month 14) pertains to Epoch 001.
  - Epoch 002: Starting at Visit 18 (Month 14) and ending at Visit 26 (Month 23). Note: the data up to Visit 27 (Month 26) pertains to Epoch 002.
  - Epoch 003: Starting at Visit 27 (Month 26) and ending at Visit 32 (Month 35). Note: the data up to Visit 33 (Month 38) pertains to Epoch 003.
  - Epoch 004: Starting at Visit 33 (Month 38) and ending at Visit 38 (Month 50).
- ***Primary completion date: Visit 18 (Month 14) or last visit of Epoch 001.***
  Refer to the GLOSSARY OF TERMS for the definition of primary completion date.
- ***End of Study (EoS): Last testing results released of samples collected at Visit 38 (Month 50).***
  Refer to the GLOSSARY OF TERMS for the definition of EoS.

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- **Sequence of analyses and conditional continuation:**
  - A first analysis will be performed on data collected up to Month 21 (Visit 25) to evaluate the primary objective and relevant secondary objectives.
  - A second analysis will be performed on data collected up to Month 33 (Visit 31) to evaluate relevant secondary objectives.
  - A final analysis will be performed at study end (Month 50) on data collected up to Month 50. An integrated study report presenting all results until Month 50 will be produced.

After the interim analyses, the Independent Data Monitoring Committee (IDMC) will have the possibility to recommend the suspension of further vaccinations and termination of specific study group(s) upon consideration of the study results. In the event that the IDMC recommend the suspension of further vaccinations, the group(s) impacted will be followed up for 12 months after their last study vaccination.

- **Study groups:**

Synopsis Table 1 Study groups and epochs foreseen in the study

Study groups	Vaccination schedule	Number of subjects	Age (Min/Max)	Epochs			
				Epoch 001	Epoch 002	Epoch 003	Epoch 004
R012-20	RTS,S/AS01$_E$ full dose at Month 0, Month 1, Month 2 + a full dose at Month 20	300	5 months - 17 months	x	x	x	x
R012-14-mD	RTS,S/AS01$_E$ full dose at Month 0, Month 1, Month 2 + yearly full doses at Month 14, Month 26, Month 38	300	5 months - 17 months	x	x	x	x
Fx012-14-mFxD	RTS,S/AS01$_E$ full dose at Month 0, Month 1 + RTS,S/AS01$_E$ 1/5th dose at Month 2, Month 14, Month 26, Month 38	300	5 months - 17 months	x	x	x	x
Fx017-mFxD	RTS,S/AS01$_E$ full dose at Month 0, Month 1 + RTS,S/AS01$_E$ 1/5th dose at Month 7, Month 20, Month 32	300	5 months - 17 months	x	x	x	x
Control	Rabies vaccine at Month 0, Month 1, Month 2	300	5 months - 17 months	x	x	x	x

Synopsis Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Injectable volume	Study groups				
			R012-20	R012-14-mD	Fx012-14-mFxD	Fx017-mFxD	Control
RTS,S/AS01$_E$ (Full dose)	RTS,S (25 µg)	0.5 ml	x	x	x	x	
	AS01E		x	x	x	x	
RTS,S/AS01$_E$ (1/5th dose)	RTS,S (25 µg)	0.1 ml			x	x	
	AS01E				x	x	
Rabies vaccine	Rabipur	1.0 ml					x

- **Control:** active control, (Active comparator: rabies vaccine).
- **Vaccination schedules:** are provided in Synopsis Table 1.
- **Treatment allocation:** randomized.
- **Blinding:** open.

Synopsis Table 3 Blinding of study epochs

Study epochs	Blinding
Epoch 001	open
Epoch 002	open
Epoch 003	open
Epoch 004	open

- **Sampling schedule:**
  - Blood samples for immunogenicity will be taken in all subjects at timepoints described in Synopsis Table 4. For the evaluation of anti-CS and anti-HBs responses, a subset of 50 subjects (25 subjects per site) in each group (immunogenicity subset) will be tested at specified timepoints [redacted]
  - In addition to the blood samples listed in Synopsis Table 4, a small amount of blood (for blood smear and filter paper) will be taken every month from Day 0 until Month 20**,** and thereafter every three months until Month 50 ***for blood smear and until Month 32 for filter paper*** in all subjects for the evaluation of *P. falciparum* infections.

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  - Blood samples for the evaluation of biochemistry and hematology parameters will be taken in a sub-cohort consisting of the first 50 subjects (25 subjects per site) enrolled in each group (reactogenicity sub-cohort). Biochemistry (ALT, creatinine) and hematology (hemoglobin, WBC, platelets) parameters will be assessed before Dose 3, seven days post-Dose 3 and 30 days post-Dose 3 (see Synopsis Table 4).

Synopsis Table 4 Blood sampling timepoints

		Visit 1	Visit 2	Visit 4	Visit 5	Visit 6	Visit 10	Visit 11	Visit 12	Visit 18	Visit 19	Visit 24	Visit 25	Visit 27	Visit 28	Visit 30	Visit 31	Visit 33	Visit 34	Visit 38
Study group	**Type of blood sampling**	**Scr**	**D0**	**M2**	**M2 + 7d**	**M3**	**M7**	**M7 + 7d**	**M8**	**M14**	**M15**	**M20**	**M21**	**M26**	**M27**	**M32**	**M33**	**M38**	**M39**	**M50**
R012-20	Safety	x*		x**	x**	x**														
	Immunogenicity§		x	x		x						x	x							x
R012-14-mD	Safety	x*		x**	x**	x**														
	Immunogenicity§		x	x		x				x	x			x	x			x	x	x
Fx012-14-mFxD	Safety	x*		x**	x**	x**														
	Immunogenicity§		x	x		x				x	x			x	x			x	x	x
Fx017-mFxD	Safety	x*					x**	x**	x**											
	Immunogenicity§		x	x			x		x			x	x			x	x			x
Control	Safety	x*		x**	x**	x**														
	Immunogenicity§		x	x		x						x								x

* At screening, hemoglobin will be assessed in all subjects screened.
** Blood samples for hematology and biochemistry will be taken in a sub-cohort consisting of the first 50 subjects enrolled in each group.
§ Blood samples for immunogenicity will be taken in all subjects enrolled.
Scr: Screening
M: Month
D: Day

- **Efficacy surveillance:**
  - Capture of malaria cases: malaria cases will be captured by passive case detection (PCD). Parents/LARs will be advised to present their child to the health center if the child is unwell. Care will be administered according to local recommendations. All children with fever and/or history of fever will have a blood sample taken for the evaluation of vaccine efficacy (blood slide ***throughout the study*** and filter paper for polymerase chain reaction [PCR] ***up until month 32***). All anti-malaria treatments administered during the study should be recorded in the subject's eCRF.

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  - Cross-sectional surveys: to evaluate the vaccine efficacy against incident and prevalent *P. falciparum* infections, monthly cross-sectional surveys will be performed from Day 0 until Month 20 to measure *P. falciparum* parasitemia. Thereafter until study end (Month 50) parasitemia will be measured every three months. Blood slides from cross-sectional surveys will not be read in real time.
  - The research team at each study center will provide all screened subjects with an ITN, and malaria diagnosis and treatment will be ensured.
- **Type of study:** self-contained.
- **Ancillary studies**:
  - The incidence of *P. falciparum* infection assessed by PCR and parasite genotyping will be evaluated in an ancillary study, with details provided in a separate protocol, using filter paper samples collected as described in the present protocol.
  - In addition, further characterization of the immune response and translational research for correlates of protection may be evaluated in ancillary studies, with details provided in a separate scope of work, using samples collected as described in the present protocol.
- **Data collection:** Electronic case report form (eCRF).
- **Safety monitoring:**
  - This study will be overseen by a formally constituted IDMC operating under a charter.
  - Each subject will be observed for at least 30 minutes after vaccination to evaluate and treat any acute AEs.

- Cases of severe malaria and cerebral malaria will be reported as part of the safety surveillance until study end (Month 50) and clinical details of each case will be reported in a specific eCRF screen.
- All SAEs will be reported until study end (Month 50).
- Where possible autopsies will be performed. Verbal autopsy will be performed on all cases of mortality occurring outside hospital if autopsies cannot be performed.
- All AEs and SAEs leading to withdrawal from further vaccination will be reported until study end (Month 50).
- Meningitis and potential immune-mediated diseases (pIMDs) are AEs of specific interest to be reported until study end (Month 50). All seizures occurring within 30 days post-vaccination are also AEs of specific interest. Clinical details according to the Brighton collaboration guidelines [Bonhoeffer, 2004] pertaining to seizures occurring within seven days of vaccination will be documented in a specific eCRF screen. All AEs of specific interest are to be reported as SAEs.
- Reactogenicity data collection will be aimed at characterizing reactions to the fractional doses relative to full doses and reactions to a fourth dose and multiple yearly doses, full or fractional. Post-Dose 1 and post-Dose 2 data will not be collected as these have already been largely characterized in previous studies including Phase III evaluation. Solicited local and general AEs will be collected in the first 50 subjects enrolled in each group (reactogenicity sub-cohort) during four days (day of vaccination and three subsequent days) after Dose 3 of study vaccine (all groups including controls), after Dose 4 (R012-20, R012-14-mD, Fx012-14-mFxD and Fx017-mFxD), after Dose 5 (R012-14-mD, Fx012-14-mFxD and Fx017-mFxD) and after Dose 6 (R012-14-mD and Fx012-14-mFxD). Evidence from Phase III evaluation showed that the significant reactogenicity reactions to RTS,S/AS01$_E$ are concentrated in the first 48 hours post-vaccination. On the day of vaccination the evaluation will be carried out by the study physician at the study center. On Days 1, 2 and 3 after vaccination, trained study personnel will visit the children to record solicited AEs on diary cards.
- Unsolicited AEs will be collected during 30 days (day of vaccination and 29 subsequent days) after each dose of study vaccine. Unsolicited AEs will be captured through

passive surveillance at inpatient and outpatient facilities and during study visits.

– Biochemistry (ALT, creatinine) and hematology (hemoglobin, WBC, platelets) parameters will be assessed in the first 50 subjects enrolled in each group (reactogenicity sub-cohort) before Dose 3, seven days post-Dose 3 and 30 days post-Dose 3.

Case definitions

- **Clinical malaria and *P. falciparum* infection**

Synopsis Table 5 Case definitions of clinical malaria

Primary case definition	*P. 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
Secondary case definition	*P. 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

Synopsis Table 6 Case definition of incident *P. falciparum* infection*

Case definition 1	A documented *P. falciparum* asexual parasite density > 0 detected by blood slide reading at a cross-sectional survey or as captured by the secondary case definition of clinical malaria (active detection of infection and passive case detection).

Synopsis Table 7 Case definition of prevalent *P. falciparum* infection

Case definition 1	A documented *P. falciparum* asexual parasite density > 0 detected by blood slide reading at a cross-sectional survey (active detection of infection [ADI]).

*Note, the incidence of *P. falciparum* infection defined by positive PCR and parasite genotyping will be evaluated in the context of an ancillary study, using samples collected as described in the present protocol.

- **Severe malaria and cerebral malaria**
  - Cases of severe malaria and cerebral malaria will be reported as part of the safety surveillance. Case definitions adapted from the WHO case definitions of severe malaria and cerebral malaria will be used as reference for diagnosis.

Number of subjects Approximately 1500 subjects (300 per group) will be enrolled in this study.

Endpoints

Primary

- **Efficacy:**
  - The occurrence of clinical malaria meeting the primary case definition from Month 2.5 up to Month 14.

Secondary

- **Efficacy:**
  - The occurrence of clinical malaria meeting the primary and secondary case definitions from Day 0 up to Month 50.
  - The occurrence of incident *P. falciparum* infections from Day 0 to Month 50.
  - The prevalence of *P. falciparum* infections defined by positive blood slide at each cross-sectional survey.
- **Immunogenicity: Immune response to the CS and HBs antigens (immunogenicity subset)**
  - ***Anti-CS antibody concentrations and seropositivity measured before Dose 1, one month post-Dose 2 (group Fx017-mFxD only), before and one month post-Dose 3, before and one month after Dose 4, before and one month after each yearly dose and at study end (Month 50).***
  - Anti-HBs antibody concentrations and seropositivity measured before Dose 1, one month post-Dose 2 (group Fx017-mFxD only), before and one month post-Dose 3, before and one month after Dose 4, before and one month after each yearly dose and at study end (Month 50).

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- **Safety**
  - The occurrence of SAEs (all, fatal and related) during the whole study period according to the MedDRA classification.
  - The occurrence of AEs and SAEs leading to withdrawal from further vaccination from Dose 1 (Day 0) up to Month 50, according to the MedDRA classification.
  - The occurrence of severe malaria cases and cerebral malaria cases during the whole study period.
  - The occurrence of pIMDs from Day 0 up to Month 50, according to the MedDRA classification.

- The occurrence of meningitis from Day 0 up to Month 50, according to the MedDRA classification.
- The occurrence of seizures within 30 days (day of vaccination and 29 subsequent days) after each dose of study vaccine, according to the MedDRA classification.
- The occurrence of generalized convulsive seizure within seven days (day of vaccination and six subsequent days) after each dose of study vaccine, according to the Brighton collaboration guidelines [Bonhoeffer, 2004].
- The occurrence of unsolicited AEs within 30 days (day of vaccination and 29 subsequent days) after each dose of study vaccine, according to the MedDRA classification.
- The concentration of biochemistry (ALT, creatinine) and hematology (hemoglobin, WBC, platelets) parameters in the first 50 subjects (25 subjects per site) enrolled in each group (reactogenicity sub-cohort) before Dose 3, seven days post-Dose 3 and 30 days post-Dose 3.

- **Reactogenicity (reactogenicity sub-cohort)**
  - The occurrence of solicited local and general AEs in a the first 50 subjects enrolled in each group within four days (day of vaccination and three subsequent days) after Dose 3 of study vaccine (all groups including controls), after Dose 4 (groups R012-20, R012-14-mD, Fx012-14-mFxD and Fx017-mFxD), after Dose 5 (groups R012-14-mD, Fx012-14-mFxD and Fx017-mFxD) and after Dose 6 (groups R012-14-mD and Fx012-14-mFxD).

Tertiary

- **Immunogenicity**
  - Anti-CS antibody avidity at specified timepoints.

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LIST OF ABBREVIATIONS

012M:	Group of subjects enrolled in study MALARIA-071, who were randomized to receive three full doses of RTS,S/AS01$_B$ at Month 0, Month 1 and Month 2.
Ab:	Antibody
ADI:	Active detection of infection
AE:	Adverse event
AI:	Avidity index
AIDS:	Acquired immune deficiency syndrome
ALT:	Alanine aminotransferase
Anti-CS:	Antibody to the *Plasmodium falciparum* circumsporozoite (CS) repeat domain
Anti-HBs:	Antibody to the hepatitis B surface antigen
AS01$_E$:	GSK's proprietary Adjuvant System containing MPL, QS-21 and liposome (25 μg MPL and 25 μg QS-21)
ATP:	According-to-protocol
CEVAC:	Center for Vaccinology, Ghent University, Belgium
CHMI:	Controlled human malaria infection
CI:	Confidence interval
CIOMS:	Council for International Organizations of Medical Sciences
CLIA:	Chemiluminescence enzyme immunoassay
CLS:	Clinical laboratory sciences
CS:	Circumsporozoite protein of *Plasmodium falciparum*
CSF:	Cerebrospinal fluid
DSUR:	Development safety update report
DTPHepB:	Diphtheria, tetanus, pertussis, hepatitis B vaccine
eCRF:	Electronic case report form

ELISA:	Enzyme-linked immunosorbent assay
EMA:	European Medicines Agency
EoS:	***End of study***
EPI:	Expanded Program on Immunization
eTDF:	Electronic temperature excursion decision form
EU/ml:	ELISA unit per milliliter
FDA:	Food and Drug Administration, United States of America
Fx:	Fractional
Fx017M:	Group of subjects enrolled in study MALARIA-071, who were randomized to receive two full doses of RTS,S/AS01$_B$ at Month 0 and Month 1 and a third fractional dose (1/5th dose) at Month 7.
g/dl:	Gram per deciliter
GCP:	Good Clinical Practice
GMC:	Geometric mean concentration
GSK:	GlaxoSmithKline
HDCV:	Human diploid cells vaccine
HIV:	Human immunodeficiency virus
ICF:	Informed consent form
ICH:	International Committee on Harmonization
IDMC:	Independent Data Monitoring Committee
IEC:	Independent Ethics Committee
IgG:	Immunoglobulin G
IM:	Intramuscular
IMP:	Investigational medicinal product
IRB:	Institutional Review Board
ITN:	Insecticide-treated bednet

IU/ml:	International unit per milliliter
KEMRI/USAMRU-K, WRP:	Kenya Medical Research Institute / US Army Medical Research Unit Kenya, Walter Reed Project
LAR:	Legally acceptable representative
MATEX:	MATerial EXcellence
MedDRA:	Medical dictionary for regulatory activities
mEq/l:	Milliequivalents per liter
mg/dl:	Milligram per deciliter
mIU/ml:	Milli-international unit per milliliter
mmol/l:	Millimole per liter
MPL:	3-O-desacyl-4'-monophosphoryl lipid A (produced by GSK)
PBS:	Phosphate buffered saline
PCD:	Passive case detection
PCECV:	Purified chick embryo cells vaccine
PCR:	Polymerase chain reaction
PDEV:	Purified duck embryo cells vaccine
P. falciparum:	*Plasmodium falciparum*
PHKCV:	Purified hamster kidney cells vaccine
pIMD:	Potential immune-mediated disease
POC:	Proof of concept
PT:	Preferred term
PVRV:	Purified Vero cell rabies vaccine
Pyr:	Person year at risk
QS-21:	*Quillaja saponaria Molina*, fraction 21 (Licensed by GSK from Antigenics Inc., a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)
RDT:	Rapid diagnostic test

RTS,S:	Particulate antigen, containing both RTS and S (hepatitis B surface antigen) proteins
RTS,S/AS01$_E$:	GSK Biologicals' candidate *Plasmodium falciparum* malaria vaccine adjuvanted with GSK Biologicals' proprietary Adjuvant System AS01$_E$
SAE:	Serious adverse event
SAS:	Statistical Analysis System
SBIR:	Randomization System on Internet
SCR:	Screening
SD:	Standard deviation
SDV:	Source document verification
SmPC:	Summary of product characteristics
SPM:	Study procedures manual
TVC:	Total vaccinated cohort
UNAIDS:	Joint United Nations Programme on HIV/AIDS
USA:	United States of America
Vacc:	Vaccination
VNA:	Virus neutralizing antibody
WBC:	White blood cells
WHO:	World Health Organization

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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.
Active detection of infection:	Detection of a malaria infection by the regular examination of each subject for malaria parasitemia i.e. regardless of whether the subject had signs or symptoms of infection.
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.
Comparator vaccine:	In this study, the comparator vaccine is a non-malaria vaccine (rabies vaccine) administered to subjects randomized in the Control group.

Compound:	A cluster of buildings in an enclosure, such as the houses of an extended family. The enclosure may be a wall, a fence, a hedge or some other structure, or it may be formed by the buildings themselves, when they are built around an open area or joined together.
Control group:	A concurrent control group is one chosen from the same population as the test group and treated in a defined way as part of the same trial that studies the test treatment, and over the same period of time. The test and control groups should be similar with regard to all baselines and on treatment variables that could influence outcome, except for the study treatment [ICH E10, 2000]. In this study the Control group will receive a non-malaria comparator vaccine (rabies vaccine).
Electronic case report form:	Auditable electronic record designed to capture information required by the clinical trial protocol to be reported to the sponsor on each trial subject.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
End of Study (EoS): ***(Synonym of End of Trial)***	***For studies without collection of human biologicals samples or imaging data EoS is the Last Subject Last Visit (LSLV).*** ***For studies with collection of Human Biologicals Samples or imaging data, EoS is defined as the date of the last testing/reading released of the Human Biologicals Samples or imaging data, related to primary and secondary endpoints. EoS must be achieved no later than 8 months after LSLV.***
Epoch:	An epoch is a self-contained set of consecutive timepoints or a single timepoint from a single protocol. Self-contained means that data collected for all subjects at all timepoints within that epoch allows to draw a complete conclusion to define or precise the targeted label of the product. Typical examples of epochs are primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.
eTrack:	GSK's tracking tool for clinical trials.

Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see Sections 7.7.2 and 11.5 for details on criteria for evaluability).
Immunological correlate of protection:	The defined immune response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.
Investigational vaccine: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Legally acceptable representative: **(The terms legal representative or legally authorized representative are used in some settings.)**	An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.
Potential immune-mediated disease:	Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology.
Passive case detection:	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.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.
Protocol amendment:	The International Conference on Harmonization (ICH) defines a protocol amendment as: ‘A written description of a change(s) to or formal clarification of a protocol.’ GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects,

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

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 or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Subset:	A group of subjects who have the same biological samples taken at the same timepoint, but the assay to be performed on that biological sample will be different.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomization or treatment allocation.
Treatment number:	A number identifying a treatment to a subject, according to the study randomization or treatment allocation.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

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TRADEMARKS

The following trademarks are used in the present protocol.

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

Trademark of the GlaxoSmithKline group of companies	Generic description
Rabipur™	Purified chick embryo cell culture rabies vaccine

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1. INTRODUCTION

1.1. Background

GlaxoSmithKline (GSK) Biologicals in partnership with PATH is developing a first generation *P. falciparum* malaria vaccine for routine immunization of infants and children living in malaria-endemic areas with the objective of reducing the risk of malaria and severe malaria during the first years of life.

GSK Biologicals has developed a candidate pre-erythrocytic *Plasmodium falciparum* (*P. falciparum*) malaria vaccine, RTS,S/AS01$_E$, which consists of sequences of the circumsporozoite (CS) protein of *P. falciparum* and hepatitis B surface antigen adjuvanted with the Adjuvant System AS01$_E$, containing two immune enhancers MPL (3'-O-desacyl-4'-monophosphoryl-lipid A) and QS-21 (*Quillaja saponaria Molina*, fraction 21), in a liposome suspension.

A large Phase III study (MALARIA-055 PRI), conducted in infants and children at 11 study sites in seven countries across sub-Saharan Africa, showed the potential for the current pediatric formulation of the candidate vaccine to play a role in future malaria control strategies. The efficacy of this pediatric formulation, RTS,S/AS01$_E$, (25 µg of RTS,S antigen with AS01$_E$ containing 25 µg MPL, 25 µg QS-21 and liposomes) against all episodes of clinical malaria, when delivered according to a 0, 1, 2-month schedule, in children aged 5-17 months was estimated to be 55.1% (95% confidence interval [CI]: 50.5; 59.3) over 12 months post-Dose 3 [The RTS,S Clinical Trials Partnership, 2011].

Long-term follow-up efficacy data showed a decline in efficacy against clinical and severe malaria over time in both children and infants who did not receive a booster dose (referred to as the fourth dose in this protocol) of the RTS,S/AS01$_E$ vaccine [The RTS,S Clinical Trials Partnership, 2015]. The administration of a RTS,S/AS01$_E$ fourth dose enhanced protection against malaria in infants and children. Efficacy against all episodes of clinical malaria over 48 months post-Dose 1 was estimated to be 28.3% (95% CI: 23.3; 32.9) in children aged 5-17 months at first dose who did not receive a fourth dose and 36.3% (95% CI: 31.8; 40.5) in children who were administered a fourth dose (intention-to-treat cohort).

While Phase III evaluation of the RTS,S/AS01$_E$ candidate malaria vaccine was ongoing, GSK Biologicals, in collaboration with PATH, continued to investigate ways to further improve vaccine efficacy levels. Higher vaccine efficacy levels may lead to improved malaria control and contribute to the malaria elimination goal set as a long term target by the global health community [Malaria Vaccine Technology Roadmap, 2013].

In a previous controlled human malaria infection (CHMI) study (WRMAL-003) evaluating, in malaria-naïve adults, vaccine formulations based on the RTS,S antigen, one study group showed high levels of vaccine efficacy against sporozoite challenge, with six out of seven subjects protected [Stoute, 1997]. Subjects in this study group had received an adjuvanted formulation of RTS,S antigen, referred to as RTS,S/AS02. The immunization schedule under evaluation was a 0, 1, 7-month schedule. After having observed high general reactogenicity in two subjects after the second immunization, and

in view of limited experience of adjuvant safety at the time, there was a decision to reduce the third immunization dose to a fifth of the standard 0.5 ml dose.

Later in the RTS,S clinical development program, immunization schedules with three subsequent identical doses given one month apart were used. In a further Phase II study, MALARIA-050, the spacing of the third (full) dose at Month 7 (i.e. a 0, 1, 7-month schedule) showed no increased benefit over the 0, 1, 2-month schedule [Asante, 2011]. In view of the supportive safety, immunogenicity and efficacy data, as well as considerations related to vaccine implementation in sub-Saharan Africa, the 0, 1, 2-month schedule was selected for further vaccine development.

The 0, 1, 7-month schedule, with a fractional dose delivered as the third immunization (Fx017M group), has been further investigated recently in a CHMI study in malaria-naïve adults (MALARIA-071). The biological hypothesis was that the delayed fractional dose has allowed a better qualitative immune maturation in the germinal center, with antigen selection of the B cells harboring surface immunoglobulin with highest antigen affinity. Preliminary analyses showed high efficacy in the Fx017M group compared to standard doses given at 0, 1, 2-months (012M group): 4/30 subjects in the Fx017M group developed parasitemia (vaccine efficacy: 86.7% [95% CI: 66.8; 94.6]); 6/16 subjects in the 012M group developed parasitemia (vaccine efficacy: 62.5% [95% CI: 29.4; 80.1]); all 12 control subjects (no vaccine) developed parasitemia confirming the validity of the malaria challenge. MALARIA-071 was not powered to detect superiority of the Fx017M group over the 012M group, but the study did show some evidence of a difference in vaccine efficacy comparing the two groups (increase in proportion of protected subjects = 64.4% [95% CI: -7.9; 88.3], p=0.0741, Fisher's exact; difference in time to parasitemia p=0.0455, logrank). In the follow-up phase of the study, subjects who were protected in the initial challenge were randomized to receive a fractional fourth dose or no fourth dose, before being exposed to a second sporozoite challenge approximately six months after the initial challenge. Amongst subjects initially in the Fx017M group, three out of seven subjects who did not receive a boost were protected in this second challenge, while nine out of 10 subjects who were initially protected and received a fractional fourth dose were protected. The results from the study follow-up phase and the second challenge suggest that there is waning immunity with the fractional schedule too but that the protection can be extended with an additional fractional dose. These results from the MALARIA-071 challenge study may indicate a simple way to improve the efficacy of the RTS,S/AS01$_E$ candidate vaccine and requires further assessment in the pediatric population, under conditions of natural exposure. Preliminary immunological analyses of serum samples from subjects participating in MALARIA-071 suggest that the fractional delayed dose does lead to the production of antibodies with higher antigen avidity as compared to a classical immunization regimen with three full doses.

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

1.2. Rationale for the study

GSK Biologicals and PATH are committed to develop a malaria vaccine for reduction of malaria disease burden in children and contribution to the malaria elimination goal. Characterization of an optimal dosing regimen and boosting schedules will be critical.

The results of the efficacy study MALARIA-055 PRI, including the long term follow-up data and efficacy of the fourth dose administered 18 months after the third dose, and the preliminary results of MALARIA-071 were reviewed by the European Medicines Agency (EMA) during the assessment of the initial Application of the RTS,S/AS01$_E$ candidate vaccine. The EMA asked the company to address the following points in ongoing or future studies: 1) the timing of the fourth dose and evaluation of the safety and efficacy of an early fourth dose; 2) the efficacy and safety of multiple yearly doses and whether the vaccine predisposes to some degree of hyporesponsiveness to sequential doses; and 3) the plans to further investigate the potential utility of a delayed and fractionated third dose schedule in the target age range.

The current study is designed to address these points in the pediatric population. It aims to:

- Establish proof-of-concept (POC) for a fractional (Fx) dose schedule under conditions of natural exposure.
- Establish the role of third dose spacing in a fractional dose schedule.
- Describe the effect of an earlier full fourth dose at Month 14.
- Describe the effect of multiple fractional or full yearly doses.

1.2.1. Rationale for the study design

A recent CHMI study (MALARIA-071) ***demonstrated superior protection against malaria infection*** associated with the use of a fractional third dose in a 0, 1, 7-month schedule with a vaccine efficacy against infection of 86.7% (95% CI: 66.8; 94.6; p<0.0001) versus 62.5% (95% CI: 29.4; 80.1; p=0.0009) in the standard 0, 1, 2-month schedule. The incremental efficacy of the 0, 1, 7-month schedule over the 0, 1, 2-month schedule was 64.4% (95% CI: -7.9; 88.3; p=0.0741) [Regules, 2016]. The current study intends to establish POC for a fractional dose schedule under conditions of natural exposure. The study will be conducted in children 5-17 months old at first vaccination living in areas of mid to high malaria transmission, in line with the age group recommended by the World Health Organization (WHO) [WHO, 2016]. Infants 6-12 weeks old will not be included in this POC study to avoid interference of co-administration with the standard Expanded Program on Immunization (EPI) vaccines.

Results from this study will be critical in informing future possibilities for the development of vaccine-based strategies which, in combination with other interventions, may contribute to the malaria elimination agenda.

The study proposed herein will include five study groups. One group (R012-20) will receive the standard schedule consisting of RTS,S/AS01$_E$ full dose given at Month 0, Month 1, Month 2 and a fourth dose at Month 20. This corresponds to the schedule that received a positive scientific opinion from EMA. The four other groups will receive alternative schedules as follow:

- Group R012-14-mD will receive RTS,S/AS01$_E$ full dose at Month 0, Month 1, Month 2, an early fourth dose at Month 14 and yearly full doses at Month 26 and Month 38.
- Group Fx012-14-mFxD will receive RTS,S/AS01$_E$ full dose at Month 0 and Month 1, RTS,S/AS01$_E$ fractional dose (1/5th dose) at Month 2 and yearly fractional doses at Month 14, Month 26, Month 38.
- Group Fx017-mFxD will receive RTS,S/AS01$_E$ full dose at Month 0 and Month 1, RTS,S/AS01$_E$ delayed fractional third dose (1/5th dose) at Month 7 and yearly fractional doses at Month 20 and Month 32.
- Control group: will receive three doses of rabies vaccine at Month 0, Month 1 and Month 2.

1.2.2. Rationale for the inclusion of a control group

This study plans to evaluate malaria occurrence in subjects vaccinated with RTS,S/AS01$_E$ according to various schedules and in subjects vaccinated with a non-malaria comparator vaccine (rabies vaccine). While partial protection provided by RTS,S/AS01$_E$ in the age range of subjects which will be enrolled in this study has been demonstrated, the use of a non-malaria comparator vaccine is deemed acceptable, in line with relevant published references about the use of placebo in vaccine trials [Rid, 2014; WHO, 2013].

It is deemed unacceptable to use a placebo control when study participants are exposed to unacceptable levels of risk from delaying administration of a safe and effective vaccine that is accessible through the public health system of the country in which the study is planned. However, the Nuffield Council on Bioethics guidelines state that the use of placebos may be acceptable if participants are not deprived of a treatment they would have otherwise received, but are provided at a minimum with the standard of care that is the best available in the country's public health system. CIOMS (Council for International Organizations of Medical Sciences), ICH (International Committee on Harmonization) and UNAIDS (Joint United Nations Programme on HIV/AIDS) guidelines stipulate that researchers must take steps to minimize any risks associated with the use of controls. The protocol should explain clearly the scientific justification for using a placebo-controlled design, and specifically address whether (1) the study question cannot be answered with an active-controlled study design; and (2) the risks of delaying an existing efficacious vaccine are adequately minimized or mitigated; and (3) the use of a placebo control is justified by the potential public health value of the research; and (4) the research is responsive to local health needs.

In accordance with these recommendations, the use of a non-malaria comparator vaccine in this study is deemed acceptable as:

1. **Local availability.** Local regulatory recommendation for RTS,S/AS01$_E$ use has not been granted. If granted, it is anticipated that availability in the local health system will take some time to deploy. It is therefore not the case that study subjects would be deprived from a locally available effective prevention tool.
2. **Risk mitigation.** Subjects will have access to the best locally available malaria prevention and treatment options. All screened subjects will be provided with an insecticide-treated bednet (ITN), and malaria diagnosis and treatment will be ensured. The investigator will make every effort to ensure that preventive measures as provided by the government are adhered to and under circumstances where this is not possible discussions with the sponsor need to take place. It is anticipated that subjects will benefit from participation in the study in terms of facilitated access to care and relatively intense health monitoring. Reduced levels of morbidity related to participation in a RTS,S/AS01$_E$ study has been documented [Hamel, 2014].
3. **Study design justification.** Without a control group, the following scientific questions could not be answered with scientific integrity:
   - Comparison of malaria incidence between different time periods.
     Without a control group, the direct comparison of post-RTS,S/AS01$_E$ vaccination malaria incidence between two different study periods (example: assessment of post-Dose 3 protection in the 0, 1, 2-month and 0, 1, 7-month schedules, evaluation of optimal timing of the fourth dose, waning of efficacy) would carry a risk of bias associated with seasonal variations in malaria incidence.
   - Evaluation of strain-specificity of protection.
     A genetic characterization of malaria infections is planned as an ancillary study (using samples collected in the present study) with the aim to determine whether vaccine efficacy varies according to the parasite strain. This requires comparison of parasite genetics in the vaccinated groups with the Control group.
4. **Public health need.** RTS,S/AS01$_E$ has been shown to prevent malaria with a moderate level of efficacy [The RTS,S Clinical Trials Partnership, 2015]. The development of a malaria vaccine with higher efficacy remains an important public health need [Malaria Vaccine Technology Roadmap, 2013]. Finding the immunization schedule able to provide the highest protection is very relevant to local public health needs.

To be noted, the study subjects in the Control group will get the benefit of receiving a rabies vaccine as comparator vaccine, also advocated as a valuable preventive health intervention by the WHO [WHO, 2007].

1.2.3. Rationale for the use of a rabies vaccine as a comparator vaccine

Subjects randomized to the Control group will receive three doses of a cell culture rabies vaccine on a 0, 1, 2-month schedule. In humans, rabies is almost invariably fatal once clinical signs occur. Bites by rabid domestic dogs cause 99% of human rabies deaths globally. More than 3.3 billion people live in regions where rabies is enzootic. Approximately 55 000 people die from rabies each year, the vast majority of these deaths occurring in Asia and Africa [WHO, 2007]. Estimates of risks of infection with rabies in Africa are available from the WHO [WHO, 2015].

The efficacy of cell culture-derived rabies vaccines including human diploid cells vaccine (HDCV), purified Vero cell rabies vaccine (PVRV), purified chick embryo cells vaccine (PCECV), purified ***hamster kidney*** cells vaccine (PHKCV) and purified duck embryo cells vaccine (PDEV) has been demonstrated [WHO, 2010]. In this study, a PCECV (*Rabipur*) will be used as comparator vaccine.

PCECV has been widely used for rabies pre-exposure prophylaxis in children. In total, PCECV has been administered to more than 1200 children in clinical studies, from toddlers to those in elementary school, demonstrating safety and immunogenicity. Various schedules of PCECV (2-doses and 3-doses) and administration route (intramuscular and intradermal) were evaluated in children. Intramuscular administration resulted in 3- to 5-fold higher titers than intradermal administration [Malerczyk, 2013]. In studies using pre-exposure prophylaxis in children, all children achieved adequate rabies virus neutralizing antibody (VNA) concentrations by Day 14, i.e., after receiving two doses of vaccine, even before the third dose of vaccine was received. Regardless of the route of administration (intramuscular or intradermal), VNA concentrations reached levels above 0.5 IU/ml [Malerczyk, 2013]. The definition of a target antibody titer varies among laboratories and is influenced by the type of test conducted. WHO specifies a titer of 0.5 IU/ml [WHO, 2007].

1.2.3.1. Rationale for the rabies vaccine schedule

In this study, the rabies vaccine will be administered according to a 0, 1, 2-month schedule which is different from the schedule recommended by the manufacturer of the rabies vaccine (i.e. days 0, 7, 21 *or* 28) [*Rabipur* SmPC, 2010]. The vaccine may therefore not provide the full protection under the 0, 1, 2-month schedule as if it was administered according to the recommended schedule. Parent(s)/Legally acceptable representative(s) (LAR[s]) will be instructed to bring their child promptly for treatment if the child is bitten by an animal.

Rabipur has been used as a comparator vaccine in several earlier studies in the GSK malaria vaccine program including a schedule as the one that will be used in this study. Over the entire follow-up period of each study (up to 24 months of follow-up), no case of rabies was reported in subjects from the control group who had received *Rabipur* according to a 0, 1, 2-month schedule [Laurens, 2013;Ogutu, 2009; Owusu-Agyei, 2009; Polhemus, 2009; Thera, 2008; Thera, 2010; Thera, 2011].

1.2.4. Cross-immunization against human catalase

Yeast cytosolic catalase is present in small quantity in RTS,S/AS01$_E$ vaccine lots. The significance of the presence of yeast cytosolic catalase was investigated in the uncontrolled study MALARIA-061 where three lots of RTS,S/AS01$_E$ formulated from commercial scale (1600L) RTS,S purified bulk and one lot of RTS,S/AS01$_E$ formulated from pilot scale (20L) RTS,S purified bulk were administered to children 5-17 months of age at first dose. Amongst the 300 children tested, one child was positive one month post-Dose 3, indicating that he has some antibodies cross-reacting with human catalase. This child was negative pre-vaccination. This child reported two adverse events (AE) not related to vaccination within 30 days post-vaccination (upper respiratory tract infection and respiratory tract infection); no AE related to vaccination and no SAE was reported during the six months follow-up period post-vaccination.

Anti-human catalase antibodies have not been evaluated in control recipients in malaria clinical studies and the background rate of anti-catalase positivity is not known. Based on the fact that only one child was highly positive amongst the three groups of children vaccinated with an RTS,S/AS01$_E$ lot formulated from a 1600L scale RTS,S purified bulk, it seems unlikely that the observed response is related to the yeast catalase contained in RTS,S/AS01$_E$. However, it cannot be ruled out that the seroconversion of this subject was induced by the RTS,S/AS01$_E$ vaccination. Cross-immunization against human catalase will be further investigated in a planned randomized controlled study.

1.3. Benefit : Risk assessment

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

Please refer to the Prescribing Information for information regarding the summary potential risks and benefits of the rabies vaccine (*Rabipur*).

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

1.3.1. Risk assessment

Table 1 Risk assessment

Important potential/identified risk	Data/rationale for risk	Mitigation strategy
Investigational study vaccine (RTS,S/AS01$_E$)		
Important identified risk: **Febrile convulsion**	The increased risk of febrile convulsion within seven days post-vaccination has been identified.	Past seizures constitute an exclusion criterion (see Section 5.3), and children will not be vaccinated if they have concurrent fever. Parent(s)/ LAR(s) will be informed of this risk and instructed how to manage high fever post-vaccination. Seizure is an AE of specific interest and will be

Important potential/identified risk	Data/rationale for risk	Mitigation strategy
		captured through the electronic Expedited Adverse Events Report (see Section 9.1.6). Clinical details according to the Brighton collaboration guidelines [Bonhoeffer, 2004] of each seizure occurring within seven days post- vaccination will be captured in a specific eCRF screen.
Important potential risk: **Meningitis**	In the large Phase III study, MALARIA-055 PRI, an imbalance of meningitis cases of any etiology (i.e. including cases with confirmed etiology and cases with no etiology found), with no cluster in time-to-onset, has been observed in children 5-17 months of age at first dose.	Parent(s)/LAR(s) will be instructed on the need to attend the clinic if their child is unwell. A high level of medical supervision is in place to detect and treat meningitis if it occurs. Meningitis is an AE of specific interest (see Section 9.1.6). Clinical details of each case will be captured through the electronic Expedited Adverse Events Report and in a specific eCRF screen.
Important potential risk: **Delayed increased incidence of severe malaria in relation with delayed acquisition of blood-stage immunity**	In the large phase III study MALARIA-055 PRI, an increased incidence of severe malaria relative to the control group has been observed, starting around two years after RTS,S/AS01$_E$ primary vaccination course, in children 5-17 months of age at first dose that did not receive a RTS,S/AS01$_E$ fourth dose. This higher risk of severe malaria might result from a delay in the acquisition of blood-stage immunity associated with a decreased exposure in children vaccinated with RTS,S/AS01$_E$ relative to controls.	All studies with long term follow-up showed that the overall benefit stays in favor of the vaccine despite delayed acquisition of blood-stage immunity. The receipt of a fourth dose increased that benefit. The study MALARIA-055 PRI showed no evidence of a delayed increased incidence in severe malaria in children who received a fourth dose, up to two years post-fourth dose. In the present study all RTS,S/AS01$_E$ groups will receive at least one additional dose (fourth dose). Severe malaria cases will be reported as serious adverse events (SAEs). The occurrence of severe malaria cases will be described.
Important potential risk: **Hypersensitivity (including anaphylaxis)**	As with other vaccines, hypersensitivity and anaphylaxis to one or several components of the vaccine can rarely occur. One case of erythema multiforme and two cases of bronchospasm within 30 days following RTS,S/AS01$_E$ vaccination were reported as hypersensitivity reactions in past studies. No case of anaphylaxis has been reported following RTS,S/AS01$_E$ vaccination to date.	Subjects will be observed closely for at least 30 minutes following administration of the vaccine with appropriate medical treatment readily available in case of anaphylaxis. History of anaphylaxis post-vaccination and history of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine are exclusion criteria in this study (see Section 5.3). Previous anaphylactic reaction to a vaccine is a contraindication to further experimental vaccinations in this study (see Section 7.5).

Important potential/identified risk	Data/rationale for risk	Mitigation strategy
Important potential risk: **potential immune-mediated disease (pIMD)**	pIMD is a theoretical concern with adjuvanted vaccines as no evidence of autoimmune disease caused by RTS,S/AS01$_E$ has been observed.	Parent(s)/LAR(s) will be informed of this theoretical risk and the need to attend the clinic if their child is unwell. pIMD diagnostic capacity will be reinforced. pIMD is an AE of specific interest (see Section 9.1.6). The occurrence of pIMD cases will be described.
Study procedures		
Pain when taking blood samples	When taking the blood samples, the subject may feel faint; or experience mild pain, bruising, irritation or redness.	Parent(s)/LAR(s) will be advised to call the study doctor immediately if their child has any side effects that they perceive as serious.
Other (comparator rabies vaccine)		
Hypersensitivity and anaphylaxis following rabies vaccination	Hypersensitivity and anaphylaxis to one or several components of the vaccine can rarely occur.	The subjects will be observed closely for at least 30 minutes following administration of the vaccine with appropriate medical treatment readily available in case of anaphylaxis. History of anaphylaxis post-vaccination and history of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine are exclusion criteria in this study (see Section 5.3). Previous anaphylactic reaction to a vaccine is a contraindication to further experimental vaccinations in this study (see Section 7.5).
Auto-immune disorders following rabies vaccination	There have been individual reports of nervous system disorders (such as paresthesia, paresis or Guillain-Barré-Syndrome) following rabies vaccination but a causal relationship has not been established.	Parent(s)/LAR(s) will be informed of this risk and the need to attend the clinic if their child is unwell. pIMD diagnostic capacity will be reinforced. pIMD is an AE of specific interest (see Section 9.1.6). The occurrence of pIMD cases will be described.

1.3.2. Benefit assessment

The results of previous clinical studies showed a significant efficacy of RTS,S/AS01$_E$ against malaria disease caused by *P. falciparum*. In children aged 5-17 months, the vaccine efficacy against all episodes of clinical malaria was estimated to be 55.1% (95% CI: 50.5; 59.3) over 12 months post-Dose 3, and over four years of follow-up (48 months post-Dose 1, intention-to-treat population) the efficacy against all episodes of clinical malaria was 28.3% (95% CI: 23.3; 32.9) in children who did not receive a fourth dose and 36.3% (95% CI: 31.8; 40.5) in children who were administered a fourth dose 18 months after the third dose [The RTS,S Clinical Trials Partnership, 2011; The RTS,S Clinical Trials Partnership, 2015].

Children randomized to the rabies Control group will not receive RTS,S/AS01$_E$ vaccination, but may benefit from study participation due to the implementation of best available standards of care according to national recommendations within the study and strengthened access to care. In addition individuals vaccinated with rabies vaccine in the study may benefit from a reduced risk of contracting rabies.

1.3.3. Overall Benefit : Risk conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential or identified risks in association with RTS,S/AS01$_E$ (SB257049) or with the rabies vaccine are justified by the potential benefits (prevention / treatment) that may be afforded to subjects receiving RTS,S/AS01$_E$ (reduced risk of clinical and severe disease due to *P. falciparum*) and to subjects receiving the rabies vaccine in the Control group (reduced risk of contracting rabies).

2. OBJECTIVES

2.1. Primary objective

- **Efficacy: Incremental efficacy of a schedule with a fractional third dose at Month 2 over the standard schedule**
  - To demonstrate the superiority of a 3-dose schedule of GSK Biologicals' malaria vaccine RTS,S/AS01$_E$ with a fractional third dose at Month 2 compared to a standard schedule of RTS,S/AS01$_E$ with three full doses in terms of vaccine efficacy against clinical malaria (primary case definition) over 12 months post-Dose 3.

  Criterion:

  The lower limit of the 95% CI of the incremental vaccine efficacy estimate is above 0.

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

2.2. Secondary objectives

- Efficacy
  - To assess the incremental vaccine efficacy against clinical malaria of a schedule with a fractional third dose at Month 2 versus a schedule with 3 full doses (primary and secondary case definitions) over 12 months post-Dose 3.
  - To assess the incremental vaccine efficacy against clinical malaria, over 7 and 12 months post-Dose 3, of a schedule with a fractional third dose at Month 7 versus a schedule with a fractional third dose at Month 2.
  - To assess the incremental vaccine efficacy against clinical malaria, over 7 and 12 months post-Dose 3, of a schedule with a fractional third dose at Month 7 versus a schedule with 3 full doses.

- To assess the incremental vaccine efficacy against clinical malaria, over 12 months post-Dose 4, post-Dose 5 and post-Dose 6 of a schedule with a fractional third dose at Month 2 and yearly fractional doses versus a schedule with full doses at Month 0, Month 1, Month 2 and yearly full doses.
- To assess the incremental vaccine efficacy against clinical malaria, over 12 months post-Dose 4, of a schedule with a fractional third dose at Month 7 versus a standard schedule with 4 full doses at 0,1,2,20 months.
- To assess the vaccine efficacy and impact of each RTS,S/AS01$_E$ schedule over the entire study period by measuring the efficacy against clinical malaria at Months 14, 20, 26, 32, 38 and 50.
- To assess the prevalence of *P. falciparum* infections of each RTS,S/AS01$_E$ schedule at cross-sectional visits (monthly from Month 0-20 and every three months thereafter till study end).
- To assess the vaccine efficacy against incident *P. falciparum* infections defined by positive blood slide over the entire study period.

- **Immunogenicity: Immune response to the CS and HBs antigens**
  - To describe the antibody response to the anti-circumsporozoite protein of *P. falciparum* (anti-CS) for each schedule.
  - To describe the antibody response to the hepatitis B surface antigen (anti-HBs) for each schedule.

- **Safety and reactogenicity**
  - To assess the safety of RTS,S/AS01$_E$ for each schedule in terms of serious adverse events (SAEs), unsolicited adverse events (AEs) and AEs of specific interest.
  - To assess the reactogenicity of RTS,S/AS01$_E$ in terms of solicited local and general AEs.
  - To assess the safety of RTS,S/AS01$_E$ in terms of biochemistry (alanine aminotransferase [ALT], creatinine) and hematology (hemoglobin, white blood cells [WBC], platelets) parameters.

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

2.3. Tertiary objectives

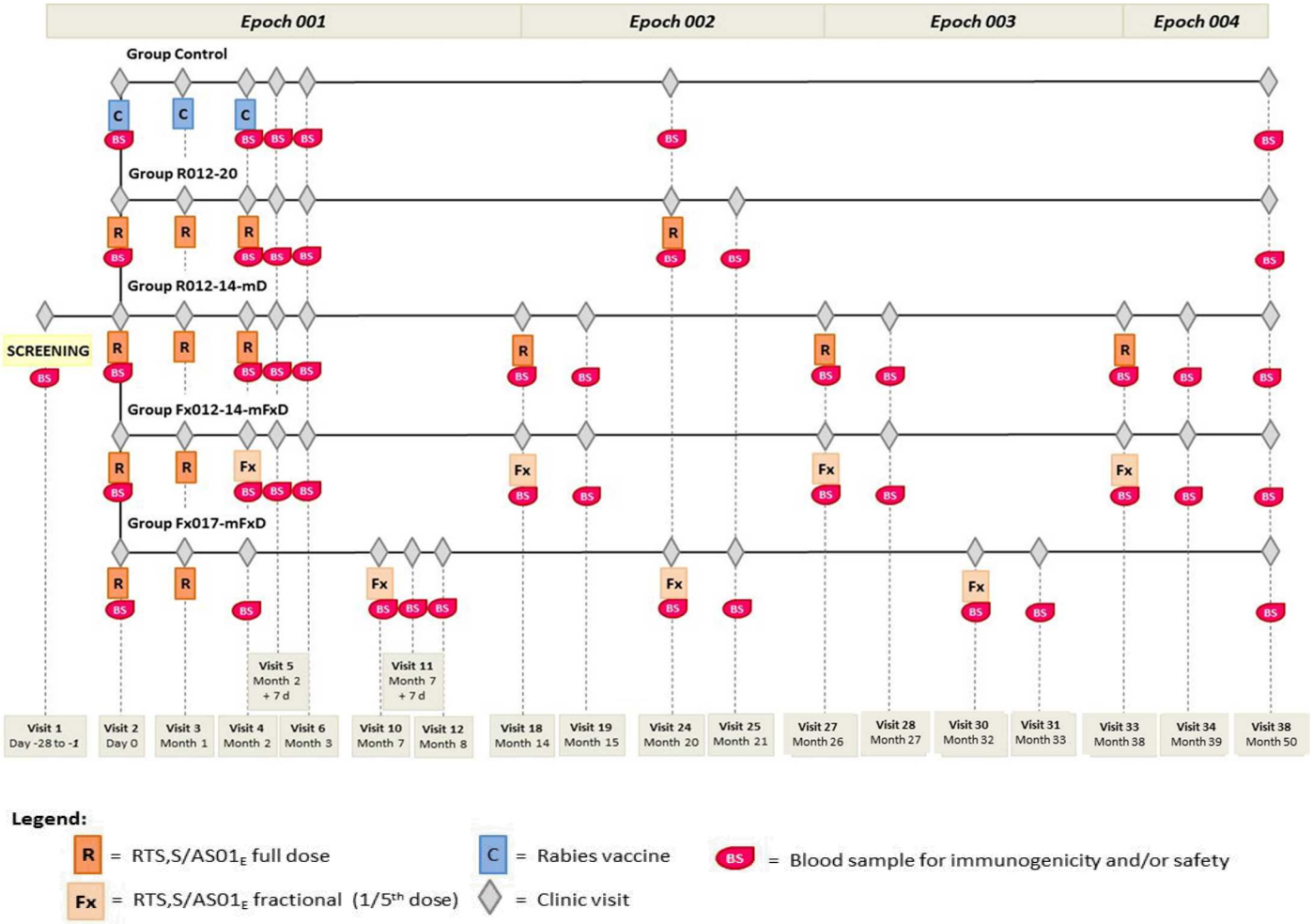
- **Immunogenicity**
  - To describe the anti-CS antibody response in terms of avidity.

Of note, blood samples taken in this study may also be used in ancillary studies. More details on ancillary studies are provided in the study design section (Section 3) of this protocol.

Refer to Section 11.3 for the definition of the tertiary endpoints.

3. STUDY DESIGN OVERVIEW

Figure 1 Study design: clinic visits



In addition to the clinic visits presented in the figure above, parasite prevalence will be assessed at the following visits (these will be fieldworker visits or clinic visits depending on the timepoint and the group):

Figure 2 Study design: visits for assessment of parasite prevalence

Visits for parasite prevalence													
Year 1	Visit 2 Day 0	Visit 3 Month 1	Visit 4 Month 2	Visit 6 Month 3	Visit 7 Month 4	Visit 8 Month 5	Visit 9 Month 6	Visit 10 Month 7	Visit 12 Month 8	Visit 13 Month 9	Visit 14 Month 10	Visit 15 Month 11	Visit 16 Month 12
Year 2		Visit 17 Month 13	Visit 18 Month 14	Visit 19 Month 15	Visit 20 Month 16	Visit 21 Month 17	Visit 22 Month 18	Visit 23 Month 19	Visit 24 Month 20			Visit 26 Month 23	
Year 3			Visit 27 Month 26			Visit 29 Month 29			Visit 30 Month 32			Visit 32 Month 35	
Year 4			Visit 33 Month 38			Visit 35 Month 41			Visit 36 Month 44			Visit 37 Month 47	
Year 5			Visit 38 Month 50										

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:** Phase IIB, randomized, open-label, controlled, multi-centric study with five parallel groups.

- **Duration of the study:** Approximately 50 months, with two interim analyses and option for conditional continuation (see next bullet point).

  – Epoch 001: Starting at Visit 1 (Screening) and ending at Visit 17 (Month 13). Note: the data up to Visit 18 (Month 14) pertains to Epoch 001.

  – Epoch 002: Starting at Visit 18 (Month 14) and ending at Visit 26 (Month 23). Note: the data up to Visit 27 (Month 26) pertains to Epoch 002.

  – Epoch 003: Starting at Visit 27 (Month 26) and ending at Visit 32 (Month 35). Note: the data up to Visit 33 (Month 38) pertains to Epoch 003.

  – Epoch 004: Starting at Visit 33 (Month 38) and ending at Visit 38 (Month 50).

- ***Primary completion date: Visit 18 (Month 14) or last visit of Epoch 001. Refer to the GLOSSARY OF TERMS for the definition of primary completion date.***

- ***End of Study (EoS): Last testing results released of samples collected at Visit 38 (Month 50). Refer to the GLOSSARY OF TERMS for the definition of EoS.***

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- **Sequence of analyses and conditional continuation:**

  – A first analysis will be performed on data collected up to Month 21 (Visit 25) to evaluate the primary objective and relevant secondary objectives.

  – A second analysis will be performed on data collected up to Month 33 (Visit 31) to evaluate relevant secondary objectives.

  – A final analysis will be performed at study end (Month 50) on data collected up to Month 50. An integrated study report presenting all results until Month 50 will be produced.

  After the interim analyses, the Independent Data Monitoring Committee (IDMC) will have the possibility to recommend the suspension of further vaccinations and termination of specific study group(s) upon consideration of the study results. In the event that the IDMC recommend the suspension of further vaccinations, the group(s) impacted will be followed up for 12 months after their last study vaccination.

- **Study groups:**

Table 2 Study groups and epochs foreseen in the study

Study groups	Vaccination schedule	Number of subjects	Age (Min/Max)	Epochs			
				Epoch 001	Epoch 002	Epoch 003	Epoch 004
R012-20	RTS,S/AS01$_E$ full dose at Month 0, Month 1, Month 2 + a full dose at Month 20	300	5 months - 17 months	x	x	x	x
R012-14-mD	RTS,S/AS01$_E$ full dose at Month 0, Month 1, Month 2 + yearly full doses at Month 14, Month 26, Month 38	300	5 months - 17 months	x	x	x	x
Fx012-14-mFxD	RTS,S/AS01$_E$ full dose at Month 0, Month 1 + RTS,S/AS01$_E$ 1/5th dose at Month 2, Month 14, Month 26, Month 38	300	5 months - 17 months	x	x	x	x
Fx017-mFxD	RTS,S/AS01$_E$ full dose at Month 0, Month 1 + RTS,S/AS01$_E$ 1/5th dose at Month 7, Month 20, Month 32	300	5 months - 17 months	x	x	x	x
Control	Rabies vaccine at Month 0, Month 1, Month 2	300	5 months - 17 months	x	x	x	x

Table 3 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Injectable volume	Study groups				
			R012-20	R012-14-mD	Fx012-14-mFxD	Fx017-mFxD	Control
RTS,S/AS01$_E$ (Full dose)	RTS,S (25 µg)	0.5 ml	x	x	X	x	
	AS01E		x	x	X	x	
RTS,S/AS01$_E$ (1/5th dose)	RTS,S (25 µg)	0.1 ml			X	x	
	AS01E				X	x	
Rabies vaccine	Rabipur	1.0 ml					x

- **Control:** active control, (Active comparator: rabies vaccine).
- **Vaccination schedules:** are provided in Table 2.
- **Treatment allocation:** randomized. Refer to Section 6.2 for a detailed description of the randomization method.
- **Blinding:** open.

Table 4 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	open
Epoch 002	open
Epoch 003	open
Epoch 004	open

- **Sampling schedule:**
  - Blood samples for immunogenicity will be taken in all subjects at timepoints described in Table 5. For the evaluation of anti-CS and anti-HBs responses, a subset of 50 subjects (25 subjects per site) in each group (immunogenicity subset, see Section 5) will be tested at specified timepoints (see Table 5 and Section 6.7.4.1). CCI [redacted].
  - In addition to the blood samples listed in Table 5, a small amount of blood (for blood smear and filter paper) will be taken every month from Day 0 until Month 20**,** and thereafter every three months until Month 50 ***for blood smear and until Month 32 for filter paper*** in all subjects for the evaluation of *P. falciparum* infections (see Section 6.7.4.2).

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  - Blood samples for the evaluation of biochemistry and hematology parameters will be taken in a sub-cohort consisting of the first 50 subjects (25 subjects per site) enrolled in each group (reactogenicity sub-cohort, see Section 5). Biochemistry (ALT, creatinine) and hematology (hemoglobin, WBC, platelets) parameters will be assessed before Dose 3, seven days post-Dose 3 and 30 days post-Dose 3 (see Table 5 and Section 6.7.4.3).

Table 5 Blood sampling timepoints

		Visit 1	Visit 2	Visit 4	Visit 5	Visit 6	Visit 10	Visit 11	Visit 12	Visit 18	Visit 19	Visit 24	Visit 25	Visit 27	Visit 28	Visit 30	Visit 31	Visit 33	Visit 34	Visit 38
Study group	**Type of blood sampling**	**Scr**	**D0**	**M2**	**M2 + 7d**	**M3**	**M7**	**M7 + 7d**	**M8**	**M14**	**M15**	**M20**	**M21**	**M26**	**M27**	**M32**	**M33**	**M38**	**M39**	**M50**
R012-20	Safety	x*		x**	x**	x**														
	Immunogenicity§		x	x		x						x	x							x
R012-14-mD	Safety	x*		x**	x**	x**														
	Immunogenicity§		x	x		x				x	x			x	x			x	x	x
Fx012-14-mFxD	Safety	x*		x**	x**	x**														
	Immunogenicity§		x	x		x				x	x			x	x			x	x	x
Fx017-mFxD	Safety	x*					x**	x**	x**											
	Immunogenicity§		x	x			x		x			x	x			x	x			x
Control	Safety	x*		x**	x**	x**														
	Immunogenicity§		x	x		x						x								x

* At screening, hemoglobin will be assessed in all subjects screened.
** Blood samples for hematology and biochemistry will be taken in a sub-cohort consisting of the first 50 subjects enrolled in each group.
§ Blood samples for immunogenicity will be taken in all subjects enrolled.
Scr: Screening
M: Month
D: Day

- **Efficacy surveillance:**
  - Capture of malaria cases: malaria cases will be captured by passive case detection (PCD). Parents/LARs will be advised to present their child to the health center if the child is unwell. Care will be administered according to local recommendations. All children with fever and/or history of fever will have a blood sample taken for the evaluation of vaccine efficacy (blood slide ***throughout the study*** and filter paper for polymerase chain reaction [PCR] ***up until month 32***). All anti-malaria treatments administered during the study should be recorded in the subject's eCRF (see Section 7.7.1).

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  - Cross-sectional surveys: to evaluate the vaccine efficacy against incident and prevalent *P. falciparum* infections, monthly cross-sectional surveys will be performed from Day 0 until Month 20 to measure *P. falciparum* parasitemia. Thereafter until study end (Month 50) parasitemia will be measured every three months. Blood slides from cross-sectional surveys will not be read in real time.
  - The research team at each study center will provide all screened subjects with an ITN, and malaria diagnosis and treatment will be ensured.
- **Type of study:** self-contained.
- **Ancillary studies**:
  - The incidence of *P. falciparum* infection assessed by PCR and parasite genotyping will be evaluated in an ancillary study, with details provided in a separate protocol, using filter paper samples collected as described in the present protocol (see Table 20).
  - In addition, further characterization of the immune response and translational research for correlates of protection may be evaluated in ancillary studies, with details provided in a separate scope of work, using samples collected as described in the present protocol (See Section 6.6.16 and Table 15).
- **Data collection:** eCRF.
- **Safety monitoring:**
  - This study will be overseen by a formally constituted IDMC operating under a charter.
  - Each subject will be observed for at least 30 minutes after vaccination to evaluate and treat any acute AEs.
  - Cases of severe malaria and cerebral malaria will be reported as part of the safety surveillance until study end (Month 50) and clinical details of each case will be reported in a specific eCRF screen.
  - All SAEs will be reported until study end (Month 50).
  - Where possible autopsies will be performed. Verbal autopsy will be performed on all cases of mortality occurring outside hospital if autopsies cannot be performed.

- All AEs and SAEs leading to withdrawal from further vaccination will be reported until study end (Month 50).
- Meningitis and pIMDs are AEs of specific interest to be reported until study end (Month 50). All seizures occurring within 30 days post-vaccination are also AEs of specific interest. Clinical details according to the Brighton collaboration guidelines [Bonhoeffer, 2004] pertaining to seizures occurring within seven days of vaccination will be documented in a specific eCRF screen. All AEs of specific interest are to be reported as SAEs (see Section 9.1.6).
- Reactogenicity data collection will be aimed at characterizing reactions to the fractional doses relative to full doses and reactions to a fourth dose and multiple yearly doses, full or fractional. Post-Dose 1 and post-Dose 2 data will not be collected as these have already been largely characterized in previous studies including Phase III evaluation. Solicited local and general AEs will be collected in the first 50 subjects enrolled in each group (reactogenicity sub-cohort) during four days (day of vaccination and three subsequent days) after Dose 3 of study vaccine (all groups including controls), after Dose 4 (R012-20, R012-14-mD, Fx012-14-mFxD and Fx017-mFxD), after Dose 5 (R012-14-mD, Fx012-14-mFxD and Fx017-mFxD) and after Dose 6 (R012-14-mD and Fx012-14-mFxD). Evidence from Phase III evaluation showed that the significant reactogenicity reactions to RTS,S/AS01$_E$ are concentrated in the first 48 hours post-vaccination. On the day of vaccination the evaluation will be carried out by the study physician at the study center. On Days 1, 2 and 3 after vaccination, trained study personnel will visit the children to record solicited AEs on diary cards.
- Unsolicited AEs will be collected during 30 days (day of vaccination and 29 subsequent days) after each dose of study vaccine. Unsolicited AEs will be captured through passive surveillance at inpatient and outpatient facilities and during study visits.
- Biochemistry (ALT, creatinine) and hematology (hemoglobin, WBC, platelets) parameters will be assessed in the first 50 subjects enrolled in each group (reactogenicity sub-cohort) before Dose 3, seven days post-Dose 3 and 30 days post-Dose 3.

4. CASE DEFINITIONS

4.1. Case definitions of clinical malaria

Table 6 Case definitions of clinical malaria

Primary case definition	*P. 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
Secondary case definition	*P. 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

4.2. Case definitions of *P. falciparum* infection

Table 7 Case definition of incident *P. falciparum* infection*

Case definition 1	A documented *P. falciparum* asexual parasite density > 0 detected by blood slide reading at a cross-sectional survey or as captured by the secondary case definition of clinical malaria (active detection of infection and passive case detection).

Table 8 Case definition of prevalent *P. falciparum* infection

Case definition 1	A documented *P. falciparum* asexual parasite density > 0 detected by blood slide reading at a cross-sectional survey (active detection of infection [ADI]).

*Note, the incidence of *P. falciparum* infection defined by positive PCR and parasite genotyping will be evaluated in the context of an ancillary study, using samples collected as described in the present protocol (see Section 6.7.4.2).

4.3. Severe malaria and cerebral malaria

Cases of severe malaria and cerebral malaria will be reported as part of the safety surveillance (see Section 9.1.5). Case definitions adapted from the WHO case definitions of severe malaria and cerebral malaria will be used as reference for diagnosis. Refer to APPENDIX C for the case definitions.

5. STUDY COHORT

5.1. Number of subjects/centers

Approximately 1500 subjects (300 per group) will be enrolled in this study. Refer to Section 11.4 for a detailed description of the criteria used in the estimation of sample size.

In this study the biochemistry and hematology parameters and the reactogenicity will be evaluated in a sub-cohort of subjects. The anti-CS and anti-HBs immune responses will be tested in a subset; see the glossary of terms for the definitions of subset and sub-cohort.

Table 9 Sub-cohort

Sub-cohort name	Description	Estimated number of subjects
Reactogenicity*	Solicited local and general AEs will be collected in a sub-cohort consisting of the first 50 subjects enrolled in each group. Hematology and biochemistry parameters will be measured in the same sub-cohort.	250 (50 subjects per group, 25 subjects per site)

* Subjects belonging to this sub-cohort will have specific study procedures performed for the assessment of reactogenicity, hematology and biochemistry parameters (refer to Table 11, Table 12 and Table 13).

Table 10 Subset

Subset name	Description	Estimated number of subjects
Immunogenicity*	Anti-CS and anti-HBs immune responses will be tested in a subset corresponding to the first 50 subjects enrolled in each group.	250 (50 subjects per group, 25 subjects per site)

*In this study, all subjects enrolled will have blood samples taken for assessment of immunogenicity. Not all samples will be used for testing: anti-CS and anti-HBs immune responses will be tested in a subset (i.e. the immunogenicity subset which includes the same subjects as in the reactogenicity sub-cohort) CCI [redacted]

5.2. Inclusion criteria for enrolment

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

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

- Subjects' parent(s)/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).
- Signed or thumb-printed and witnessed informed consent obtained from the parent(s)/LAR(s) of the subject prior to performance of any study specific procedure. Where parent(s)/LAR(s) are illiterate, the consent form will be countersigned by an independent witness.
- A male or female between, and including, five and 17 months of age at the time of the first vaccination.
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Previously received three documented doses of diphtheria, tetanus, pertussis, hepatitis B vaccine (DTPHepB), and at least three doses of oral polio vaccine.

5.3. Exclusion criteria for enrolment

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

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

- Child in care.

  Please refer to the glossary of terms for the definition of child in care.

- Use of a drug or vaccine that is not approved for that indication (by one of the following regulatory authorities: Food and Drug Administration [FDA; USA] or European Union member state or WHO [with respect to prequalification]) other than the study vaccines during the period starting 30 days before the first dose of study vaccines (Day -29 to Day 0), or planned use during the study period.
- Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting six months prior to the first vaccine dose. For corticosteroids, this will mean prednisone (0.5 mg/kg/day (for pediatric subjects) or equivalent. Inhaled and topical steroids are allowed.
- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting seven days before each dose and ending seven days after each dose of vaccine administration.
- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Family history of congenital or hereditary immunodeficiency.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccines.
- History of anaphylaxis post-vaccination.
- History of any, or documented, serious adverse reaction to rabies vaccination.
- Contraindication to rabies vaccination (*Rabipur* is contraindicated in subjects with an history of a severe hypersensitivity to any of the ingredients in the vaccine. Note that the vaccine contains polygeline and residues of chicken proteins, and may contain traces of neomycin, chlortetracycline and amphotericin B) (Refer to the [*Rabipur* SmPC, 2010]).
- Major congenital defects.

- Serious chronic illness.
- Children with a past history of a neurological disorder or atypical febrile seizure (a febrile seizure is atypical if it meets one of the following criteria: not associated with fever; lasts > 5 minutes; focal (not generalized); followed by transient or persistent neurological abnormality; occurs in a child < 6 months of age).
- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature ≥ 37.5°C/99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C/100.4°F for rectal route.
  - Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator.
- Administration of immunoglobulins and/or any blood products during the period starting three months before the first dose of study vaccine or planned administration during the study period.
- Moderate or severe malnutrition at screening defined as weight for age or weight for height Z-score < -2.
- Hemoglobin concentration < 8 g/dl at screening.
- Same sex twins (to avoid misidentification).
- Maternal death.
- Prior receipt of an investigational malaria vaccine.

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 ICH Guideline for 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.
- Investigator reporting requirements as stated in the protocol.

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

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

GSK Biologicals will prepare a model informed consent form (ICF) which will embody the ICH GCP and GSK Biologicals required elements. While it is strongly recommended that this model ICF is to be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, 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 assigned sequentially to the subjects who have consented to participate in the study, according to the range of subject identification numbers allocated to each study center.

Subject identification cards with the subject number will be provided to each subject's parents/LAR(s).

6.2.2. Randomization of treatment

6.2.2.1. Randomization of supplies

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

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

6.2.2.2. Treatment allocation to the subject

The treatment numbers will be allocated by dose.

6.2.2.2.1. Study group and treatment number allocation

The target will be to enroll approximately 1500 eligible subjects who will be randomly assigned to five study groups in a (1: 1: 1: 1: 1) ratio (approximately 300 subjects in each group).

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

After obtaining the signed (or thumb-printed and witnessed) and dated ICF from the subject's parent(s)/LAR(s) and having checked the eligibility of the subject, the site staff in charge of the vaccine administration will access SBIR. Upon providing the subject identification number, the randomization system will determine the study group and will provide the treatment number to be used for the first dose.

The number of each administered treatment must be recorded in the eCRF on the vaccine administration screen.

When SBIR is not available, please refer to the SBIR user guide or the study procedures manual (SPM) for specific instructions.

6.2.2.2.2. Treatment number allocation for subsequent doses

For each dose subsequent to the first dose, the study staff in charge of the vaccine administration will access SBIR, provide the subject identification number, and the system will provide a treatment number consistent with the allocated study group.

The number of each administered treatment must be recorded in the eCRF on the vaccine administration screen.

6.2.3. Allocation of subjects to assay subsets

Blood samples for immunogenicity will be taken in all subjects at timepoints described in Table 5. Not all samples will be used for testing:

- Anti-CS and anti-HBs immune responses will be tested in a subset which includes the same subjects as in the reactogenicity sub-cohort (the first 50 subjects enrolled in each group).

CCI [redacted]

6.3. Method of blinding

Due to the different vaccination schedules between the various study groups the study will be open-label.

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

6.4. General study aspects

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

6.4.1. Independent Data Monitoring Committee oversight

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

The IDMC will review the study protocol and the statistical analysis plan. Meetings will be documented and the minutes of open sessions of the IDMC meetings will be made available to the sponsor. The IDMC may, if deemed necessary, convene a meeting with, or request further information from the principal investigators and GSK Biologicals' designated project representatives at any stage of the study.

The IDMC may recommend to the sponsor to suspend the enrollment to the study and/or vaccination based on their ongoing review of safety data.

The IDMC will receive the following safety data:

- Periodic safety reports (such as the annual development safety update reports [DSUR]).

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

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

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

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

Subjects should continue with their routine EPI immunizations as applicable to their age whilst participating in the study.

Clinical malaria episodes are detected by PCD and treatment will be guided by rapid diagnostic test (RDT)/clinical evaluation at the discretion of the investigator. Blood slides will also be collected, however, these will not be read in real time but sent to a central laboratory (see Table 17) where all blood samples will be read according to a standardized method. Case definitions of clinical malaria will be based on final parasite density obtained from this process.

Malaria infections will be detected through active detection of infections through cross-sectional blood sampling. Blood slides obtained will not be read in real time and will follow the same process as described above. As a result, non-febrile parasite positive children with no symptoms will not be treated for malaria at the time of cross-sectional visits.

6.5. Outline of study procedures

Table 11 List of study procedures for clinic visits

Epoch	Epoch 001									Epoch 002				Epoch 003				Epoch 004		
Type of contact: Clinic visits	Visit 1[m] Screening	Visit 2	Visit 3	Visit 4	Visit 5[a]	Visit 6[a]	Visit 10[b]	Visit 11[b]	Visit 12[b]	Visit 18[c]	Visit 19[c]	Visit 24[d]	Visit 25[e]	Visit 27[c]	Visit 28[c]	Visit 30[f]	Visit 31[f]	Visit 33[c]	Visit 34[c]	Visit 38
Timepoints	D-28 to D-1	D0	M1	M2	M2 + 7d	M3	M7	M7 + 7d	M8	M14	M15	M20	M21	M26	M27	M32	M33	M38	M39	M50
Children age (Months)		5-17 m																		
Control group																				
Informed consent	●																			
Check inclusion/exclusion criteria	●	O																		
Check the subject's vaccination card	O																			
Check screening lab results (hemoglobin)	●[g]																			
Collect demographic data	●																			
Check medical history	●																			
Physical examination	●	O	O	O	O	O						O								O
Measure and record length and weight	●																			
Issue subject's identification card		O																		
Check subject's identification card			O	O	O	O						O								O
Randomization		●																		
Distribute ITN	O																			
Record if the subject belongs to the reactogenicity sub-cohort		●																		
Check contraindications and warnings and precautions		●[h]	●[h]	●[h]																
Record pre-vaccination body temperature		●	●	●																
Treatment number allocation		O	O	O																
Administer study vaccine		●	●	●																
Recording of administered treatment number		●	●	●																
Blood sampling for assessment of immunogenicity for ALL subjects (2.5 ml)		●		●		●						●								●

Epoch	Epoch 001									Epoch 002				Epoch 003				Epoch 004		
Type of contact: Clinic visits	Visit 1[m] Screening	Visit 2	Visit 3	Visit 4	Visit 5[a]	Visit 6[a]	Visit 10[b]	Visit 11[b]	Visit 12[b]	Visit 18[c]	Visit 19[c]	Visit 24[d]	Visit 25[e]	Visit 27[c]	Visit 28[c]	Visit 30[f]	Visit 31[f]	Visit 33[c]	Visit 34[c]	Visit 38
Timepoints	D-28 to D-1	D0	M1	M2	M2 + 7d	M3	M7	M7 + 7d	M8	M14	M15	M20	M21	M26	M27	M32	M33	M38	M39	M50
Children age (Months)		5-17 m																		
Blood sampling for assessment of hemoglobin at screening (0.5 ml)	●[i]																			
Blood sampling for assessment of parasitemia for ALL subjects (0.5 ml) [n,o]		●	●	●		●						●								●
Record any concomitant medications/vaccinations		●	●	●	●	●						●								●
Record any intercurrent medical conditions		●	●	●	●	●						●								●
Record unsolicited AEs (Days 0-29)		●[k]	●[k]	●[k]	●[k]	●[k]														
Record AEs/SAEs leading to withdrawal from further vaccination		●	●	●	●	●						●								●
Record SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●						●								●
Record SAEs (All, fatal, related to the investigational vaccine) [p]		●	●	●	●	●						●								●
Record AEs of specific interest [l]		●	●	●	●	●						●								●
Study Conclusion																				●
For the reactogenicity sub-cohort only:																				
Blood sampling for assessment of safety (1.0 ml)				●	●	●														
Record solicited local and general AEs (Days 0-3)				●[j]																
Group R012-20																				
Informed consent	●																			
Check inclusion/exclusion criteria	●	O																		
Check the subject's vaccination card	O																			
Check screening lab results (hemoglobin)	●[g]																			
Collect demographic data	●																			
Check medical history	●																			
Physical examination	●	O	O	O	O	O						O	O							O
Measure and record length and weight	●																			

Epoch	Epoch 001									Epoch 002				Epoch 003				Epoch 004		
Type of contact: Clinic visits	Visit 1[m] Screening	Visit 2	Visit 3	Visit 4	Visit 5[a]	Visit 6[a]	Visit 10[b]	Visit 11[b]	Visit 12[b]	Visit 18[c]	Visit 19[c]	Visit 24[d]	Visit 25[e]	Visit 27[c]	Visit 28[c]	Visit 30[f]	Visit 31[f]	Visit 33[c]	Visit 34[c]	Visit 38
Timepoints	D-28 to D-1	D0	M1	M2	M2 + 7d	M3	M7	M7 + 7d	M8	M14	M15	M20	M21	M26	M27	M32	M33	M38	M39	M50
Children age (Months)		5-17 m																		
Issue subject's identification card		O																		
Check subject's identification card			O	O	O	O						O	O							O
Randomization		●																		
Distribute ITN	O																			
Record if the subject belongs to the reactogenicity sub-cohort		●																		
Check contraindications and warnings and precautions		●[h]	●[h]	●[h]								●[h]								
Record pre-vaccination body temperature		●	●	●								●								
Treatment number allocation		O	O	O								O								
Administer study vaccine		●	●	●								●								
Recording of administered treatment number		●	●	●								●								
Blood sampling for assessment of immunogenicity for ALL subjects (2.5 ml)		●		●		●						●	●							●
Blood sampling for assessment of hemoglobin at screening (0.5 ml)	●[i]																			
Blood sampling for assessment of parasitemia for ALL subjects (0.5 ml) [n, o]		●	●	●		●						●								●
Record any concomitant medications/vaccinations		●	●	●	●	●						●	●							●
Record any intercurrent medical conditions		●	●	●	●	●						●	●							●
Record unsolicited AEs (Days 0-29)		●[k]	●[k]	●[k]	●[k]	●[k]						●[k]	●[k]							
Record AEs/SAEs leading to withdrawal from further vaccination		●	●	●	●	●						●	●							●
Record SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●						●	●							●
Record SAEs (All, fatal, related to the investigational vaccine) [p]		●	●	●	●	●						●	●							●
Record AEs of specific interest [l]		●	●	●	●	●						●	●							●
Study Conclusion																				●

Epoch	Epoch 001									Epoch 002				Epoch 003				Epoch 004		
Type of contact: Clinic visits	Visit 1[m] Screening	Visit 2	Visit 3	Visit 4	Visit 5[a]	Visit 6[a]	Visit 10[b]	Visit 11[b]	Visit 12[b]	Visit 18[c]	Visit 19[c]	Visit 24[d]	Visit 25[e]	Visit 27[c]	Visit 28[c]	Visit 30[f]	Visit 31[f]	Visit 33[c]	Visit 34[c]	Visit 38
Timepoints	D-28 to D-1	D0	M1	M2	M2 + 7d	M3	M7	M7 + 7d	M8	M14	M15	M20	M21	M26	M27	M32	M33	M38	M39	M50
Children age (Months)		5-17 m																		
For the reactogenicity sub-cohort only:																				
Blood sampling for assessment of safety (1.0 ml)				●	●	●														
Record solicited local and general AEs (Days 0-3)				●[j]								●[j]								
Groups R012-14-mD and Fx012-14-mFxD																				
Informed consent	●																			
Check inclusion/exclusion criteria	●	O																		
Check the subject's vaccination card	O																			
Check screening lab results (hemoglobin)	●[g]																			
Collect demographic data	●																			
Check medical history	●																			
Physical examination	●	O	O	O	O	O				O	O			O	O			O	O	O
Measure and record length and weight	●																			
Issue subject's identification card		O																		
Check subject's identification card			O	O	O	O				O	O			O	O			O	O	O
Randomization		●																		
Distribute ITN	O																			
Record if the subject belongs to the reactogenicity sub-cohort		●																		
Check contraindications and warnings and precautions		●[h]	●[h]	●[h]						●[h]				●[h]				●[h]		
Record pre-vaccination body temperature		●	●	●						●				●				●		
Treatment number allocation		O	O	O						O				O				O		
Administer study vaccine		●	●	●						●				●				●		
Recording of administered treatment number		●	●	●						●				●				●		
Blood sampling for assessment of immunogenicity for ALL subjects (2.5 ml)		●		●		●				●	●			●	●			●	●	●

Epoch	Epoch 001									Epoch 002				Epoch 003				Epoch 004		
Type of contact: Clinic visits	**Visit 1[m] Screening**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5[a]**	**Visit 6[a]**	**Visit 10[b]**	**Visit 11[b]**	**Visit 12[b]**	**Visit 18[c]**	**Visit 19[c]**	**Visit 24[d]**	**Visit 25[e]**	**Visit 27[c]**	**Visit 28[c]**	**Visit 30[f]**	**Visit 31[f]**	**Visit 33[c]**	**Visit 34[c]**	**Visit 38**
Timepoints	**D-28 to D-1**	**D0**	**M1**	**M2**	**M2 + 7d**	**M3**	**M7**	**M7 + 7d**	**M8**	**M14**	**M15**	**M20**	**M21**	**M26**	**M27**	**M32**	**M33**	**M38**	**M39**	**M50**
Children age (Months)		**5-17 m**																		
Blood sampling for assessment of hemoglobin at screening (0.5 ml)	●[i]																			
Blood sampling for assessment of parasitemia for ALL subjects (0.5 ml) [n, 0]		●	●	●		●				●	●			●				●		●
Record any concomitant medications/vaccinations		●	●	●	●	●				●	●			●	●			●	●	●
Record any intercurrent medical conditions		●	●	●	●	●				●	●			●	●			●	●	●
Record unsolicited AEs (Days 0-29)		●[k]	●[k]	●[k]	●[k]	●[k]				●[k]	●[k]			●[k]	●[k]			●[k]	●[k]	
Record AEs/SAEs leading to withdrawal from further vaccination		●	●	●	●	●				●	●			●	●			●	●	●
Record SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●				●	●			●	●			●	●	●
Record SAEs (All, fatal, related to the investigational vaccine) [p]		●	●	●	●	●				●	●			●	●			●	●	●
Record AEs of specific interest [l]		●	●	●	●	●				●	●			●	●			●	●	●
Study Conclusion																				●
For the reactogenicity sub-cohort only:																				
Blood sampling for assessment of safety (1.0 ml)				●	●	●														
Record solicited local and general AEs (Days 0-3)				●[j]						●[j]				●[j]				●[j]		
Group Fx017-mFxD																				
Informed consent	●																			
Check inclusion/exclusion criteria	●	O																		
Check the subject's vaccination card	O																			
Check screening lab results (hemoglobin)	●[g]																			
Collect demographic data	●																			
Check medical history	●																			
Physical examination	●	O	O	O			O	O	O			O	O			O	O			O
Measure and record length and weight	●																			

Epoch	Epoch 001									Epoch 002				Epoch 003				Epoch 004		
Type of contact: Clinic visits	Visit 1[m] Screening	Visit 2	Visit 3	Visit 4	Visit 5[a]	Visit 6[a]	Visit 10[b]	Visit 11[b]	Visit 12[b]	Visit 18[c]	Visit 19[c]	Visit 24[d]	Visit 25[e]	Visit 27[c]	Visit 28[c]	Visit 30[f]	Visit 31[f]	Visit 33[c]	Visit 34[c]	Visit 38
Timepoints	D-28 to D-1	D0	M1	M2	M2 + 7d	M3	M7	M7 + 7d	M8	M14	M15	M20	M21	M26	M27	M32	M33	M38	M39	M50
Children age (Months)		5-17 m																		
Issue subject's identification card		O																		
Check subject's identification card			O	O			O	O	O			O	O			O	O			O
Randomization		●																		
Distribute ITN	O																			
Record if the subject belongs to the reactogenicity sub-cohort		●																		
Check contraindications and warnings and precautions		●[h]	●[h]				●[h]					●[h]				●[h]				
Record pre-vaccination body temperature		●	●				●					●				●				
Treatment number allocation		O	O				O					O				O				
Administer study vaccine		●	●				●					●				●				
Recording of administered treatment number		●	●				●					●				●				
Blood sampling for assessment of immunogenicity for ALL subjects (2.5 ml)		●		●			●		●			●	●			●	●			●
Blood sampling for assessment of hemoglobin at screening (0.5 ml)	●[i]																			
Blood sampling for assessment of parasitemia for ALL subjects (0.5 ml) [n, o]		●	●	●			●		●			●				●				●
Record any concomitant medications/vaccinations		●	●	●			●	●	●			●	●			●	●			●
Record any intercurrent medical conditions		●	●	●			●	●	●			●	●			●	●			●
Record unsolicited AEs (Days 0-29)		●[k]	●[k]	●[k]			●[k]	●[k]	●[k]			●[k]	●[k]			●[k]	●[k]			
Record AEs/SAEs leading to withdrawal from further vaccination		●	●	●			●	●	●			●	●			●	●			●
Record SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●			●	●	●			●	●			●	●			●
Record SAEs (All, fatal, related to the investigational vaccine) [p]		●	●	●			●	●	●			●	●			●	●			●
Record AEs of specific interest [l]		●	●	●			●	●	●			●	●			●	●			●
Study Conclusion																				●

Epoch	Epoch 001									Epoch 002				Epoch 003				Epoch 004		
Type of contact: Clinic visits	Visit 1[m] Screening	Visit 2	Visit 3	Visit 4	Visit 5[a]	Visit 6[a]	Visit 10[b]	Visit 11[b]	Visit 12[b]	Visit 18[c]	Visit 19[c]	Visit 24[d]	Visit 25[e]	Visit 27[c]	Visit 28[c]	Visit 30[f]	Visit 31[f]	Visit 33[c]	Visit 34[c]	Visit 38
Timepoints	D-28 to D-1	D0	M1	M2	M2 + 7d	M3	M7	M7 + 7d	M8	M14	M15	M20	M21	M26	M27	M32	M33	M38	M39	M50
Children age (Months)		5-17 m																		
For the reactogenicity sub-cohort only:																				
Blood sampling for assessment of safety (1.0 ml)							●	●	●											
Record solicited local and general AEs (Days 0-3)							●[j]					●[j]				●[j]				

Note: The double-line border following Month 21 (Visit 25) and Month 33 (Visit 31) indicates the two interim analyses which will be performed on all data collected up to respectively Month 21 and up to Month 33 (i.e. data that are as clean as possible, except clinical malaria fully cleaned up to Month 14). The final analysis will be performed on fully cleaned data collected up to study end (Month 50).

D: Day, M: Month.

● is used to indicate a study procedure that requires documentation in the individual eCRF.

O is used to indicate a study procedure that does not require documentation in the individual eCRF.

a. Clinic visit 5 (Month 2 + 7 days) and clinic visit 6 (Month 3) are only for groups R012-20, R012-14-mD, Fx012-14-mFxD and Control. The group FX017-mFXD has a field worker visit at Month 3 for assessment of parasitemia.
b. Clinic visit 10 (Month 7), clinic visit 11 (Month 7 + 7 days) and clinic visit 12 (Month 8) are only for group Fx017-mFxD. The other groups have field worker visits at Month 7 and Month 8 respectively for assessment of parasitemia.
c. Clinic visit 18 (Month 14), clinic visit 19 (Month 15), clinic visit 27 (Month 26), clinic visit 28 (Month 27), clinic visit 33 (Month 38) and clinic visit 34 (Month 39) are only for groups R012-14-mD and Fx012-14-mFxD. The other groups have field worker visits at Month 14, Month 15, Month 26 and Month 38 respectively for assessment of parasitemia.
d. Clinic visit 24 (Month 20) is only for groups R012-20, Fx017-mFxD and Control. The other groups have a field worker visit at Month 20 for assessment of parasitemia.
e. Clinic visit 25 (Month 21) is only for groups R012-20 and Fx017-mFxD.
f. Clinic visit 30 (Month 32) and clinic visit 31 (Month 33) are only for group Fx017-mFxD. The other groups have a field worker visit at Month 32 for assessment of parasitemia.
g. The screening laboratory results (hemoglobin) must be checked during the screening activities and before randomization.
h. There is no specific section in the eCRF to record the contraindications, warnings and precautions. The absolute contraindications to further administration of study vaccines have to be recorded in the AE or SAE section of the eCRF.
i. At screening, hemoglobin will be assessed in all subjects screened.
j. Solicited local and general AEs will be collected in the first 50 subjects enrolled in each group (reactogenicity sub-cohort) during four days (day of vaccination and three subsequent days) after vaccination as indicated in the table above. On the day of vaccination the evaluation will be carried out by the study physician at the study center. On Days 1, 2 and 3 after vaccination, trained study personnel will visit the children to record solicited AEs on diary cards.
k. Unsolicited AEs will be collected during 30 days (day of vaccination and 29 subsequent days) after each dose of study vaccine. Unsolicited AEs will be captured through passive surveillance at inpatient and outpatient facilities and during study visits.

l. AEs of specific interest include all seizures occurring within 30 days post-vaccination, meningitis and pIMDs (see Section 9.1.6). pIMDs will be reported via the electronic Expedited Adverse Events Report. Meningitis and seizures will be reported via the electronic Expedited Adverse Events Report and in addition clinical details of each case will be reported in a specific eCRF screen.

m. If a subject is considered momentarily ineligible on the day of the screening visit (i.e. failing to meet one or more eligibility criteria) procedures for screening can be repeated one further time, within the time window allowed for screening (see Table 14). No more than one repeat is allowed.

n. Blood for parasitemia (0.5 ml) includes the blood for the slide reading ***(to Month 50)*** and for the filter paper ***(to Month 32)***. The parasitemia assessment by blood slide reading will include blood-stage parasites and gametocytes counts.

o. In addition to the scheduled clinic visits, malaria cases will be captured by PCD throughout the study. All sick children presenting with fever and/or history of fever will have a blood sample taken for the evaluation of vaccine efficacy (for blood slide ***to Month 50*** and filter paper for PCR ***to Month 32***).

p. Case of severe malaria or cerebral malaria will be reported via the electronic Expedited Adverse Events Report (refer to Section 9.3.1) and in addition clinical details of each case will be reported in a specific eCRF screen.

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Table 12 List of study procedures for field worker visits - Part 1 (Day 0 to Month 19)

Epochs	Epoch 001																		Epoch 002								
Type of contact: Field worker visits	Visit a*	Visit b*	Visit c*	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	Visit d*	Visit e*	Visit f*	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**	**Visit 16**	**Visit 17**	**Visit 18**	Visit g*	Visit h*	Visit i*	**Visit 19**	**Visit 20**	**Visit 21**	**Visit 22**	**Visit 23**
Timepoints	M2 + 1d	M2 + 2d	M2 + 3d	**M3**	**M4**	**M5**	**M6**	**M7**	M7 + 1d	M7 + 2d	M7 + 3d	**M8**	**M9**	**M10**	**M11**	**M12**	**M13**	**M14**	M14 + 1d	M14 + 2d	M14 + 3d	**M15**	**M16**	**M17**	**M18**	**M19**
Control group																										
Check subject's identification card	O	O	O		O	O	O	O				O	O	O	O	O	O	O				O	O	O	O	O
Blood sampling for assessment of parasitemia for ALL subjects (0.5 ml) †, §					●	●	●	●				●	●	●	●	●	●	●				●	●	●	●	●
For the reactogenicity sub-cohort only: Record solicited local and general AEs (Days 0-3)	●	●	●																							
Group R012-20																										
Check subject's identification card	O	O	O		O	O	O	O				O	O	O	O	O	O	O				O	O	O	O	O
Blood sampling for assessment of parasitemia for ALL subjects (0.5 ml) †, §					●	●	●	●				●	●	●	●	●	●	●				●	●	●	●	●
For the reactogenicity sub-cohort only: Record solicited local and general AEs (Days 0-3)	●	●	●																							
Groups R012-14-mD and Fx012-14-mFxD																										
Check subject's identification card	O	O	O		O	O	O	O				O	O	O	O	O	O		O	O	O		O	O	O	O
Blood sampling for assessment of parasitemia for ALL subjects (0.5 ml) †, §					●	●	●	●				●	●	●	●	●	●						●	●	●	●
For the reactogenicity sub-cohort only: Record solicited local and general AEs (Days 0-3)	●	●	●																●	●	●					
Group Fx017-mFxD																										
Check subject's identification card				O	O	O	O		O	O	O		O	O	O	O	O	O				O	O	O	O	O
Blood sampling for assessment of parasitemia for ALL subjects (0.5 ml) †, §				●	●	●	●						●	●	●	●	●	●				●	●	●	●	●
For the reactogenicity sub-cohort only: Record solicited local and general AEs (Days 0-3)									●	●	●															

M: Month, d: day.

● is used to indicate a study procedure that requires documentation in the individual eCRF.

O is used to indicate a study procedure that does not require documentation in the individual eCRF.

* Visits a-u are restricted to the subjects in the reactogenicity sub-cohort; these visits are for the recording of solicited local and general AEs in the three days following each vaccination.

† Blood for parasitemia (0.5 ml) includes the blood for the slide reading and for the filter paper. The parasitemia assessment by blood slide reading will include blood-stage parasites and gametocytes counts.

§ In addition to the scheduled clinic visits, malaria cases will be captured by PCD throughout the study. All sick children presenting with fever and/or history of fever will have a blood sample taken for the evaluation of vaccine efficacy (for blood slide and filter paper for PCR).

Table 13 List of study procedures for field worker visits - Part 2 (Month 20 to Month 50)

Epochs	Epoch 002						Epoch 003											Epoch 004						
Type of contact: Field worker visits	**Visit 24**	Visit j*	Visit k*	Visit l*	**Visit 25**	**Visit 26**	**Visit 27**	Visit m*	Visit n*	Visit o*	**Visit 28**	**Visit 29**	**Visit 30**	Visit p*	Visit q*	Visit r*	**Visit 32**	**Visit 33**	Visit s*	Visit t*	Visit u*	**Visit 35**	**Visit 36**	**Visit 37**
Timepoints	**M20**	M20 + 1d	M20 + 2d	M20 + 3d	**M21**	**M23**	**M26**	M26 + 1d	M26 + 2d	M26 + 3d	**M27**	**M29**	**M32**	M32+ 1d	M32 + 2d	M32 + 3d	**M35**	**M38**	M38 + 1d	M38 + 2d	M38 + 3d	**M41**	**M44**	**M47**
Control group																								
Check subject's identification card	O				O	O	O					O	O				O	O				O	O	O
Blood sampling for assessment of parasitemia for ALL subjects (0.5 ml) †, §	●					●	●					●	●				●	●				●	●	●
For the reactogenicity sub-cohort only: Record solicited local and general AEs (Days 0-3)																								
Group R012-20																								
Check subject's identification card	O	O	O	O		O	O					O	O				O	O				O	O	O
Blood sampling for assessment of parasitemia for ALL subjects (0.5 ml) †, §	●					●	●					●	●				●	●				●	●	●
For the reactogenicity sub-cohort only: Record solicited local and general AEs (Days 0-3)		●	●	●																				
Groups R012-14-mD and Fx012-14-mFxD																								
Check subject's identification card	O				O	O		O	O	O		O	O				O		O	O	O	O	O	O
Blood sampling for assessment of parasitemia for ALL subjects (0.5 ml) †, §	●					●						●	●				●					●	●	●
For the reactogenicity sub-cohort only: Record solicited local and general AEs (Days 0-3)								●	●	●									●	●	●			
Group Fx017-mFxD																								
Check subject's identification card	O	O	O	O		O	O					O		O	O	O	O	O				O	O	O
Blood sampling for assessment of parasitemia for ALL subjects (0.5 ml) †, §	●					●	●					●					●	●				●	●	●

Epochs	Epoch 002						Epoch 003											Epoch 004						
Type of contact: Field worker visits	**Visit 24**	Visit j*	Visit k*	Visit l*	**Visit 25**	**Visit 26**	**Visit 27**	Visit m*	Visit n*	Visit o*	**Visit 28**	**Visit 29**	**Visit 30**	Visit p*	Visit q*	Visit r*	**Visit 32**	**Visit 33**	Visit s*	Visit t*	Visit u*	**Visit 35**	**Visit 36**	**Visit 37**
Timepoints	**M20**	M20 + 1d	M20 + 2d	M20 + 3d	**M21**	**M23**	**M26**	M26 + 1d	M26 + 2d	M26 + 3d	**M27**	**M29**	**M32**	M32+ 1d	M32 + 2d	M32 + 3d	**M35**	**M38**	M38 + 1d	M38 + 2d	M38 + 3d	**M41**	**M44**	**M47**
For the reactogenicity sub-cohort only: Record solicited local and general AEs (Days 0-3)		●	●	●										●	●	●								

M: Month, d: day.

● is used to indicate a study procedure that requires documentation in the individual eCRF.

O is used to indicate a study procedure that does not require documentation in the individual eCRF.

* Visits a-u are restricted to the subjects in the reactogenicity sub-cohort; these visits are for the recording of solicited local and general AEs in the three days following each vaccination.

† Blood for parasitemia (0.5 ml) includes the blood for the slide reading ***(to Month 50)*** and for the filter paper ***(to Month 32)***. The parasitemia assessment by blood slide reading will include blood-stage parasites and gametocytes counts.

§ In addition to the scheduled clinic visits, malaria cases will be captured by PCD throughout the study. All sick children presenting with fever and/or history of fever will have a blood sample taken for the evaluation of vaccine efficacy (for blood slide ***to Month 50*** and filter paper for PCR ***to Month 32***).

In addition to the field worker visits detailed in Table 12 and Table 13, field workers may visits the subjects ahead of the planned visit to ensure presence during the next visit an d maintain subject compliance.

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Table 14 Intervals between study visits

Interval	Optimal length of interval [1]	Allowed interval[2]
Visit 1→Visit 2 (Vacc)	0 to 28 days	0 - 28 days
Visit 2→Visit 3 (Vacc)	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 3→Visit 4 (Vacc)	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 4→Visit 5	7 days	Minimum 6 days - Maximum 8 days
Visit 4→Visit 6	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 6→Visit 7	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 7→Visit 8	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 8→Visit 9	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 3→Visit 10 (Vacc)	6 months	Minimum 161 days (23 weeks) - Maximum 203 days (29 weeks)
Visit 10→Visit 11	7 days	Minimum 6 days - Maximum 8 days
Visit 10→Visit 12	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 12→Visit 13	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 13→Visit 14	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 14→Visit 15	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 15→Visit 16	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 16→Visit 17	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 4→Visit 18 (Vacc)	12 months	Minimum 336 days (48 weeks) - Maximum 392 days (56 weeks)
Visit 18→Visit 19	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 19→Visit 20	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 20→Visit 21	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 21→Visit 22	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 22→Visit 23	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 4→Visit 24 (Vacc)*	18 months	Minimum 518 days (74 weeks) - Maximum 574 days (82 weeks)
Visit 10→Visit 24 (Vacc)**	13 months	Minimum 364 days (52 weeks) - Maximum420 days (60 weeks)
Visit 24→Visit 25	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 24 → Visit 26	3 months	Minimum 77 days (11 weeks) - Maximum 105 days (15 weeks)
Visit 18→Visit 27 (Vacc)	12 months	Minimum 336 days (48 weeks) - Maximum 392 days (56 weeks)
Visit 27→Visit 28	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 27→Visit 29	3 months	Minimum 77 days (11 weeks) - Maximum 105 days (15 weeks)
Visit 24→Visit 30 (Vacc)	12 months	Minimum 336 days (48 weeks) - Maximum 392 days (56 weeks)
Visit 30→Visit 31	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 30→Visit 32	3 months	Minimum 77 days (11 weeks) - Maximum 105 days (15 weeks)
Visit 27→Visit 33 (Vacc)	12 months	Minimum 336 days (48 weeks) - Maximum 392 days (56 weeks)
Visit 33→Visit 34	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 33→Visit 35	3 months	Minimum 77 days (11 weeks) - Maximum 105 days (15 weeks)
Visit 35→Visit 36	3 months	Minimum 77 days (11 weeks) - Maximum 105 days (15 weeks)
Visit 36→Visit 37	3 months	Minimum 77 days (11 weeks) - Maximum 105 days (15 weeks)
Visit 37→Visit 38	3 months	Minimum 77 days (11 weeks) - Maximum 105 days (15 weeks)

[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) cohorts if they make the study visit outside this interval: to be included in the ATP cohort for efficacy, subjects should receive all vaccinations within the protocol specified intervals; to be included in the ATP cohort for immunogenicity, subjects should receive all vaccinations within the protocol specified intervals and perform all blood samplings for immunogenicity within the protocol specified intervals.

* Interval between Visit 4 and Visit 24 is for groups Control and R012-20.

** Interval between Visit 10 and Visit 24 is for group Fx017-mFxD.

Vacc: vaccination in at least one group.

6.6. Detailed description of study procedures

6.6.1. Informed consent

The signed/witnessed/thumb-printed informed consent of the subject's parent(s)/LAR(s) must be obtained before study participation. Refer to Section 6.1 for the requirements on how to obtain informed consent.

6.6.2. Check inclusion and exclusion criteria

Check all inclusion and exclusion criteria as described in Sections 5.2 and 5.3 before enrolment.

If a subject is considered momentarily ineligible on the day of the screening visit (i.e. failing to meet one or more eligibility criteria) procedures for screening can be repeated one further time, within the time window allowed for screening (see Table 14). No more than one repeat is allowed.

6.6.3. Check the subject's vaccination card

Check the subjects' vaccination card to assess if the subject meets the related inclusion criterion described in Section 5.2.

6.6.4. Check screening laboratory results

Check the result of the hemoglobin level to assess if the subject meets the related exclusion criterion described in Section 5.3.

6.6.5. Collect demographic data

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

6.6.6. Check medical history

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

6.6.7. Physical examination

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

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

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

6.6.8. Measure and record length and weight

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

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

6.6.9. Issue subject's identification card

At Visit 2, take a picture of the subject and his/her parent(s)/LAR(s) to make an identification card with subject's picture and number. Give this identification card to the subject's parent(s)/LAR(s).

6.6.10. Check subject's identification card

At each subsequent clinic visits AND field worker visits, check the subject's identification card.

6.6.11. Study group and treatment number allocation (randomization)

Study group and treatment number allocation will be performed as described in Section 6.2.2. The number of each administered treatment must be recorded in the eCRF.

6.6.12. Record if the subject belongs to the reactogenicity sub-cohort

The reactogenicity sub-cohort will consist of the first 50 subjects enrolled in each group (see Section 5). Record in the eCRF if the subject belongs to the reactogenicity sub-cohort.

6.6.13. Check contraindications, warnings and precautions to vaccination

Contraindications, warnings and precautions to vaccination must be checked at the beginning of each vaccination visit. Refer to Sections 7.5 and 7.6 for more details.

6.6.14. Record pre-vaccination body temperature

The axillary, rectal, oral or tympanic body temperature of all subjects needs to be measured prior to any study vaccines administration. The preferred route for recording temperature in this study will be axillary. If the subject has fever (fever is defined as temperature ≥ 37.5°C/99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C/100.4°F for

rectal route) on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 14).

6.6.15. Study vaccines administration

After completing all prerequisite procedures prior to vaccination, one dose of study vaccine will be administered intramuscularly in the left deltoid (refer to Section 7.3 for detailed description of the vaccines administration procedure). If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccine administration, the visit will be rescheduled within the allowed interval for this visit (refer to Table 14).

The subjects will be observed closely for at least 30 minutes following the administration of the vaccine, with appropriate medical treatment readily available in case of anaphylaxis.

Vaccination will take place at the vaccination center. All vaccinations will be given by a qualified person: a nurse or a doctor. A staff member experienced in the resuscitation of children will be available at all vaccination sessions.

6.6.16. Blood sampling for all subjects

Blood samples will be taken during certain study visits as specified in Table 11, Table 12 and Table 13.

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

- **Blood sampling for assessment of immunogenicity**

  A volume of approximately 2.5 ml of whole blood should be drawn from all subjects at each pre-defined timepoint. Out of this, a volume of approximately 1.5 ml of whole blood will provide 600 µl of serum (300 µl of serum for anti-CS enzyme-linked immunosorbent assay [ELISA] + anti-CS avidity and 250 µl of serum for anti-HBs) and serum from a volume of approximately 1.0 ml of whole blood will be stored to support potential ancillary studies for the further characterization of the immune response and translational research for correlates of protection.

  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.

- **Blood sampling for assessment of hemoglobin at screening**

  A volume of approximately 0.5 ml of whole blood should be drawn from all subjects screened at Visit 1 (Screening) to measure hemoglobin concentration.

- **Blood sampling for assessment of parasitemia**

  A volume of approximately 0.5 ml of whole blood should be drawn from all subjects at each pre-defined timepoint for the assessment of *P. falciparum* parasitemia (***until Month 50*** for blood slide and ***until Month 32 for*** filter paper).

In addition to the scheduled clinic visits, malaria cases will be captured by PCD throughout the study. All sick children presenting with fever and/or history of fever will have a blood sample taken for the evaluation of vaccine efficacy (***until Month 50*** for blood slide and ***until Month 32 for*** filter paper).

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6.6.17. Blood sampling for the reactogenicity sub-cohort

Blood samples for the assessment of hematology and biochemistry parameters will be taken in subjects belonging to the reactogenicity sub-cohort (i.e. the first 50 subjects enrolled in each group) during certain study visits as specified in Table 11.

- **Blood sampling for assessment of safety**

  A volume of approximately 1.0 ml of whole blood should be drawn at each pre-defined timepoint for the assessment of hematology (hemoglobin, WBC, platelets) biochemistry (ALT, creatinine) parameters.

6.6.18. Check and record concomitant medication/vaccination and intercurrent medical conditions

Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 7.7.

Intercurrent medical conditions must be checked and recorded in the eCRF as described in Section 7.8.

6.6.19. Recording of unsolicited AEs, SAEs and AEs of specific interest

Refer to Section 9.2 for procedures for the investigator to record AEs, SAEs and AEs of specific interest. Refer to Section 9.3 for guidelines and how to report SAE and AEs of specific interest reports to GSK Biologicals.

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

Unsolicited AEs will be collected during 30 days (day of vaccination and 29 subsequent days) after each dose of study vaccine. Unsolicited AEs will be captured through passive surveillance at inpatient and outpatient facilities and during study visits.

Where possible autopsies will be performed. Verbal autopsy will be performed on all cases of mortality occurring outside hospital if it is not possible to perform the autopsies (Refer to Section 9.2.3.6).

6.6.20. Recording of solicited AEs in the reactogenicity sub-cohort

Solicited local and general AEs will be collected in the first 50 subjects enrolled in each group (reactogenicity sub-cohort) during four days (day of vaccination and three subsequent days) after Dose 3 of study vaccine (all groups including controls), after Dose

4 (R012-20, R012-14-mD, Fx012-14-mFxD and Fx017-mFxD), after Dose 5 (R012-14-mD, Fx012-14-mFxD and Fx017-mFxD) and after Dose 6 (R012-14-mD and Fx012-14-mFxD). On the day of vaccination the evaluation will be carried out by the study physician at the study center. On Days 1, 2 and 3 after vaccination, trained study personnel will visit the children to record solicited AEs on diary cards.

6.6.21. Study conclusion

The investigator will:

- review data collected 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 labelled with information that directly identifies the subject but will be coded with the identification number for the subject (subject number).

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

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

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

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

If additional testing is performed, the marker priority ranking given in Section 6.7.4 may be changed.

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

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 11.5 for the definition of cohorts to be analyzed). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, appropriate materials from the investigator's site must be used. Refer to the Module on Clinical Trial Supplies in the SPM.

6.7.2. Biological samples

Sample type to be collected in the study: whole blood.

Table 15 Biological samples (whole blood)

Timepoint	Assessment	Total volume of blood per visit (ml)				
		R012-20	R012-14-mD	Fx012-14-mFxD	Fx017-mFxD	Control
Visit 1 (Screening)	Safety (hemoglobin)†	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 2 (Day 0)	Immunogenicity	2.5 ml	2.5 ml	2.5 ml	2.5 ml I	2.5 ml
	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**3.0 ml**	**3.0 ml**	**3.0 ml**	**3.0 ml**	**3.0 ml**
Visit 3 (Month 1)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 4 (Month 2)	Safety*	1.0 ml*	1.0 ml*	1.0 ml*	-	1.0 ml*
	Immunogenicity	2.5 ml	2.5 ml	2.5 ml	2.5 ml	2.5 ml
	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**4.0 or 3.0 ml****	**4.0 or 3.0 ml****	**4.0 or 3.0 ml****	**3.0 ml**	**4.0 or 3.0 ml****
Visit 5 (Month 2 + 7d)	Safety*	1.0 ml*	1.0 ml*	1.0 ml*	-	1.0 ml*
Visit 6 (Month 3)	Safety*	1.0 ml*	1.0 ml*	1.0 ml*	-	1.0 ml*
	Immunogenicity	2.5 ml	2.5 ml	2.5 ml	-	2.5 ml
	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**4.0 or 3.0 ml****	**4.0 or 3.0 ml****	**4.0 or 3.0 ml****	**0.5 ml**	**4.0 or 3.0 ml****
Visit 7 (Month 4)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 8 (Month 5)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 9 (Month 6)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 10 (Month 7)	Safety*	-	-	-	1.0 ml*	-
	Immunogenicity	-	-	-	2.5 ml	-
	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**0.5 ml**	**0.5 ml**	**0.5 ml**	**4.0 or 3.0 ml****	**0.5 ml**
Visit 11 (Month 7 + 7d)	Safety*	-	-	-	1.0 ml*	-
Visit 12 (Month 8)	Safety*	-	-	-	1.0 ml*	-
	Immunogenicity	-	-	-	2.5 ml	-
	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**0.5 ml**	**0.5 ml**	**0.5 ml**	**4.0 or 3.0 ml****	**0.5 ml**
Visit 13 (Month 9)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 14 (Month 10)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 15 (Month 11)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 16 (Month 12)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 17 (Month 13)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 18 (Month 14)	Immunogenicity	-	2.5 ml	2.5 ml	-	-
	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**0.5 ml**	**3.0 ml**	**3.0 ml**	**0.5 ml**	**0.5 ml**
Visit 19 (Month 15)	Immunogenicity	-	2.5 ml	2.5 ml	-	-
	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**0.5 ml**	**3.0 ml**	**3.0 ml**	**0.5 ml**	**0.5 ml**
Visit 20 (Month 16)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 21 (Month 17)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 22 (Month 18)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 23 (Month 19)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 24 (Month 20)	Immunogenicity	2.5 ml	-	-	2.5 ml	2.5 ml
	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**3.0 ml**	**0.5 ml**	**0.5 ml**	**3.0 ml**	**3.0 ml**
Visit 25 (Month 21)	Immunogenicity	2.5 ml	-	-	2.5 ml	-
Visit 26 (Month 23)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml

Timepoint	Assessment	Total volume of blood per visit (ml)				
		R012-20	R012-14-mD	Fx012-14-mFxD	Fx017-mFxD	Control
Visit 27 (Month 26)	Immunogenicity Parasitemia‡ **Total:**	- 0.5 ml **0.5 ml**	2.5 ml 0.5 ml **3.0 ml**	2.5 ml 0.5 ml **3.0 ml**	- 0.5 ml **0.5 ml**	- 0.5 ml **0.5 ml**
Visit 28 (Month 27)	Immunogenicity	-	2.5 ml	2.5 ml	-	-
Visit 29 (Month 29)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 30 (Month 32)	Immunogenicity Parasitemia‡ **Total:**	- 0.5 ml **0.5 ml**	- 0.5 ml **0.5 ml**	- 0.5 ml **0.5 ml**	2.5 ml 0.5 ml **3.0 ml**	- 0.5 ml **0.5 ml**
Visit 31 (Month 33)	Immunogenicity	-	-	-	2.5 ml	-
Visit 32 (Month 35)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 33 (Month 38)	Immunogenicity Parasitemia‡ **Total:**	- 0.5 ml **0.5 ml**	2.5 ml 0.5 ml **3.0 ml**	2.5 ml 0.5 ml **3.0 ml**	- 0.5 ml **0.5 ml**	- 0.5 ml **0.5 ml**
Visit 34 (Month 39)	Immunogenicity	-	2.5 ml	2.5 ml	-	-
Visit 35 (Month 41)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 36 (Month 44)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 37 (Month 47)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 38 (Month 50)	Immunogenicity Parasitemia‡ **Total:**	2.5 ml 0.5 ml **3.0 ml**	2.5 ml 0.5 ml **3.0 ml**	2.5 ml 0.5 ml **3.0 ml**	2.5 ml 0.5 ml **3.0 ml**	2.5 ml 0.5 ml **3.0 ml**

† At screening, hemoglobin will be assessed in all subjects screened.
* Blood samples for hematology and biochemistry will be taken only in subjects belonging to the reactogenicity sub-cohort.
** The total volume of blood to be taken depends if the subject belongs to the reactogenicity sub-cohort or not.
d: day.
‡ Blood for parasitemia (0.5 ml) includes the blood for the slide reading (to Month 50) and for the filter paper (to Month 32).

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6.7.3. Laboratory assays

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

Serological assays for the determination of anti-CS antibodies will be performed by ELISA at a laboratory designated by GSK Biologicals using standardized and validated procedures (refer to Table 16).

Serological assays for the determination of anti-CS antibody avidity will be performed by ELISA at a laboratory designated by GSK Biologicals using standardized procedures (refer to Table 16).

Serological assays for the determination of anti-HBs antibodies will be performed by chemiluminescence enzyme immunoassay (CLIA) at a GSK Biologicals laboratory using standardized and validated procedures (refer to Table 16).

Table 16 Humoral immunity (antibody determination)

System*	Component	Method	Kit / Manufacturer	Unit	Cut-off	Laboratory
SERUM	Plasmodium falciparum.Circumsporozoite Protein.R32LR Ab.IgG	ELISA	in house	EU/ml	0.5	CEVAC
SERUM	Hepatitis B Virus.Surface Ab	CLIA	ADVIA Centaur anti-HBs2 (Siemens Healthcare)	mIU/ml	6.2	GSK Biologicals**
SERUM	Plasmodium falciparum.Circumsporozoide Protein.R32LR Ab.IgG Avidity	ELISA	in house	%	Not applicable	CEVAC

CCI [redacted].

** GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium.
Ab: antibody
CEVAC: Center for Vaccinology, Ghent, Belgium
CLIA: chemiluminescence enzyme immunoassay
ELISA: Enzyme-linked immunosorbent assay
EU/ml: ELISA unit per milliliter
IgG: Immunoglobulin G
mIU/ml: milli-international unit per milliliter

Table 17 Assessment of *P. falciparum* infection

System	Component	Method	Unit	Laboratory
Whole Blood*	Plasmodium falciparum parasites**	Not applicable***	Not applicable	KEMRI/USAMRU-K, WRP, Malaria Diagnostics Center, Kisumu§

KEMRI/USAMRU-K, WRP: Kenya Medical Research Institute / US Army Medical Research Unit Kenya, Walter Reed Project.
* The incidence of *P. falciparum* infection assessed by PCR and parasite genotyping will be evaluated in an ancillary study, using samples collected as described in the present protocol (see Table 20).
** *P. falciparum* parasite count includes blood-stage parasites and gametocytes counts.
*** Method used will be blood slide microscope reading.
§ And/or other GSK designated laboratory.

Table 18 Hematology and biochemistry

System	Component	Method	Scale	Laboratory
Whole blood	Hemoglobin Leukocytes (White Blood Cells) Platelets	Not applicable	Quantitative	Study site*
Serum	Alanine Aminotransferase Creatinine	Not applicable	Quantitative	Study site*

* And/or other GSK-designated laboratory

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

6.7.4. Biological samples evaluation

6.7.4.1. Immunological read-outs

In this study, all subjects enrolled will have blood samples taken for assessment of immunogenicity. Not all samples will be used for testing: Anti-CS and anti-HBs immune responses will be tested in a subset corresponding to the first 50 subjects enrolled in each group (i.e. the immunogenicity subset which include the same subjects as in the reactogenicity sub-cohort; see Section 5) [redacted]

Table 19 Immunological read-outs

Blood sampling timepoint		Study groups	Subset name	No. subjects	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint					
Visit 2 (Day 0)	Pre-Vacc	All groups	Immunogenicity	250	Anti- CS	1
		All groups	Immunogenicity	250	Anti-CS avidity	2
		All groups	Immunogenicity	250	Anti-HBs	3
Visit 4 (Month 2)	Post-Dose 2 (Fx017-mFxD) / Pre-Dose 3 (other groups)	All groups	Immunogenicity	250	Anti-CS	1
		All groups	Immunogenicity	250	Anti-CS avidity	2
		All groups	Immunogenicity	250	Anti-HBs	3
Visit 6 (Month 3)	Post-Dose 3	R012-20 R012-14-mD Fx012-14-mFxD Control	Immunogenicity	200	Anti-CS	1
		R012-20 R012-14-mD Fx012-14-mFxD Control	Immunogenicity	200	Anti-CS avidity	2
		R012-20 R012-14-mD Fx012-14-mFxD Control	Immunogenicity	200	Anti-HBs	3
Visit 10 (Month 7)	Pre-Dose 3	Fx017-mFxD	Immunogenicity	50	Anti-CS	1
		Fx017-mFxD	Immunogenicity	50	Anti-CS avidity	2
		Fx017-mFxD	Immunogenicity	50	Anti-HBs	3
Visit 12 (Month 8)	Post-Dose 3	Fx017-mFxD	Immunogenicity	50	Anti-CS	1
		Fx017-mFxD	Immunogenicity	50	Anti-CS avidity	2
		Fx017-mFxD	Immunogenicity	50	Anti-HBs	3
Visit 18 (Month 14)	Pre-Dose 4	R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-CS	1
		R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-CS avidity	2
		R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-HBs	3

Blood sampling timepoint		Study groups	Subset name	No. subjects	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint					
Visit 19 (Month 15)	Post-Dose 4	R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-CS	1
		R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-CS avidity	2
		R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-HBs	3
Visit 24 (Month 20)	Pre-Dose 4	R012-20 Fx017-mFxD Control	Immunogenicity	150	Anti-CS	1
		R012-20 Fx017-mFxD Control	Immunogenicity	150	Anti-CS avidity	2
		R012-20 Fx017-mFxD Control	Immunogenicity	150	Anti-HBs	3
Visit 25 (Month 21)	Post-Dose 4	R012-20 Fx017-mFxD	Immunogenicity	100	Anti-CS	1
		R012-20 Fx017-mFxD	Immunogenicity	100	Anti-CS avidity	2
		R012-20 Fx017-mFxD	Immunogenicity	100	Anti-HBs	3
Visit 27 (Month 26)	Pre-Dose 5	R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-CS	1
		R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-CS avidity	2
		R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-HBs	3
Visit 28 (Month 27)	Post-Dose 5	R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-CS	1
		R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-CS avidity	2
		R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-HBs	3
Visit 30 (Month 32)	Pre-Dose 5	Fx017-mFxD	Immunogenicity	50	Anti-CS	1
		Fx017-mFxD	Immunogenicity	50	Anti-CS avidity	2
		Fx017-mFxD	Immunogenicity	50	Anti-HBs	3
Visit 31 (Month 33)	Post-Dose 5	Fx017-mFxD	Immunogenicity	50	Anti-CS	1
		Fx017-mFxD	Immunogenicity	50	Anti-CS avidity	2
		Fx017-mFxD	Immunogenicity	50	Anti-HBs	3
Visit 33 (Month 38)	Pre-Dose 6	R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-CS	1
		R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-CS avidity	2
		R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-HBs	3
Visit 34 (Month 39)	Post-Dose 6	R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-CS	1
		R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-CS avidity	2
		R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-HBs	3

Blood sampling timepoint		Study groups	Subset name	No. subjects	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint					
Visit 38 (Month 50)	Study end	All groups	Immunogenicity	250	Anti-CS	1
		All groups	Immunogenicity	250	Anti-CS avidity	2
		All groups	Immunogenicity	250	Anti-HBs	3

CCI [redacted]

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analyzed according to priority ranking provided in Table 19.

6.7.4.2. Parasitemia

Table 20 Parasitemia (blood smear *and blood for ancillary study*)

Blood sampling timepoint	Study groups	No. subjects	Component	Components priority rank
Visit 2 (Day 0)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 3 (Month 1)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 4 (Month 2)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 6 (Month 3)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 7 (Month 4)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 8 (Month 5)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 9 (Month 6)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 10 (Month 7)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 12 (Month 8)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 13 (Month 9)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 14 (Month 10)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 15 (Month 11)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 16 (Month 12)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 17 (Month 13)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 18 (Month 14)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 19 (Month 15)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 20 (Month 16)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 21 (Month 17)	All groups	1500	Blood smear + blood for ancillary study*	1

Blood sampling timepoint	Study groups	No. subjects	Component	Components priority rank
Visit 22 (Month 18)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 23 (Month 19)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 24 (Month 20)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 26 (Month 23)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 27 (Month 26)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 29 (Month 29)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 30 (Month 32)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 32 (Month 35)	All groups	1500	Blood smear	1
Visit 33 (Month 38)	All groups	1500	Blood smear	1
Visit 35 (Month 41)	All groups	1500	Blood smear	1
Visit 36 (Month 44)	All groups	1500	Blood smear	1
Visit 37 (Month 47)	All groups	1500	Blood smear	1
Visit 38 (Month 50)	All groups	1500	Blood smear	1

* The incidence of *P. falciparum* infection assessed by PCR and parasite genotyping will be evaluated in an ancillary study, using samples collected ***until Month 32*** as described in the present protocol. The blood for the ancillary study will be collected on filter paper.

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6.7.4.3. Hematology/Blood chemistry

At screening, hemoglobin will be assessed in all subjects screened. Other hematology and biochemistry parameters will be measured in the first 50 subjects enrolled in each group (reactogenicity sub-cohort).

Table 21 Hematology/Blood chemistry

Blood sampling timepoint		Study groups	Sub-cohort name	No. subjects	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint					
Visit 1 (Day -28 to 0)	Screening	All groups	Not applicable	All screened subjects	Hemoglobin	Not applicable
Visit 4 (Month 2)	Before Dose 3	R012-20 R012-14-mD Fx012-14-mFxD Control	Reactogenicity	200	Hemoglobin	Not applicable
					White blood cells	
					Platelets	
					Alanine aminotransferase	
					Creatinine	
Visit 5 (Month 2 + 7d)	7 days post-Dose 3	R012-20 R012-14-mD Fx012-14-mFxD Control	Reactogenicity	200	Hemoglobin	Not applicable
					White blood cells	
					Platelets	
					Alanine aminotransferase	
					Creatinine	
Visit 6 (Month 3)	30 days post-Dose 3	R012-20 R012-14-mD Fx012-14-mFxD Control	Reactogenicity	200	Hemoglobin	Not applicable
					White blood cells	
					Platelets	
					Alanine aminotransferase	
					Creatinine	
Visit 10 (Month 7)	Before Dose 3	Fx017-mFxD	Reactogenicity	50	Hemoglobin	Not applicable
					White blood cells	
					Platelets	
					Alanine aminotransferase	
					Creatinine	
Visit 11 (Month 7 + 7d)	7 days post-Dose 3	Fx017-mFxD	Reactogenicity	50	Hemoglobin	Not applicable
					White blood cells	
					Platelets	
					Alanine aminotransferase	
					Creatinine	
Visit 12 (Month 8)	30 days post-Dose 3	Fx017-mFxD	Reactogenicity	50	Hemoglobin	Not applicable
					White blood cells	
					Platelets	
					Alanine aminotransferase	
					Creatinine	

6.7.5. Immunological correlates of protection

No correlate of protection has been demonstrated so far for the CS antigen.

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

All subjects enrolled in the study should have received three doses of a hepatitis B-containing vaccine (DTPHepB) prior to enrollment (refer to inclusion criteria in Section 5.2).

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

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

7. STUDY VACCINES AND ADMINISTRATION

7.1. Description of study vaccines

The candidate RTS,S/AS01$_E$ vaccine has been developed and manufactured by GSK Biologicals. The quality control standards and requirements for the candidate vaccine are described in separate quality assurance documents (e.g. release protocols, certificate of analysis) and the required approvals have been obtained.

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

Commercial vaccines are assumed to comply with the specifications given in the manufacturer's summary of product characteristics (SmPC).

Table 22 Study vaccines

Treatment name	Vaccine/product name	Formulation	Presentation	Volume to be administered	Number of doses
RTS,S/AS01$_E$ (Full dose)	RTS,S	RTS,S=25µg	Lyophilized pellet in a two-dose glass vial	0.5 ml	2 to 6*
	AS01E	MPL=25µg; QS21=25µg; Liposomes	Liquid solution in a two-dose glass vial		
RTS,S/AS01$_E$ (1/5th dose)	RTS,S	RTS,S=25µg	Lyophilized pellet in a two-dose glass vial	0.1 ml	3 to 4**
	AS01E	MPL=25µg; QS21=25µg; Liposomes	Liquid solution in a two-dose glass vial		
Rabies vaccine	*Rabipur*	Rabies virus=2.5IU	Powder and solvent for solution for injection. After dissolution of the white lyophilisate (powder), a clear colorless solution is obtained.	1.0 ml	3

* RTS,S/AS01$_E$ full dose (0.5 ml): Group R012-20 will receive four doses, group R012-14-mD will receive six doses, group Fx012-14-mFxD and group Fx017-mFxD will receive two doses.
** RTS,S/AS01$_E$ 1/5th dose (0.1 ml): Group Fx012-14-mFxD will receive four doses and group Fx017-mFxD will receive three doses.

7.2. Storage and handling of study vaccines

The study vaccines must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorized study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccines.

Temperature excursions must be reported in degree Celsius.

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

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

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

7.3. Dosage and administration of study vaccines

7.3.1. RTS,S/AS01$_E$

In this study, the commercial presentation of RTS,S/AS01$_E$ will be used, i.e. a two-dose glass vial of lyophilized RTS,S antigen (50 µg) to be reconstituted with a two-dose glass vial of AS01$_E$ Adjuvant System (1.0 ml). The final product for administration will be prepared by reconstitution of the lyophilized antigen with the liquid adjuvant. From the reconstituted vaccine vial, 0.5 ml will be withdrawn to administer the RTS,S/AS01$_E$ full doses or 0.1 ml will be withdrawn to administered the RTS,S/AS01$_E$ fractional doses (1/5th dose). All vials of vaccine provided in this study are intended for single use only.

Disinfect the top of the vaccine vial (pellet) and adjuvant vial with alcohol swabs and let dry. Withdraw the content of the adjuvant vial in a syringe and inject the adjuvant into the vial of lyophilized antigen. The pellet is then dissolved by gently shaking the vial. Wait for one minute to ensure the complete dissolution of the vial content before withdrawing one full dose of RTS,S/AS01$_E$ (0.5 ml) or a fractional dose of RTS,S/AS01$_E$ (0.1 ml). For the full dose of RTS,S/AS01$_E$, 0.5 ml should be administered using a fresh 25 gauge needle with a length of one inch (25 mm). For the fractional dose of RTS,S/AS01$_E$, 0.1 ml should be administered using a 1 ml syringe and fresh 25 gauge needle with a length of one inch (25 mm). The reconstituted vaccine should be administered by slow intramuscular injection into the left deltoid. The vaccine should be injected within four hours of reconstitution (storage at +2°C to +8°C). Refer to the SPM for full details of how to fill the syringe and inject the fractional dose.

7.3.2. Rabies vaccine

Disinfect the top of the vaccine vial (pellet) with alcohol swabs and let dry. Inject the entire content of the diluent ampoule into the vaccine vial. The lyophilized vaccine pellet is dissolved by gently shaking the vial. Wait for one minute to ensure the complete dissolution of the vial content before withdrawing a sufficient volume to provide a 1.0 ml dose. The original needle should then be replaced with a fresh needle for intramuscular injection. The reconstituted vaccine should be administered by slow intramuscular injection, using a fresh 25 gauge needle with a length of one inch (25 mm), into the left deltoid directly after reconstitution. The vaccine should be stored at +2°C to +8°C.

Table 23 Dosage and administration

Type of contact and timepoint	Volume to be administered	Study group	Treatment name	Route [1]	Site	Side
Visit 2 (Day 0)	0.5 ml	R012-20 R012-14-mD Fx012-14-mFxD Fx017-mFxD	RTS,S/AS01$_E$ (Full dose)	IM	Deltoid	Left
	1.0 ml	Control	Rabies vaccine	IM	Deltoid	Left
Visit 3 (Month 1)	0.5 ml	R012-20 R012-14-mD Fx012-14-mFxD Fx017-mFxD	RTS,S/AS01$_E$ (Full dose)	IM	Deltoid	Left
	1.0 ml	Control	Rabies vaccine	IM	Deltoid	Left
Visit 4 (Month 2)	0.5 ml	R012-20 R012-14-mD	RTS,S/AS01$_E$ (Full dose)	IM	Deltoid	Left
	0.1 ml	Fx012-14-mFxD	RTS,S/AS01$_E$ (1/5th dose)	IM	Deltoid	Left
	1.0 ml	Control	Rabies vaccine	IM	Deltoid	Left
Visit 10 (Month 7)	0.1 ml	Fx017-mFxD	RTS,S/AS01$_E$ (1/5th dose)	IM	Deltoid	Left
Visit 18 (Month 14)	0.5 ml	R012-14-mD	RTS,S/AS01$_E$ (Full dose)	IM	Deltoid	Left
	0.1 ml	Fx012-14-mFxD	RTS,S/AS01$_E$ (1/5th dose)	IM	Deltoid	Left
Visit 24 (Month 20)	0.5 ml	R012-20	RTS,S/AS01$_E$ (Full dose)	IM	Deltoid	Left
	0.1 ml	Fx017-mFxD	RTS,S/AS01$_E$ (1/5th dose)	IM	Deltoid	Left
Visit 27 (Month 26)	0.5 ml	R012-14-mD	RTS,S/AS01$_E$ (Full dose)	IM	Deltoid	Left
	0.1 ml	Fx012-14-mFxD	RTS,S/AS01$_E$ (1/5th dose)	IM	Deltoid	Left
Visit 30 (Month 32)	0.1 ml	Fx017-mFxD	RTS,S/AS01$_E$ (1/5th dose)	IM	Deltoid	Left
Visit 33 (Month 38)	0.5 ml	R012-14-mD	RTS,S/AS01$_E$ (Full dose)	IM	Deltoid	Left
	0.1 ml	Fx012-14-mFxD	RTS,S/AS01$_E$ (1/5th dose)	IM	Deltoid	Left

[1] Intramuscular (IM)

The subjects will be observed closely for at least 30 minutes following the administration of the vaccines, with appropriate medical treatment readily available in case of anaphylaxis.

7.4. Replacement of unusable vaccine doses

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

7.5. Contraindications to subsequent vaccination

The following events constitute absolute contraindications to further administration of RTS,S/AS01$_E$ or the rabies vaccine. If any of these events occur during the study, the subject must not receive additional doses of vaccines but may continue other study procedures at the discretion of the investigator (see Section 9.4).

- Anaphylaxis following the administration of vaccine(s).
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.
- RTS,S/AS01$_E$ malaria vaccine should not be administered to subjects with known hypersensitivity to any component of the vaccine or to a previous dose of RTS,S/AS01 $_E$ malaria vaccine or hepatitis B vaccines. Any subject who shows signs of hypersensitivity to the vaccine should not be given further doses.
- *Rabipur* is contraindicated in subjects with an history of a severe hypersensitivity to any of the ingredients in the vaccine. Note that the vaccine contains polygeline and residues of chicken proteins, and may contain traces of neomycin, chlortetracycline and amphotericin B) (Refer to the [*Rabipur* SmPC, 2010]).
- Occurrence of a new pIMD or the exacerbation of an existing pIMD that, in the opinion of the investigator, expose the subject to unacceptable risk from subsequent vaccination. In such cases, the investigator should use his/her clinical judgement prior to administering the next dose of the vaccine(s)/product(s). Refer to Section 9.1.6.1 for the definition of pIMDs.

The following events constitute contraindications to administration of RTS,S/AS01$_E$ or the rabies vaccine at that point in time; if any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (see Section 6.5), or the subject may be withdrawn at the discretion of the investigator (see Section 9.4).

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

7.6. Warnings and precautions

Refer to the approved product label/package insert for the marketed rabies vaccine (*Rabipur*) used in the study.

7.7. Concomitant medications/products and concomitant vaccinations

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

7.7.1. Recording of concomitant medications/products and concomitant vaccinations

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

- Anti-inflammatory, analgesics, anti-pyretic, and systemic antibiotics administered during the period starting seven days following each dose of study vaccines (Day 0 to Day 6).
- Any concomitant vaccination administered in the period starting seven days before the first dose of study vaccines and ending at the last study visit (Day -7 to Month 50).
- Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

  E.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring [fever is defined as temperature ≥ 37.5°C/99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C/100.4°F for rectal route].
- Any concomitant medications/products/vaccines listed in Section 7.7.2.
- Anti-malaria medication administered at any time during the study (Day 0 to Month 50).
- Any concomitant medications/products/vaccines relevant to a SAE/pIMD to be reported as per protocol or administered at any time during the study period for the treatment of a SAE/pIMD. In addition, concomitant medications relevant to SAEs and pIMD need to be recorded on the Expedited Adverse Events Report.
- In this study, medications administered for the treatment of any solicited local or general AE should be recorded for subjects belonging to the reactogenicity sub-cohort and during the time period for collection of solicited AEs. Medications administered for the treatment of unsolicited AEs should be recorded for all subjects during the time period for collection of unsolicited AEs (see Section 9.2.1 and Table 27), except for anti-malaria treatments that must be collected for all subjects during the entire study period.

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

The use of the following concomitant medications/products/vaccines will not require withdrawal of the subject from the study but may determine a subject's evaluability in the ATP analysis. See Section 11.5 for cohorts to be analyzed.

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

  * In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organized by the public health authorities, outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its SmPC or Prescribing Information and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.
- Immunoglobulins and/or any blood products administered during the study period.

7.8. Intercurrent medical conditions that may lead to elimination of a subject from ATP analyses

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

Subjects may be eliminated from the ATP cohort for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response (i.e. confirmed HIV/AIDS) or are confirmed to have an alteration of their initial immune status.

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 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 vaccines 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 vaccines or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with vaccines administration.
- Significant failure of expected pharmacological or biological action.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

AEs to be recorded as endpoints (solicited AEs) are described in Section 9.1.3. All other AEs will be recorded as UNSOLICITED AEs.

Examples of an AE DO NOT include:

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

9.1.2. Definition of a serious adverse event

A SAE is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

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

c. Requires hospitalization or prolongation of existing hospitalization,

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

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

d. Results in disability/incapacity.

   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 judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

In this study, the AEs of specific interest (i.e. pIMDs, meningitis and seizure within 30 post-vaccination) will be reported as SAEs.

All cases of severe malaria and cerebral malaria will be reported as SAEs and clinical details of each case will be reported in a specific eCRF screen (refer to Section 9.1.5).

9.1.3. Solicited adverse events

9.1.3.1. Solicited local (injection-site) adverse events

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

Table 24 Solicited local adverse events

All age groups
Pain at injection site
Redness* at injection site
Swelling at injection site

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

9.1.3.2. Solicited general adverse events

The following general AEs will be solicited:

Table 25 Solicited general adverse events

Infant/Toddler/Child (< 6 years)
Drowsiness
Fever
Irritability/Fussiness
Loss of appetite

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

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

In absence of diagnosis, abnormal laboratory findings (e.g. clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g. failure to thrive) 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.

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

9.1.5. Severe malaria and cerebral malaria

All cases of severe malaria and cerebral malaria will be reported as SAEs as part of the safety surveillance until study end (Month 50) and clinical details of each case will be reported in a specific eCRF screen. Case definitions adapted from the WHO case definitions of severe malaria and cerebral malaria will be used as reference for diagnosis. Refer to APPENDIX C for the case definitions.

9.1.6. Adverse events of specific interest

AEs of specific interest for safety monitoring include all seizures occurring within 30 days post-vaccination, meningitis and pIMDs.

9.1.6.1. 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 26.

However, the investigator will exercise his/her medical and scientific judgement 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.

To support the diagnosis of pIMDs, access to reference laboratories will be initiated so that serum samples or histopathologic specimens could be sent to perform analyses which would not be available locally.

Table 26 List of potential immune-mediated diseases

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• Cranial nerve disorders, including paralyses/paresis (e.g. Bell's palsy) • Optic neuritis • Multiple sclerosis • Transverse myelitis • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants • Acute disseminated encephalomyelitis, including site specific variants: e.g. non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome • Immune-mediated peripheral neuropathies and plexopathies, (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy). • Narcolepsy	• Systemic lupus erythematosus and associated conditions • Systemic scleroderma (Systemic sclerosis), including diffuse systemic form and CREST syndrome Idiopathic inflammatory myopathies, including dermatomyositis • Polymyositis • Antisynthetase syndrome • Rheumatoid arthritis, and associated conditions including juvenile chronic arthritis and Still's disease • Polymyalgia rheumatica • Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis • Psoriatic arthropathy • Relapsing polychondritis • Mixed connective tissue disorder	• Psoriasis • Vitiligo • Erythema nodosum • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis) • Alopecia areata • Lichen planus • Sweet's syndrome • Localized Scleroderma (Morphoea)
Vasculitides	**Blood disorders**	**Others**
• Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis. • Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome (allergic granulomatous angiitis), Buerger's disease (thromboangiitis obliterans), necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis.	• Autoimmune hemolytic anemia • Autoimmune thrombocytopenia • Antiphospholipid syndrome • Pernicious anemia • Autoimmune aplastic anaemia • Autoimmune neutropenia • Autoimmune pancytopenia	• Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) • Ocular autoimmune diseases (including autoimmune uveitis and autoimmune retinopathy) • Autoimmune myocarditis/cardiomyopathy Sarcoidosis • Stevens-Johnson syndrome • Sjögren's syndrome • Idiopathic pulmonary fibrosis • Goodpasture syndrome • Raynaud's phenomenon

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

When there is enough evidence to make any of the above diagnoses, the AE must be reported as a pIMD. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as 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.

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. Tests for further evaluation of pIMDs may be conducted at Clinical Laboratory Sciences (CLS) South Africa if there is an indication for the test (see APPENDIX D for details of tests available at CLS South Africa).

9.1.6.2. Seizures within 30 days post-vaccination

All seizures occurring within 30 days post-vaccination will be reported as SAEs in the eCRF. Clinical details according to the Brighton collaboration guidelines [Bonhoeffer, 2004] pertaining to seizures occurring within seven days of vaccination will be documented in a specific eCRF screen.

9.1.6.3. Meningitis

For further evaluation of the safety signal of meningitis, all cases of meningitis occurring during the study will be reported as a SAE and additional clinical details of each case will be reported in a specific eCRF screen.

Investigators will be instructed to report cases according to the following case definitions:

- **Clinically suspected meningitis:** A child with sudden onset of fever and one of the following signs: neck stiffness, altered consciousness not due to an alternative more probable cause, or other meningeal sign such as bulging fontanelle in children less than one year of age.
- **Confirmed meningitis:** A child with clinically suspected meningitis with confirmatory evidence of meningitis from cerebrospinal fluid (CSF) examination.
- **Etiology-confirmed meningitis:** A child with confirmed meningitis and evidence from CSF examination of a specific causative agent.

The recommended method for evaluation of meningitis will be through CSF analysis. Lumbar puncture should be performed by qualified medical personnel in subjects when there is an indication for testing. The initial CSF testing to aid in the diagnosis of meningitis including, and not limited to, microscopy and gram staining, differential white cell and red blood cell count, CSF biochemistry, antigen/agglutination tests and culture, amongst others, is to be carried out by the site. For every suspected meningitis case, a CSF sample will be collected and from this approximately 500 µl will be sent to CLS South Africa for CSF polymerase chain reaction (PCR) testing for selected common aetiological pathogens of meningitis (see APPENDIX D for details of additional tests available at CLS South Africa for the evaluation of meningitis).

9.2. Detecting and recording adverse events and serious adverse events

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

All AEs starting within 30 days following administration of each dose of study vaccines (Day 0 to Day 29) must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The time period for collecting and recording SAEs will begin at the first receipt of study vaccine (Day 0) and will end at the last study visit (Month 50) for each subject. See Section 9.3 for instructions on reporting of SAEs.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the first receipt of study vaccine (Day 0) until study end (Month 50).

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

The time period for collecting and recording of AEs of specific interest will begin at the first receipt of study vaccine (Day 0) and will end at the last study visit (Month 50) See section 9.3 for instructions on reporting of AEs of specific interest.

Solicited local and general AEs will be collected in the first 50 subjects enrolled in each group (reactogenicity sub-cohort) during four days (day of vaccination and three subsequent days) after Dose 3 of study vaccine (all groups including controls), after Dose 4 (R012-20, R012-14-mD, Fx012-14-mFxD and Fx017-mFxD), after Dose 5 (R012-14-mD, Fx012-14-mFxD and Fx017-mFxD) and after Dose 6 (R012-14-mD and Fx012-14-mFxD). On the day of vaccination the evaluation will be carried out by the study physician at the study center. On Days 1, 2 and 3 after vaccination, trained study personnel will visit the children to record solicited AEs on diary cards.

An overview of the protocol-required reporting periods for AEs and SAEs is given in Table 27.

Table 27 Reporting periods for collecting safety information

Study visits	1	2			3			4			10			18			24			27			30			33			38
Event	Scr*	Vac 1			Vac 2			Vac 3			Vac 4			Vac 5			Vac 6			Vac 7			Vac 8			Vac 9			Study end
Study timepoint:	D -28 to -1	D0	D0 + 3d	D0 + 29d	M1	M1 + 3d	M1 + 29d	M2	M2 + 3d	M2 + 29d	M7	M7 + 3d	M7 + 29d	M14	M14 + 3d	M14 + 29d	M20	M20 + 3d	M20 + 29d	M26	M26 + 3d	M26 + 29d	M32	M32 + 3d	M32 + 29d	M38	M38 + 3d	M38 + 29d	M50
For ALL groups																													
AEs/SAEs leading to withdrawal from further vaccination		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
SAEs related to study participation or concurrent GSK medication/vaccine	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
SAEs (All, fatal, related to the investigational vaccine)		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
AEs of specific interest**		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Group R012-20																													
Solicited local and general AEs***								■	■								■	■											
Unsolicited AEs		■	■	■	■	■	■	■	■	■							■	■	■										
Group R012-14-mD and Fx012-14-mFxD																													
Solicited local and general AEs***								■	■					■	■					■	■					■	■		

Study visits	1	2			3			4			10			18			24			27			30			33			38
Event	Scr*	Vac 1			Vac 2			Vac 3			Vac 4			Vac 5			Vac 6			Vac 7			Vac 8			Vac 9			Study end
Study timepoint:	D -28 to -1	D0	D0 + 3d	D0 + 29d	M1	M1 + 3d	M1 + 29d	M2	M2 + 3d	M2 + 29d	M7	M7 + 3d	M7 + 29d	M14	M14 + 3d	M14 + 29d	M20	M20 + 3d	M20 + 29d	M26	M26 + 3d	M26 + 29d	M32	M32 + 3d	M32 + 29d	M38	M38 + 3d	M38 + 29d	M50
Unsolicited AEs																													
Group Fx017-mFxD																													
Solicited local and general AEs***																													
Unsolicited AEs																													
Control group																													
Solicited local and general AEs***																													
Unsolicited AEs																													

* i.e. consent obtained.
** AEs of specific interest include seizures occurring within 30 days post-vaccination, meningitis and pIMDs.
*** Solicited local and general AEs will be collected in the first 50 subjects enrolled in each group (reactogenicity sub-cohort).
Scr: Screening; Vac: Vaccination; D: Day; M: Month; 3d: 3 days; 29d: 29 days.

9.2.2. Post-study adverse events and serious adverse events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 27. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational vaccines, the investigator will promptly notify the Study Contact for Reporting SAEs.

9.2.3. Evaluation of adverse events and serious adverse events

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

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

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

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

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

9.2.3.2. Assessment of adverse events

9.2.3.2.1. Assessment of intensity

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

Table 28 Intensity scales for solicited symptoms in infants/toddlers

Infant/Toddler (15–24 months)		
Adverse event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Minor reaction to touch
	2	Moderate: Cries/protests on touch
	3	Severe: Cries when limb is moved/spontaneously painful
Redness* at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever**		Record temperature in °C/°F
Irritability/Fussiness	0	Behavior as usual
	1	Mild: Crying more than usual/no effect on normal activity
	2	Moderate: Crying more than usual/interferes with normal activity
	3	Severe: Crying that cannot be comforted/prevents normal activity
Drowsiness	0	Behavior as usual
	1	Mild: Drowsiness easily tolerated
	2	Moderate: Drowsiness that interferes with normal activity
	3	Severe: Drowsiness that prevents normal activity
Loss of appetite	0	Appetite as usual
	1	Mild: Eating less than usual/no effect on normal activity
	2	Moderate: Eating less than usual/interferes with normal activity
	3	Severe: Not eating at all

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

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

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

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

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

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

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

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

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 9.1.2.

9.2.3.2.2. Assessment of causality

The investigator is obligated to assess the relationship between investigational vaccines and the occurrence of each AE/SAE. The investigator will use clinical judgement 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(s) will be considered and investigated. The investigator will also consult the investigator brochure and/or prescribing information for marketed products to determine his/her assessment.

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

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

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

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

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

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 vaccines, 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. Toxicity grading scale for hematology and biochemistry parameters

Table 29 Toxicity grading scales for analysis of hematology and biochemistry parameters

Test	Acceptable limit/Normal range	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	≥ 8.0 g/dl	7.9 to 6.0 g/dl	5.9 to 5.0 g/dl	< 5.0 g/dl	< 5.0 g/dl and clinical signs of heart failure
WBC	≥ 4.0 x10^3/µl < 17 x10^3/µl	2.5 to 4.0 x 10^3/µl	1.5 to 2.4 x 10^3/µl	1.0 to 1.4 x 10^3/µl	< 1.0 x 10^3/µl
Platelets	≥ 100 x10^3/µl	50 to 99 x 10^3/µl	25 to 49 x 10^3/µl	< 25 x 10^3/µl	< 25 x 10^3/µl and clinical signs of bleeding
ALT	≤ 60 IU/L	1.1 to 2.5 x ULN	2.6 to 5.0 x ULN	5.1 to 10.0 x ULN	> 10.0 x ULN
Creatinine	≤ 60 µmol/L (or 0.6 mg/dl)	1.1 to 1.5 x ULN	1.6 to 3.0 x ULN	3.1 to 6.0 x ULN	> 6.0 x ULN or requires dialysis

ALT = alanine aminotransferase; ULN = upper limit of the normal range; WBC = white blood cells
Grading scale adapted from: [NIAID, 2004] Division of AIDS table for grading the severity of adult and pediatric adverse events, December 2004.

9.2.3.5. Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject's parent(s)/LAR(s) will be asked if the subject received medical attention defined as hospitalization, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the in the eCRF.

9.2.3.6. Verbal autopsy process

Where possible autopsies will be performed. Verbal autopsies will be carried out on all children who die outside a health facility to ascribe the cause of death if it is not possible to perform the autopsies. The questionnaire used will be based on the INDEPTH standard and adapted to be locally appropriate [WHO, 2007].

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 30, once the investigator determines that the event meets the protocol definition of a SAE. In addition, clinical details of each case of severe malaria and cerebral malaria will be reported in a specific eCRF screen.

AEs of specific interest (i.e. seizures occurring within 30 days post-vaccination, pIMDs and meningitis) that occur in the time period defined in Section 9.2 will be reported promptly to GSK within the timeframes described in Table 30, once the investigator determines that the event meets the protocol definition of an AE of specific interest.

Table 30 Timeframes for submitting serious adverse event and other events reports to GSK Biologicals

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	Electronic Expedited Adverse Events Report§	24 hours*	Electronic Expedited Adverse Events Report§
AEs of specific interest**	24 hours*‡	Electronic Expedited Adverse Events Report***	24 hours*	Electronic Expedited Adverse Events Report***

‡ The investigator will be required to confirm review of the SAE/AE of specific interest causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE/AE of specific interest.
* Timeframe allowed after receipt or awareness of the information.
** AEs of specific interest include seizures occurring within 30 days post-vaccination, pIMDs and meningitis.
*** pIMDs will be reported via the electronic Expedited Adverse Events Report. Meningitis and seizures will be reported via the electronic Expedited Adverse Events Report and in addition clinical details of each case will be reported in a specific eCRF screen.
§ Case of severe malaria or cerebral malaria will be reported via the electronic Expedited Adverse Events Report (refer to Section 9.3.1) and in addition clinical details of each case will be reported in a specific eCRF screen.

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

Study Contact for Reporting SAEs, and AEs of specific interest
Refer to the local study contact information document.
Back-up Study Contact for Reporting SAEs and AEs of specific interest
24/24 hour and 7/7 day availability: **GSK Biologicals Clinical Safety & Pharmacovigilance** Outside US & Canada sites: Fax: +32 2 656 51 16 or +32 2 656 80 09 Email address: Rix.CT-safety-vac@gsk.com

9.3.3. Completion and transmission of serious adverse events reports to GSK Biologicals

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

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

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

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

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

9.3.4. Reporting of adverse events of specific interest to GSK Biologicals

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

The investigator will always provide an assessment of causality at the time of the initial report.

The investigator will be required to confirm the review of the causality of an AE of specific interest by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the AE of specific interest.

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

9.3.5. Updating of serious adverse events and adverse events of specific interest information after removal of write access to the subject's eCRF

When additional SAE and AEs of specific interest information is received after removal of the write access to the subject's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 30.

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.

In addition, the investigators will report SAEs to their IRB/IEC in accordance with the IRB/IEC requirements.

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

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

9.4.1. Follow-up during the study

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide additional relevant information on the subject's condition to GSK Biologicals (within 24 hours for SAEs; refer to Table 30).

All SAEs and AEs of specific interest (i.e. seizures occurring within 30 days post-vaccination, pIMDs and meningitis) (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.

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

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

The investigator will follow subjects:

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

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

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

9.5. Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the subject's eCRF (refer to Section 7.7).

In this study, medications administered for the treatment of any solicited local or general AE should be recorded for subjects belonging to the reactogenicity sub-cohort and during the time period for collection of solicited AEs. Medications administered for the treatment of unsolicited AEs should be recorded for all subjects during the time period for collection of unsolicited AEs (see Section 9.2.1 and Table 27), except for anti-malaria treatments that must be collected for all subjects during the entire study period (see Section 7.7.1).

Cases of suspected malaria will be tested with a rapid diagnostic test (RDT) or blood slide and managed on the basis of their result. These tests are separate to samples taken for determination of efficacy against *P. falciparum* infection by blood slide reading and filter paper for PCR (see Section 6.7.3).

9.6. Subject card

Study 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 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 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)/LAR(s), or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

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

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

Subjects who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of a SAE/AE until resolution of the event (see Section 9.4.2).

10.2.2. Subject withdrawal from investigational vaccines

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

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

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

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. Reason for screening failure will be collected.

11. STATISTICAL METHODS

11.1. Primary endpoint

- **Efficacy:**
  - The occurrence of clinical malaria meeting the primary case definition from Month 2.5 up to Month 14.

11.2. Secondary endpoints

- **Efficacy:**
  - The occurrence of clinical malaria meeting the primary and secondary case definitions from Day 0 up to Month 50.
  - The occurrence of incident *P. falciparum* infections from Day 0 to Month 50.
  - The prevalence of *P. falciparum* infections defined by positive blood slide at each cross-sectional survey.

- **Immunogenicity: Immune response to the CS and HBs antigens (immunogenicity subset)**
  - ***Anti-CS antibody concentrations and seropositivity measured before Dose 1, one month post-Dose 2 (group Fx017-mFxD only), before and one month post-Dose 3, before and one month after Dose 4, before and one month after each yearly dose and at study end (Month 50).***
  - Anti-HBs antibody concentrations and seropositivity measured before Dose 1, one month post-Dose 2 (group Fx017-mFxD only), before and one month post-Dose 3, before and one month after Dose 4, before and one month after each yearly dose and at study end (Month 50).

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- **Safety**
  - The occurrence of SAEs (all, fatal and related) during the whole study period according to the MedDRA classification.
  - The occurrence of AEs and SAEs leading to withdrawal from further vaccination from Dose 1 (Day 0) up to Month 50, according to the MedDRA classification.
  - The occurrence of severe malaria cases and cerebral malaria cases during the whole study period.
  - The occurrence of pIMDs from Day 0 up to Month 50, according to the MedDRA classification.
  - The occurrence of meningitis from Day 0 up to Month 50, according to the MedDRA classification.
  - The occurrence of seizures within 30 days (day of vaccination and 29 subsequent days) after each dose of study vaccine, according to the MedDRA classification.
  - The occurrence of generalized convulsive seizure within seven days (day of vaccination and six subsequent days) after each dose of study vaccine, according to the Brighton collaboration guidelines [Bonhoeffer, 2004].

  - The occurrence of unsolicited AEs within 30 days (day of vaccination and 29 subsequent days) after each dose of study vaccine, according to the MedDRA classification.
  - The concentration of biochemistry (ALT, creatinine) and hematology (hemoglobin, WBC, platelets) parameters in the first 50 subjects (25 subjects per site) enrolled in each group (reactogenicity sub-cohort) before Dose 3, seven days post-Dose 3 and 30 days post-Dose 3.

- **Reactogenicity (reactogenicity sub-cohort)**
  - The occurrence of solicited local and general AEs in a the first 50 subjects enrolled in each group within four days (day of vaccination and three subsequent days) after Dose 3 of study vaccine (all groups including controls), after Dose 4 (groups R012-20, R012-14-mD, Fx012-14-mFxD and Fx017-mFxD), after Dose 5 (groups R012-14-mD, Fx012-14-mFxD and Fx017-mFxD) and after Dose 6 (groups R012-14-mD and Fx012-14-mFxD).

11.3. Tertiary endpoints

- **Immunogenicity**
  - Anti-CS antibody avidity at specified timepoints.

11.4. Determination of sample size

For the primary endpoint, demonstrating incremental vaccine efficacy against clinical malaria of a fractional dose schedule over the standard schedule, the study has at least 90% power to show a significant incremental vaccine efficacy (lower limit of 95% CI above 0), assuming 250 evaluable subjects per group and an incidence of at least 0.5 episodes/person year at risk (pyr) in the Control group, 0.29 episodes/pyr in the standard schedule groups and 0.16 episodes/pyr in the fractional dose schedule. This corresponds to an incremental efficacy (1-Hazard Rate) of 50% of the fractional dose schedule over the standard schedule. The primary endpoint compares the R012-20+R012-14-mD groups versus the Fx012-14-mFxD group (2:1). For secondary endpoints evaluating efficacy against *P. falciparum* infections, it is anticipated that incidence of infection in the study will be higher than incidence of clinical malaria resulting in adequate power.

In this study the reactogenicity (solicited local and general AEs) and the biochemistry and hematology parameters will be evaluated in a sub-cohort consisting of the first 50 subjects enrolled in each group (total 250 subjects). The anti-CS and anti-HBs immune responses will be tested in a subset consisting of the first 50 subjects enrolled in each group (total 250 subjects); see the glossary of terms for the definitions of subset and sub-cohort.

Assuming a post-vaccination anti-CS GMC of approximately 50 IU/ml for the fractional dose schedules and a log SD of 0.5 the precision obtained by 95%CIs of the GMC with a sample size of 50 subjects per group is (36.3-68.8).

11.5. Cohorts for analyses

11.5.1. Total vaccinated cohort

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

11.5.2. ATP cohort for efficacy

The ATP cohort for efficacy will include all subjects included in the TVC who fulfilled eligibility criteria and who received all vaccinations according to protocol procedures within the protocol specified intervals that contribute to the time at risk in the follow-up period starting 14 days post-Dose 3. Subjects who have not received Dose 4 of study vaccine or subsequent yearly doses (Dose 5 and Dose 6) according to protocol will be censored at the last contact date recorded and will contribute to the ATP analysis up to censoring.

Of note, subjects with a prevalent *P. falciparum* infection at the beginning of the follow-up period will not be included in the ATP analysis of vaccine efficacy against first or only incident *P. falciparum* infection. Sensitivity analyses by left censoring (i.e. start of follow up defined as first negative ADI visit for all children) will be performed.

11.5.3. ATP cohort for immunogenicity

The ATP population for immunogenicity will include all subjects included in the TVC who received all vaccinations according to protocol procedures within the protocol specified intervals, performed blood samplings for immunogenicity according to protocol intervals, met all eligibility criteria, did not use any medication or blood products forbidden by the protocol and did not have any reported underlying medical condition influencing immune responses.

11.6. Derived and transformed data

- **Immunogenicity**
  - A subject seropositive for anti-CS antibody will be a subject whose antibody concentration will be greater than or equal to the cut-off value (anti-CS ≥ 0.5 EU/ml).
  - Seroprotection rate for anti-HBs antibody is defined as the percentage of subjects with antibody concentration greater than or equal to an established cut-off (anti-HBs ≥ 10 mIU/ml).
  - The geometric mean concentration (GMC) calculations will be performed by taking the anti-log of the mean of the log transformations (base 10). Antibody concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC calculation.

  - Handling of missing data: For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

- **Reactogenicity and safety**
  - Handling of missing data: subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) will be treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively). In case of significant non-compliance of study procedures for reporting symptoms, the analysis plan will be reassessed to ensure more accurate reporting of study data by further analysis.
  - For the analysis of solicited symptom, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the TVC will include only subjects/doses with documented safety data (i.e. symptom screen/sheet completed).

11.7. Analysis of efficacy

The effect of the vaccine will be characterized using different complementary standard methodologies.

11.7.1. Strategy of analysis and rationale

The strategy of analysis for the present study has been developed considering the following points:

- Prevalent infections are only captured by ADI during the cross-sectional surveys performed at pre-defined timepoints throughout the study. Incident infections are captured via both ADI at cross-sectional surveys and via passive detection upon spontaneous presentation at health centers (see Section 4.2 for case definitions of *P. falciparum* infections). Episodes of clinical malaria will be treated when diagnosed. Samples collected at cross-sectional visits in asymptomatic children will not be processed in real time and will not lead to systematic treatment.
- Vaccine efficacy against prevalent *P. falciparum* infections at the successive cross-sectional surveys is an important measure as it is not influenced by care seeking behavior and possibly less influenced by blood-stage immunity. Reducing the prevalence of blood-stage infections at successive timepoints will be a good indicator of the potential to reduce transmission as it is directly associated with the potential to infect mosquitoes.
- Vaccine efficacy against first or only episode of incident *P. falciparum* infection or against first or only episode of clinical malaria minimizes the bias related to differential acquisition of blood-stage immunity in the vaccine and Control groups, and is assumed to be the best way to assess the biological effect of the third dose fractioning and spacing.

- Vaccine efficacy against all episodes of incident *P. falciparum* infection or clinical malaria is more relevant to public health but over longer time periods. There is a possibility of bias related to the fact that it will compare a Control group with frequent exposure and an intervention group with reduced exposure and a different build-up of blood-stage immunity over time, possibly influencing health seeking behaviors (hence the importance of also evaluating vaccine efficacy against prevalent infection and first or only episode).
- Considering the measures of incidence:
  - For group comparisons with identical calendar time follow-up periods, the incidence rates will be directly compared. The incremental vaccine efficacy estimate is defined as 1-Incidence Rate Ratio in each group.
  - When different calendar time follow-up periods are compared, in order to account for seasonal variations in exposure, the incidences of the Control group over the relevant time frame will be taken into account. When comparing the 0, 1, 2-month schedules against the 0, 1, 7-month schedule, the incremental efficacy will be defined as 1 minus the rate ratio of the relative reductions of each group versus the Control group, during the corresponding time frames.
- The estimation of the number of cases of clinical malaria averted will inform on how the vaccine efficacy translates into impact, in a way that is dependent on exposure and hence transmission intensity.

11.7.2. Measures of incidence (*P. falciparum* infection and clinical malaria)

- **First or only episode**

Vaccine efficacy against first or only episode of incident *P. falciparum* infection or clinical malaria will be analyzed by Cox regression stratified by study site. The 95% CI and p-values of the vaccine efficacy estimates (1- Hazard Ratio) will be calculated from this model. Cumulative incidence graphs will be produced.

- **All episodes**

Vaccine efficacy against all episodes of incident *P. falciparum* infection or clinical malaria will be analyzed by negative binomial regression allowing for interdependence between episodes within the same subject (non-linear mixed model with overdispersion parameter estimated from the random effect). The 95% CI and p-values of the vaccine efficacy estimates (1- Incidence Rate Ratio) will be calculated from this model. In case models do not converge or showed poor fit, alternative negative binomial models without random effects will be applied. ***Fourteen*** days following an episode meeting the case definition under evaluation will be subtracted from the follow-up time. The distribution of the total number of events per subject will be tabulated by group.

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11.7.3. Measure of prevalence (*P. falciparum* infection)

The prevalence of *P. falciparum* infection will be evaluated on the cross-sectional ADI samples only. At each pre-defined timepoint, the prevalence of *P. falciparum* infection will be calculated by group as well as between groups by relative risks together with 95% CIs. Graphical presentations of the prevalence over time will be produced.

11.7.4. Measure of impact (clinical malaria)

The vaccine impact will be estimated by the number of cases of clinical malaria averted over the relevant time frame per 1000 subjects vaccinated. The number of cases averted will be calculated as the difference of the estimated cases between the Control group and the vaccine group. Estimated cases in each group will be calculated as the area under the curve of the incidence of clinical malaria over time and expressed as cumulative cases averted per 1000 subjects followed-up during the relevant period.

11.7.5. Primary analysis of efficacy (primary objective)

A) Clinical malaria:

Analysis performed at Month 21:

- Incremental efficacy of Fx012-14-mFxD versus (R012-20 + R012-14-mD) over M2.5-M14 (first or only episode, ATP).

11.7.6. Secondary analyses of efficacy

A) Clinical malaria:

Early follow-up time periods (up to Month 14): Vaccine efficacy against first or only episode as well as all episodes of clinical malaria will be assessed both in the ATP and TVC cohorts.

Longer follow-up time periods (longer than Month 14): Vaccine efficacy against all episodes of clinical malaria will be assessed on the TVC. The analysis of vaccine impact will also be performed on the TVC.

Analysis performed at Month 21:

- Incremental efficacy of Fx012-14-mFxD versus (R012-20 + R012-14-mD) over M2.5-M14 (all episodes, ATP).
- Incremental efficacy of Fx012-14-mFxD versus (R012-20 + R012-14-mD) over D0-M14 (first or only and all episode, TVC).
- Vaccine efficacy of Fx012-14-mFxD versus Control group over M2.5-M9 (first or only and all episodes, ATP).
- Vaccine efficacy of Fx017-mFxD versus Control group over M7.5-M14 (first or only and all episodes, ATP).

- Vaccine efficacy of R012-20 + R012-14-mD versus Control group over M2.5-M9 (first or only and all episodes, ATP).
- Vaccine efficacy of Fx012-14-mFxD versus Control group over M2.5-M14 (first or only and all episodes, ATP).
- Vaccine efficacy of Fx017-mFxD versus Control group over M7.5-M19 (first or only and all episodes, ATP).
- Vaccine efficacy of R012-20 + R012-14-mD versus Control group over M2.5-M14 (first or only and all episodes, ATP).
- Incremental efficacy taking into account incidence in controls: Fx017-mFxD/Control group over M7.5-M14 versus Fx012-14-mFxD/Control group over M2.5-M9 (first or only and all episodes, ATP).
- Incremental efficacy taking into account incidence in controls: Fx017-mFxD/Control group over M7.5-M14 versus groups (R012-20 + R012-14-mD)/Control group over M2.5-M9 (first or only and all episodes, ATP).
- Incremental efficacy taking into account incidence in controls: Fx017-mFxD/Control group over M7.5-M19 versus Fx012-14-mFxD/Control group over M2.5-M14 (first or only and all episodes, ATP).
- Incremental efficacy taking into account incidence in controls: Fx017-mFxD/Control group over M7.5-M19 versus groups R012-20 + R012-14-mD /Control group over M2.5-M14 (first or only and all episodes, ATP).
- Vaccine efficacy of R012-20 + R012-14-mD versus Control group over D0-M14 (first or only and all episodes, TVC).
- Vaccine efficacy of Fx012-14-mFxD versus Control group over D0-M14 (first or only and all episodes, TVC).
- Vaccine efficacy of Fx017-mFxD versus Control group over D0-M14 (first or only and all episodes, TVC).
- Vaccine efficacy and impact of R012-20 versus Control group over D0-M20 (all episodes, TVC).
- Vaccine efficacy and impact of R012-14-mD versus Control group over D0-M20 (all episodes, TVC).
- Vaccine efficacy and impact of Fx012-14-mFxD versus Control group over D0-M20 (all episodes, TVC).
- Vaccine efficacy and impact of Fx017-mFxD versus Control group over D0-M20 (all episodes, TVC).

Analysis performed at Month 33:

- Vaccine efficacy and impact of R012-20 versus Control group over D0-M26 (all episodes, TVC).
- Vaccine efficacy and impact of R012-14-mD versus Control group over D0-M26 (all episodes, TVC).

- Vaccine efficacy and impact of Fx012-14-mFxD versus Control group over D0-M26 (all episodes, TVC).
- Vaccine efficacy and impact of Fx017-mFxD versus Control group over D0-M26 (all episodes, TVC).
- Incremental efficacy of Fx017-mFxD versus R012-20 over M20-M32 (all episodes, ATP).
- Incremental efficacy of Fx012-14-mFxD versus R012-14-mD over M14-M26 (all episodes, ATP).

Analysis performed at Month 50:

- Vaccine efficacy and impact of R012-20 versus Control group over D0-M38 (all episodes, TVC).
- Vaccine efficacy and impact of R012-20 versus Control group over D0-M50 (all episodes, TVC).
- Vaccine efficacy and impact of R012-14-mD versus Control group over D0-M38 (all episodes, TVC).
- Vaccine efficacy and impact of R012-14-mD versus Control group over D0-M50 (all episodes, TVC).
- Vaccine efficacy and impact of Fx012-14-mFxD versus Control group over D0-M38 (all episodes, TVC).
- Vaccine efficacy and impact of Fx012-14-mFxD versus Control group over D0-M50 (all episodes, TVC).
- Vaccine efficacy and impact of Fx017-mFxD versus Control group over D0-M38 (all episodes, TVC).
- Vaccine efficacy and impact of Fx017-mFxD versus Control group over D0-M50 (all episodes, TVC).
- Incremental efficacy of Fx012-14-mFxD versus R012-14-mD over M26-M38 (all episodes, ATP).
- Incremental efficacy of Fx012-14-mFxD versus R012-14-mD over M38-M50 (all episodes, ATP).

B) Incident *P. falciparum* infections

Early follow-up time periods (up to Month 14): Vaccine efficacy against first or only episode as well as all episodes of incident *P. falciparum* infection will be assessed both in the ATP and TVC cohorts.

Longer follow-up time periods (longer than Month 14): Vaccine efficacy against all episodes of incident *P. falciparum* infection will be assessed on the TVC.

Analysis performed at Month 21:

- Incremental efficacy of Fx012-14-mFxD versus (R012-20 + R012-14-mD) over M2.5-M14 (first or only and all episodes, ATP).
- Incremental efficacy of Fx012-14-mFxD versus (R012-20 + R012-14-mD) over D0-M14 (first or only and all episodes, TVC).
- Vaccine efficacy of Fx012-14-mFxD versus Control group over M2.5-M9 (first or only and all episodes, ATP).
- Vaccine efficacy of Fx017-mFxD versus Control group over M7.5-M14 (first or only and all episodes, ATP).
- Vaccine efficacy of R012-20 + R012-14-mD versus Control group over M2.5-M9 (first or only and all episodes, ATP).
- Vaccine efficacy of Fx012-14-mFxD versus Control group over M2.5-M14 (first or only and all episodes, ATP).
- Vaccine efficacy of Fx017-mFxD versus Control group over M7.5-M19 (first or only and all episodes, ATP).
- Vaccine efficacy of R012-20 + R012-14-mD versus Control group over M2.5-M14 (first or only and all episodes, ATP).
- Incremental efficacy taking into account incidence in controls: Fx017-mFxD/Control group over M7.5-M14 versus Fx012-14-mFxD/Control group over M2.5-M9 (first or only and all episodes, ATP).
- Incremental efficacy taking into account incidence in controls: Fx017-mFxD/Control group over M7.5-M14 versus groups (R012-20 + R012-14-mD)/Control group over M2.5-M9 (first or only and all episodes, ATP).
- Incremental efficacy taking into account incidence in controls: Fx017-mFxD/Control group over M7.5-M19 versus Fx012-14-mFxD/Control group over M2.5-M14 (first or only and all episodes, ATP).
- Incremental efficacy taking into account incidence in controls: Fx017-mFxD/Control group over M7.5-M19 versus groups R012-20 + R012-14-mD /Control group over M2.5-M14 (first or only and all episodes, ATP).
- Vaccine efficacy of R012-20 + R012-14-mD versus Control group over D0-M14 (first or only and all episodes, TVC).
- Vaccine efficacy of Fx012-14-mFxD versus Control group over D0-M14 (first or only and all episodes, TVC).
- Vaccine efficacy of Fx017-mFxD versus Control group over D0-M14 (first or only and all episodes, TVC).
- Vaccine efficacy of R012-20 versus Control group over D0-M20 (all episodes, TVC).
- Vaccine efficacy of R012-14-mD versus Control group over D0-M20 (all episodes, TVC).

- Vaccine efficacy of Fx012-14-mFxD versus Control group over D0-M20 (all episodes, TVC).
- Vaccine efficacy of Fx017-mFxD versus Control group over D0-M20 (all episodes, TVC).

Analysis performed at Month 33:

- Vaccine efficacy of R012-20 versus Control group over D0-M26 (all episodes, TVC).
- Vaccine efficacy of R012-14-mD versus Control group over D0-M26 (all episodes, TVC).
- Vaccine efficacy of Fx012-14-mFxD versus Control group over D0-M26 (all episodes, TVC).
- Vaccine efficacy of Fx017-mFxD versus Control group over D0-M26 (all episodes, TVC).
- Incremental efficacy of Fx017-mFxD versus R012-20 over M20-M32 (all episodes, ATP).
- Incremental efficacy of Fx012-14-mFxD versus R012-14-mD over M14-M26 (all episodes, ATP).

Analysis performed at Month 50:

- Vaccine efficacy of R012-20 versus Control group over D0-M38 (all episodes, TVC).
- Vaccine efficacy of R012-20 versus Control group over D0-M50 (all episodes, TVC).
- Vaccine efficacy of R012-14-mD versus Control group over D0-M38 (all episodes, TVC).
- Vaccine efficacy of R012-14-mD versus Control group over D0-M50 (all episodes, TVC).
- Vaccine efficacy of Fx012-14-mFxD versus Control group over D0-M38 (all episodes, TVC).
- Vaccine efficacy of Fx012-14-mFxD versus Control group over D0-M50 (all episodes, TVC).
- Vaccine efficacy of Fx017-mFxD versus Control group over D0-M38 (all episodes, TVC).
- Vaccine efficacy of Fx017-mFxD versus Control group over D0-M50 (all episodes, TVC).
- Incremental efficacy of Fx012-14-mFxD versus R012-14-mD over M26-M38 (all episodes, ATP).
- Incremental efficacy of Fx012-14-mFxD versus R012-14-mD over M38-M50 (all episodes, ATP).

C) Prevalent *P. falciparum* infections

Prevalent *P. falciparum* infections will be assessed in the TVC.

Analysis performed at Month 21:

- Prevalent *P. falciparum* infections at each cross-sectional survey at Month 14 (TVC).
- Prevalent *P. falciparum* infections at each cross-sectional survey at Month 20 (TVC).

Analysis performed at Month 33:

- Prevalent *P. falciparum* infections at each cross-sectional survey at Month 26 (TVC).

Analysis performed at Month 50:

- Prevalent *P. falciparum* infections at each cross-sectional survey at Month 38 (TVC).
- Prevalent *P. falciparum* infections at each cross-sectional survey at Month 50 (TVC).

11.8. Analysis of demographics

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

Demographic characteristics (age and gender) and the baseline hemoglobin level will be tabulated per study group overall, and by site, for each cohort (TVC, ATP cohort for immunogenicity and ATP cohort for efficacy).

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

11.9. Analysis of immunogenicity

The primary analysis will be based on the ATP cohort for immunogenicity; however, analyses on the TVC will also be performed.

In the immunogenicity subset (first 50 subjects enrolled in each group), the percentage of subjects with seropositive levels of anti-CS (proportion of subjects with anti-CS antibody concentrations greater than or equal to 0.5 EU/ml) with 95% CI will be determined at specified blood sampling timepoints in each group (see Section 6.7.4.1). Anti-CS antibody concentrations will be summarized by GMCs with 95% CI. Anti-CS antibody concentrations after the third dose and each subsequent dose of study vaccine will also be investigated using reverse cumulative curves.

The seroprotective level for anti-HBs is ≥ 10 mIU/ml. In the immunogenicity subset, the percentage of subjects with protective levels of anti-HBs (≥ 10 mIU/ml) with 95% CI will be determined at specified blood sampling timepoints in each group (see Section 6.7.4.1). Anti-HBs antibody concentrations will be summarized by GMCs with 95% CI. Anti-HBs antibody concentrations after the third dose and each subsequent dose of study vaccine will also be investigated using reverse cumulative curves.

For the analysis of the tertiary objective, avidity/affinity index and avidity maturation will be summarized by mean, SD, median and quartile. CCI [redacted]

11.10. Analysis of safety

The primary analysis will be based on the TVC.

Among the reactogenicity sub-cohort (first 50 subjects enrolled in each group) the percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the solicited follow-up period (i.e. four days post-Dose 3, Dose 4, Dose 5 and Dose 6) will be tabulated with exact 95% CI after each vaccine dose and overall. The percentage of doses followed by at least one local AE (solicited and unsolicited), by at least one general AE (solicited and unsolicited) and by any AE will be tabulated for the whole solicited follow-up period (i.e. four days post-Dose 3, Dose 4, Dose 5 and Dose 6), with exact 95% CI. Similar tables will be generated for Grade 3 AEs and AEs considered as causally related to vaccination.

Among the reactogenicity sub-cohort (first 50 subjects enrolled in each group), the percentage of subjects reporting each individual solicited local and general AE during the solicited follow-up period (i.e. four days post-Dose 3, Dose 4, Dose 5 and Dose 6) will be tabulated with exact 95% CI. The percentage of doses followed by each individual solicited local and general AE will be tabulated for each dose and for the whole solicited follow-up period (i.e. four days post-Dose 3, Dose 4, Dose 5 and Dose 6), with exact 95% CI. Similar tables will be generated for Grade 3 AEs, causal events and for fever, temperature in 0.5°C increments.

The verbatim reports of unsolicited symptoms will be reviewed by a physician and the signs and symptoms will be coded according to the MedDRA. The percentage of subjects with at least one report of unsolicited AE classified by the MedDRA preferred term level, occurring within 30 days (day of vaccination and 29 subsequent days) after each dose of study vaccine will be tabulated with exact 95% CI.

The percentage of subjects reporting an SAE (all, fatal, related) occurring within 30 days (day of vaccination and 29 subsequent days) after each dose of study vaccine, classified by the MedDRA preferred term level will be tabulated with exact 95% CI.

The percentage of subjects reporting an SAE (all, fatal, related) from Dose 1 (Day 0) until Month 14, from Day 0 until Month 26 and over the whole study duration (Dose 1 [Day 0] until Month 50), classified by the MedDRA preferred term level, will be tabulated with exact 95% CI.

The percentage of subjects reporting an AE or SAE leading to withdrawal from further vaccination from Dose 1 (Day 0) until Month 50, classified by the MedDRA preferred term level, will be tabulated with exact 95% CI.

The percentage of subjects reporting severe malaria cases and cerebral malaria cases from Day 0 up to Month 14, Day 0 up to Month 26, Day 0 up to Month 50 and over successive years within the study will be tabulated with exact 95% CI. The percentage of subjects reporting pIMDs from Dose 1 (Day 0) until Month 14, from Day 0 until Month 26 and from Day 0 until Month 50, classified by the MedDRA preferred term level will be tabulated with exact 95% CI.

The percentage of subjects reporting meningitis from Dose 1 (Day 0) until Month 14, from Day 0 until Month 26 and from Day 0 until Month 50, classified by the MedDRA preferred term level will be tabulated with exact 95% CI.

The percentage of subjects reporting seizures occurring within 30 days (day of vaccination and 29 subsequent days) after each dose of study vaccine, classified by the MedDRA preferred term level will be tabulated with exact 95% CI.

For generalized convulsive seizures occurring within seven days following a dose of study vaccine, an analysis will be performed based on the Brighton Collaboration guidelines [Bonhoeffer, 2004]. This includes descriptive tables of the time relationship of seizures to vaccination, the duration of seizures and the level of diagnostic certainty.

Biochemistry (ALT, creatinine) and hematology (hemoglobin, WBC, platelets) values that are outside of the reference ranges (see Table 29) will be described in the reactogenicity sub-cohort (first 50 subjects enrolled in each group) before Dose 3, seven days post-Dose 3 and 30 days post-Dose 3. Frequency distribution of results by toxicity grades will be tabulated by group.

11.11. Interpretation of analyses

Vaccine efficacy estimates with a lower limit of the 95% CI above 0 are to be considered statistically significant.

11.12. 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.

11.12.1. Sequence of analyses

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

- **Sequence of analyses and conditional continuation:**
  - A first analysis will be performed on data collected up to Month 21 (Visit 25) to evaluate the primary objective (cleaned data) and relevant secondary objectives.

  - A second analysis will be performed on data collected up to Month 33 (Visit 31) to evaluate relevant secondary objectives.
  - A final analysis will be performed at study end (Month 50) on data collected up to Month 50. An integrated study report presenting all results until Month 50 will be produced.

- After the interim analyses, the IDMC will have the possibility to recommend the suspension of further vaccinations and termination of specific study group(s) upon consideration of the study results. In the event that the IDMC recommend the suspension of further vaccinations, the group(s) impacted will be followed up for 12 months after their last study vaccination.

11.12.2. Statistical considerations for interim analyses

The analysis of the primary endpoint will be performed after Month 21 (Visit 25) on cleaned data collected up to Month 14. No alpha adjustment is foreseen because final analysis of the primary endpoint will occur at the time of the first interim analysis after Month 21 (Visit 25) on cleaned data collected up to Month 14.

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. Electronic case report form instructions

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

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

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

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

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 an eCRF review and a source document verification (SDV). By SDV we understand verifying eCRF entries by comparing them with the source data that will be made available by the investigator for this purpose.

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

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

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

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.

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

GSK assures that the key design elements of this protocol will be posted on the GSK website and in publicly accessible database(s) such as clinicaltrials.gov, in compliance with the current regulations.

GSK also assures that results of this study will be posted on the GSK website and in publicly accessible regulatory registry(ies) within the required time-frame, in compliance with the current regulations. The minimal requirement is to have primary endpoint summary results disclosed at latest 12 months post primary completion date and to have secondary endpoint disclosed at latest 12 months after the Last Subject Last Visit (LSLV) as described in the protocol.

GSK also aims to publish the results of these studies in searchable, peer reviewed scientific literature and follows the guidance from the International Committee of Medical Journal Editors.

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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 LABORATORY ASSAYS

Anti-CS antibody

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

Anti-HBs antibody

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

Anti-CS avidity

For the measurement of avidity of IgG against *P. falciparum* CS-repeat region, samples will be evaluated as described by Clement *et al*. [Clement, 2012], but in two different plates; one treated with a chaotropic agent and one untreated plate. As chaotropic agent a 1 M solution of ammonium thiocyanate (NH_4SCN) is added in the treatment plate while 0.05% Tween-20 in phosphate buffered saline (PBS) is added in the untreated plate and both CS ELISA plates are further washed and developed as described [Clement, 2012]. The avidity index (AI) is calculated as the ratio of the concentration of anti-CS IgG (EU/ml) that remained bound to the coated antigen after treatment with NH_4SCN, divided by the concentration of IgG (EU/ml) that remained bound to the coated antigen in the untreated plate.

Blood smear and filter paper for assessment of *P. falciparum* parasitemia

Blood slide preparation and slide reading will be performed according to standard operating procedure from the Malaria Diagnostics Centre of Excellence, Kisumu, Kenya.

Blood drops will be collected on a filter paper for the ancillary study that will evaluate the incidence of *P. falciparum* infection assessed by PCR and parasite genotyping.

Hemoglobin, WBC, platelets, ALT and creatinine

The measure of hematology and biochemistry parameters will be done at each study center using validated automated analyzers and according to the equipment specifications.

APPENDIX B CLINICAL LABORATORIES

Table 31 GSK Biologicals' laboratories

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

Table 32 Outsourced laboratories

Laboratory	Address
Clinical Laboratory Services, South Africa	4th Floor Spencer Lister Building Corner of Hospital and de Korte Streets Braamfontein Johannesburg 2000, South Africa
CEVAC - University of Gent	De Pintelaan, 185 Gent Belgium
Kenya Medical Research Institute / US Army Medical Research Unit Kenya, Walter Reed Project.(KEMRI/USAMRU-K, WRP), Malaria Diagnostics Center, Kisumu	PO Box 54, Kisumu 40100, Kenya

Collaborators for filter paper assessment of molecular detection and genotyping of *Plasmodium falciparum* parasites

This ancillary analysis will be carried out in partnership with the Harvard School of Public Health (Holyoke Center 727, 1350 Massachusetts Avenue, Cambridge, Massachusetts 02138, USA) and the Broad Institute (415 Main St, Cambridge, MA 02142, USA).

APPENDIX C CASE DEFINITIONS OF SEVERE MALARIA AND CEREBRAL MALARIA

Cases of severe malaria and cerebral malaria will be reported as part of the safety surveillance. Case definitions adapted from the WHO case definitions of severe malaria and cerebral malaria will be used as reference for diagnosis.

Table 33 Case definition of severe *P. falciparum* malaria

Adapted from [WHO, 2015].

P. falciparum parasitemia > 0 detected by microscopy and/or rapid diagnostic test (RDT)

AND one or more of the following, occurring in the absence of an identified alternative cause:

- Impaired consciousness: a Blantyre coma score < 3;
- Prostration: generalized weakness so that the person is unable to sit, stand or walk without assistance;
- Multiple convulsions: more than two episodes within 24h;
- Acidosis: a base deficit of > 8 mEq/l or, if not available, a plasma bicarbonate level of < 15 mmol/l or venous plasma lactate ≥ 5 mmol/l. Severe acidosis manifests clinically as respiratory distress (rapid, deep, labored breathing).
- Hypoglycemia: blood or plasma glucose < 2.2 mmol/l (< 40 mg/dl);
- Severe malarial anemia: hemoglobin concentration ≤ 5 g/dl or a hematocrit of ≤ 15% in children < 12 years of age with a parasite count > 10 000/µl;
- Renal impairment: plasma or serum creatinine > 265 µmol/l (3 mg/dl) or blood urea > 20 mmol/l;
- Jaundice: plasma or serum bilirubin > 50 µmol/l (3 mg/dl) with a parasite count > 100 000/µl;
- Pulmonary edema: radiologically confirmed or oxygen saturation < 92% on room air with a respiratory rate > 30/min, often with chest indrawing and crepitations on auscultation;
- Significant bleeding: including recurrent or prolonged bleeding from the nose, gums or venipuncture sites; hematemesis or melaena;
- Shock: compensated shock is defined as capillary refill ≥ 3 s or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure < 70 mm Hg in children, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill);
- Hyperparasitemia: *P. falciparum* parasitemia > 10% (i.e. percentage of infected red blood cells > 10%; corresponding to > 500 000/µl).

Table 34 Case definition of cerebral *P. falciparum* malaria

Adapted from [WHO, 2015].

Severe *P. falciparum* malaria with coma (Blantyre coma score < 3);

AND

If malaria with seizure: coma persisting for > 30 min after the seizure.
Other treatable causes of coma should be excluded before diagnosing cerebral malaria (e.g. hypoglycaemia, bacterial meningitis).

Amended 14 November 2019

APPENDIX D SAFETY LABORATORY TESTING: CLS SOUTH AFRICA

Cerebrospinal fluid (CSF) for meningitis testing

The recommended method for evaluation of meningitis will be through CSF analysis.

For all suspected meningitis cases, a CSF sample will be sent to CLS South Africa for CSF polymerase chain reaction (PCR) testing for selected common aetiological pathogens of meningitis as listed below. An approximate volume of CSF should be 500 µl.

- **CSF: PCR testing**

	TEST
Bacteria	Haemophilus influenzae**
	Streptococcus pneumoniae**
	Neisseria meningitidis**
	Salmonella enterica
	Mytobacterium tuberculosis
Viruses	Adenovirus*
	Cytomegalovirus*
	Enterovirus*
	Epstein Bar virus*
	Herpes simplex virus 1 & 2*
	HHV 6 ***& 7****
	Rabies
	Mumps virus*
	Parechovirus*
	Parvovirus B19*
	Varicella Zoster Virus*
Parasite	*Plasmodium* spp

****These tests are currently available as a single multiplex PCR.***
*****These tests are currently available as a single multiplex PCR.***

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

- **CSF: Other possible PCR testing**

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

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

Optionally, if indicated, an additional blood sample of approximately 5 ml whole blood may be taken by the treating clinician to aid in the diagnosis of meningitis through serum PCR or serum serology. The following tests will be available at CLS South Africa.

- **Serum: PCR**

	TEST
Bacteria	***Rickettsia****
Viruses	Cytomegalovirus*
	Enterovirus*
	Haemophilus Influenza
	Parvovirus
	Varicella*
Parasite	Toxoplasmosis

****These tests are currently available as a single multiplex PCR.***

- **Serum: Serology**

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

Analysis of potential Immune-Mediated Diseases (pIMDs)

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

Optionally, if indicated, an additional blood sample of approximately 5 ml whole blood may be taken by the treating clinician to aid in the diagnosis of pIMDs. A list of potential serum autoimmune tests that can be performed at CLS South Africa is provided below.

- **Serum: Autoimmune tests**

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

Amended 14 November 2019

APPENDIX E AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals Vaccine Value & Health Science (VVHS) **Protocol Amendment 1**	
eTrack study number and Abbreviated Title	204889 (MALARIA-094)
Amendment number:	Amendment 1
Amendment date:	13 September 2016
Co-ordinating author:	PPD Scientific Writer, Freelance Contractor for GSK Biologicals

Rationale/background for changes:

The sample blood volume for immunogenicity assessment has been increased from 2.1 ml to 2.5 ml to ensure that an adequate blood volume is obtained for the analysis. The volume of whole blood to be collected was increased to take into account the dead volume due to aliquoting, and also to enable repeat testing of samples in case of invalid results

More detailed instructions have been included for evaluation of suspected meningitis cases and pIMD.

Following Investigator request, the exclusion criteria for subjects with a history of seizure and/or malnutrition have been revised to provide clarification.

Bednets will be given to all subjects screened and not only those enrolled.

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

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

Detailed title

Phase IIb randomized, open-label, controlled, multi-center study of the efficacy, safety and immunogenicity of GSK Biologicals' candidate malaria vaccine RTS,S/AS01$_E$ evaluating schedules with or without fractional doses, early Dose 4 and yearly doses, in children 5-17 months of age living in sub-Saharan Africa.

Coordinating author

PPD
Project Manager Science Writing, Malaria Vaccines

Contributing authors

- PPD ***, Clinical Laboratory Sciences Study Manager***
- PPD ***Business and Decision Life Sciences, and*** PPD ***, TCS,*** Project Data Managers, contractors for GSK Biologicals
- ~~Sponsor representative:~~ PPD Clinical Research & Development, R&D Center Belgium ***and*** PPD ***, Clinical & Epidemiology Project Lead, DDW Vaccines, Belgium***

SYNOPSIS

Rationale for the study and study design

Rationale for the study

Rationale for the study design

A recent controlled human malaria infection (CHMI) study (MALARIA-071) ***demonstrated superior protection against malaria infection*** associated with the use of a fractional third dose in a 0, 1, 7-month schedule with a vaccine efficacy against infection of 86.7% (95% CI: 66.8; 94.6; p<0.0001) versus 62.5% (95% CI: 29.4; 80.1; p=0.0009) in the standard 0, 1, 2-month schedule. The incremental efficacy of the 0, 1, 7-month schedule over the 0, 1, 2-month schedule was 64.4% (95% CI: -7.9; 88.3; p=0.0741) [~~Data on file~~***Regules, 2016***]. The current study intends to establish POC for a fractional dose schedule under conditions of natural exposure. The study will be conducted in children 5-17 months old at first vaccination living in areas of mid to high malaria transmission, in line with the age group recommended by the World Health Organization (WHO) [WHO, 2016]. Infants 6-12 weeks old will not be included in this POC study to avoid interference of co-administration with the standard Expanded Program on Immunization (EPI) vaccines.

Rationale for the inclusion of a control group

It is deemed unacceptable to use a placebo control when study participants are exposed to unacceptable levels of risk from delaying administration of a safe and effective vaccine that is accessible through the public health system of the country in which the study is planned. However, the Nuffield Council on Bioethics guidelines state that the use of placebos may be acceptable if participants are not deprived of a treatment they would have otherwise received, but are provided at a minimum with the standard of care that is the best available in the country's public health system. CIOMS (Council for International Organizations of Medical Sciences), ICH (International Committee on Harmonization) and UNAIDS (Joint United Nations Programme on HIV/AIDS) guidelines stipulate that researchers must take steps to minimize any risks associated with the use of controls. The protocol should explain clearly the scientific justification for using a placebo-controlled design, and specifically address whether (1) the study question cannot be answered with an active-controlled study design; and (2) the risks of delaying an existing efficacious vaccine are adequately minimized or mitigated; and (3) the use of a placebo control is justified by the potential public health value of the

research; and (4) the research is responsive to local health needs.

In accordance with these recommendations, the use of a non-malaria comparator vaccine in this study is deemed acceptable as:

1. **Local availability.**
2. **Risk mitigation.** Subjects will have access to the best locally available malaria prevention and treatment options. ***All screened subjects will be provided with an*** ~~**Access to**~~ insecticide-treated bednet~~s~~ (IT~~Ns) will be ensured~~, and ~~there will be capacity strengthening for~~ malaria diagnosis and treatment ***will be ensured***. ***The investigator will make every effort to ensure that preventive measures as provided by the government are adhered to and under circumstances where this is not possible discussions with the sponsor need to take place.*** It is anticipated that subjects will benefit from participation in the study in terms of facilitated access to care and relatively intense health monitoring. Reduced levels of morbidity related to participation in a RTS,S/AS0$_{1E}$ study has been documented [Hamel, 2014].

- **Sampling schedule:**
  - Blood samples for immunogenicity will be taken in all subjects at timepoints described in Synopsis Table 4. For the evaluation of anti-CS and anti-HBs responses, a subset of 50 subjects ***(25 subjects per site)*** in each group (immunogenicity subset) will be tested at specified timepoints. CCI [redacted]
  - In addition to the blood samples listed in Synopsis Table 4, a small amount of blood (for blood smear and filter paper) will be taken every month from Day 0 until Month 23 and then every three months from Month 23 until Month 50 in all subjects for the evaluation of *P. falciparum* infections.
  - Blood samples for the evaluation of biochemistry and hematology parameters will be taken in a sub-cohort consisting of the first 50 subjects ***(25 subjects per site)*** enrolled in each group (reactogenicity sub-cohort). Biochemistry (ALT, creatinine) and hematology (hemoglobin, WBC, platelets) parameters will be assessed before Dose 3, seven days post-Dose 3 and 30 days post-Dose 3 (see Synopsis Table 4).

- **Efficacy surveillance:**
  - The research team at each study center will ***provide all screened subjects with an*** ~~ensure that~~ ITN ~~use is optimized~~ ***and there will be capacity strengthening for malaria diagnosis and treatment will be ensured***.

LIST OF ABBREVIATIONS

PVRV:	Purified Vero cell ***rabie***s vaccine

1 Introduction

1.2.1. Rationale for the study design

A recent CHMI study (MALARIA-071) 6 associated with the use of a fractional third dose in a 0, 1, 7-month schedule with a vaccine efficacy against infection of 86.7% (95% CI: 66.8; 94.6; p<0.0001) versus 62.5% (95% CI: 29.4; 80.1; p=0.0009) in the standard 0, 1, 2-month schedule. The incremental efficacy of the 0, 1, 7-month schedule over the 0, 1, 2-month schedule was 64.4% (95% CI: -7.9; 88.3; p=0.0741) [***Regules, 2016***~~Data on file~~]. The current study intends to establish POC for a fractional dose schedule under conditions of natural exposure. The study will be conducted in children 5-17 months old at first vaccination living in areas of mid to high malaria transmission, in line with the age group recommended by the World Health Organization (WHO) [WHO, 2016]. Infants 6-12 weeks old will not be included in this POC study to avoid interference of co-administration with the standard Expanded Program on Immunization (EPI) vaccines.

1.2.2. Rationale for the inclusion of a control group

It is deemed unacceptable to use a placebo control when study participants are exposed to unacceptable levels of risk from delaying administration of a safe and effective vaccine that is accessible through the public health system of the country in which the study is planned. However, the Nuffield Council on Bioethics guidelines state that the use of placebos may be acceptable if participants are not deprived of a treatment they would have otherwise received, but are provided at a minimum with the standard of care that is the best available in the country's public health system. CIOMS (Council for International Organizations of Medical Sciences), ICH (International Committee on Harmonization)and UNAIDS (Joint United Nations Programme on HIV/AIDS) guidelines stipulate that researchers must take steps to minimize any risks associated with the use of controls. The protocol should explain clearly the scientific justification for using a placebo-controlled design, and specifically address whether (1) the study question cannot be answered with an active-controlled study design; and (2) the risks of delaying an existing efficacious vaccine are adequately minimized or mitigated; and (3) the use of a placebo control is justified by the potential public health value of the research; and (4) the research is responsive to local health needs.

In accordance with these recommendations, the use of a non-malaria comparator vaccine in this study is deemed acceptable as:

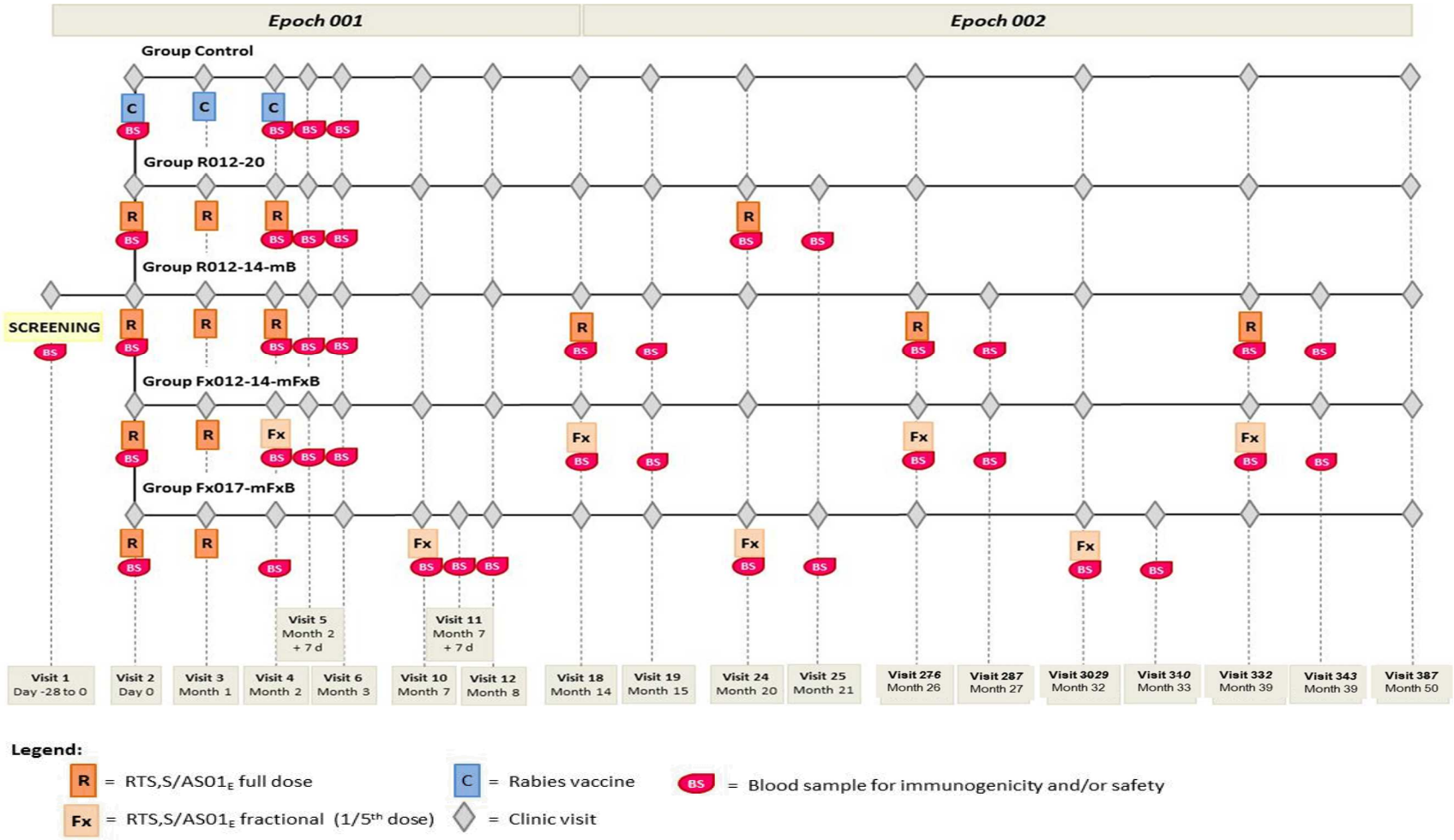
1. **Local availability.**
2. **Risk mitigation.** Subjects will have access to the best locally available malaria prevention and treatment options. ***All screened subjects will be provided with an*** ~~Access to~~ insecticide-treated bednet~~s~~ (ITNs) ~~will be ensured~~, and ~~there will be capacity strengthening for~~ malaria diagnosis and treatment ***will be ensured***. ***The investigator will make every effort to ensure that preventive measures as provided by the government are adhered to and under circumstances where this is not possible discussions with the sponsor need to take place.*** It is anticipated that subjects will benefit from participation in the study in terms of facilitated access to care and relatively intense health monitoring. Reduced levels of morbidity related to participation in a RTS,S/AS01$_E$ study has been documented [Hamel, 2014].

1.2.3. Rationale for the use of a rabies vaccine as a comparator vaccine

The efficacy of cell culture-derived rabies vaccines including human diploid cells vaccine (HDCV), purified Vero cell ***rabie***s vaccine (PVRV), purified chick embryo cells vaccine (PCECV), purified chick embryo cells vaccine (PHKCV) and purified duck embryo cells vaccine (PDEV) has been demonstrated [WHO, 2006]. In this study, a PCECV (*Rabipur*) will be used as comparator vaccine.

3. STUDY DESIGN OVERVIEW

Figure 1 Study design: clinic visits



- **Sampling schedule:**
  - Blood samples for immunogenicity will be taken in all subjects at timepoints described in Table 5. For the evaluation of anti-CS and anti-HBs responses, a subset of 50 subjects ***(25 subjects per site)*** in each group (immunogenicity subset, see Section 5) will be tested at specified timepoints (see Table 5 and Section 6.7.4.1). CCI [redacted]
  - In addition to the blood samples listed in Table 5, a small amount of blood (for blood smear and filter paper) will be taken every month from Day 0 until Month 23 and then every three months from Month 23 until Month 50 in all subjects for the evaluation of *P. falciparum* infections (see Section 6.7.4.2).
  - Blood samples for the evaluation of biochemistry and hematology parameters will be taken in a sub-cohort consisting of the first 50 subjects ***(25 subjects per site)*** enrolled in each group (reactogenicity sub-cohort, see Section 5). Biochemistry (ALT, creatinine) and hematology (hemoglobin, WBC, platelets) parameters will be assessed before Dose 3, seven days post-Dose 3 and 30 days post-Dose 3 (see Table 5 and Section 6.7.4.3).

- **Efficacy surveillance:**
  - The research team at each study center will ***provide all screened subjects with an*** ~~ensure that~~ ITN ~~use is optimized~~ , ***and*** ~~***there will be capacity strengthening for***~~ ***malaria diagnosis and treatment will be ensured***.

5.1. Number of subjects/centers

Table 9 Sub-cohort

Sub-cohort name	Description	Estimated number of subjects
Reactogenicity*	Solicited local and general AEs will be collected in a sub-cohort consisting of the first 50 subjects enrolled in each group. Hematology and biochemistry parameters will be measured in the same sub-cohort.	250 (50 subjects per group, ***25 subjects per site***)

* Subjects belonging to this sub-cohort will have specific study procedures performed for the assessment of reactogenicity, hematology and biochemistry parameters (refer to Table 11, Table 12 and Table 13).

Table 10 Subset

Subset name	Description	Estimated number of subjects
Immunogenicity*	Anti-CS and anti-HBs immune responses will be tested in a subset corresponding to the first 50 subjects enrolled in each group.	250 (50 subjects per group, ***25 subjects per site***)

*In this study, all subjects enrolled will have blood samples taken for assessment of immunogenicity. Not all samples will be used for testing: anti-CS and anti-HBs immune responses will be tested in a subset (i.e. the immunogenicity subset which includes the same subjects as in the reactogenicity sub-cohort) CCI [redacted]

5.3. Exclusion criteria for enrolment

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:

- ~~History of any neurological disorders or seizures~~. ***Children with a past history of a neurological disorder or atypical febrile seizure (a febrile seizure is atypical if it meets one of the following criteria: not associated with fever; lasts > 5 minutes; focal (not generalized); followed by transient or persistent neurological abnormality; occurs in a child < 6 months of age)***
- ~~Moderate or severe malnutrition at screening defined as weight for age Z-score < -2 (by WHO growth standard) [WHO, 2006].~~***Moderate or severe malnutrition at screening defined as weight for age or weight for height Z-score < -2.***

6.5. Outline of study procedures

Table 11 List of study procedures for clinic visits

Epoch	Epoch 001									Epoch 002				Epoch 003				Epoch 004		
Type of contact: Clinic visits	Visit 1[m] Screening	Visit 2	Visit 3	Visit 4	Visit 5[a]	Visit 6[a]	Visit 10[b]	Visit 11[b]	Visit 12[b]	Visit 18[c]	Visit 19[c]	Visit 24[d]	Visit 25[e]	Visit 28[c]	Visit 29[c]	Visit 31[f]	Visit 32[f]	Visit 34[c]	Visit 35[c]	Visit 39
Timepoints	D-28 to ~~D0~~*D-1*	D0	M1	M2	M2 + 7d	M3	M7	M7 + 7d	M8	M14	M15	M20	M21	M26	M27	M32	M33	M38	M39	M50
Children age (Months)		5-17 m																		
Control group																				
Informed consent	●																			
Check inclusion/exclusion criteria	●	O																		
Check the subject's vaccination card	O																			
Check screening lab results (hemoglobin)	●[g]																			
Collect demographic data	●																			
Check medical history	●																			
Physical examination	●	O	O	O	O	O						O								O
Measure and record length and weight	●																			
Issue subject's identification card	~~O~~	***O***																		
Check subject's identification card		~~O~~	O	O	O	O						O								O
Randomization		●																		
Distribute ITN [n]	***O***	~~O~~																		
Record if the subject belongs to the reactogenicity sub-cohort		●																		
Check contraindications and warnings and precautions		●[h]	●[h]	●[h]																
Record pre-vaccination body temperature		●	●	●																
Treatment number allocation		O	O	O																
Administer study vaccine		●	●	●																
Recording of administered treatment number		●	●	●																
Blood sampling for assessment of immunogenicity for ALL subjects (2.~~1~~***5*** ml)		●		●		●						●								●

Epoch	Epoch 001									Epoch 002				Epoch 003				Epoch 004		
Type of contact: Clinic visits	**Visit 1[m] Screening**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5[a]**	**Visit 6[a]**	**Visit 10[b]**	**Visit 11[b]**	**Visit 12[b]**	**Visit 18[c]**	**Visit 19[c]**	**Visit 24[d]**	**Visit 25[e]**	**Visit 28[c]**	**Visit 29[c]**	**Visit 31[f]**	**Visit 32[f]**	**Visit 34[c]**	**Visit 35[c]**	**Visit 39**
Timepoints	**D-28 to ~~D0~~*D-1***	**D0**	**M1**	**M2**	**M2 + 7d**	**M3**	**M7**	**M7 + 7d**	**M8**	**M14**	**M15**	**M20**	**M21**	**M26**	**M27**	**M32**	**M33**	**M38**	**M39**	**M50**
Children age (Months)		**5-17 m**																		
Blood sampling for assessment of hemoglobin at screening (0.5 ml)	●[i]																			
Blood sampling for assessment of parasitemia for ALL subjects (0.5 ml) [n,o,p]		●	●	●		●						●								●
Record any concomitant medications/vaccinations		●	●	●	●	●						●								●
Record any intercurrent medical conditions		●	●	●	●	●						●								●
Record unsolicited AEs (Days 0-29)		●[k]	●[k]	●[k]	●[k]	●[k]														
Record AEs/SAEs leading to withdrawal from further vaccination		●	●	●	●	●						●								●
Record SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●						●								●
Record SAEs (All, fatal, related to the investigational vaccine) [p,q]		●	●	●	●	●						●								●
Record AEs of specific interest [l]		●	●	●	●	●						●								●
Study Conclusion																				●
For the reactogenicity sub-cohort only:																				
Blood sampling for assessment of safety (1.0 ml)				●	●	●														
Record solicited local and general AEs (Days 0-3)				●[j]																
Group R012-20																				
Informed consent	●																			
Check inclusion/exclusion criteria	●	O																		
Check the subject's vaccination card	O																			
Check screening lab results (hemoglobin)	●[g]																			
Collect demographic data	●																			
Check medical history	●																			
Physical examination	●	O	O	O	O	O						O	O							O
Measure and record length and weight	●																			

Epoch	Epoch 001									Epoch 002				Epoch 003				Epoch 004		
Type of contact: Clinic visits	Visit 1[m] Screening	Visit 2	Visit 3	Visit 4	Visit 5[a]	Visit 6[a]	Visit 10[b]	Visit 11[b]	Visit 12[b]	Visit 18[c]	Visit 19[c]	Visit 24[d]	Visit 25[e]	Visit 28[c]	Visit 29[c]	Visit 31[f]	Visit 32[f]	Visit 34[c]	Visit 35[c]	Visit 39
Timepoints	D-28 to ~~D0~~*D-1*	D0	M1	M2	M2 + 7d	M3	M7	M7 + 7d	M8	M14	M15	M20	M21	M26	M27	M32	M33	M38	M39	M50
Children age (Months)		5-17 m																		
Issue subject's identification card	~~O~~	***O***																		
Check subject's identification card		~~O~~	O	O	O	O						O	O							O
Randomization		●																		
Distribute ITN [n]	***O***	~~O~~																		
Record if the subject belongs to the reactogenicity sub-cohort		●																		
Check contraindications and warnings and precautions		●[h]	●[h]	●[h]								●[h]								
Record pre-vaccination body temperature		●	●	●								●								
Treatment number allocation		O	O	O								O								
Administer study vaccine		●	●	●								●								
Recording of administered treatment number		●	●	●								●								
Blood sampling for assessment of immunogenicity for ALL subjects (2.~~1~~***5*** ml)		●		●		●						●	●							●
Blood sampling for assessment of hemoglobin at screening (0.5 ml)	●[i]																			
Blood sampling for assessment of parasitemia for ALL subjects (0.5 ml) ***[n,o,p]***		●	●	●		●						●	●							●
Record any concomitant medications/vaccinations		●	●	●	●	●						●	●							●
Record any intercurrent medical conditions		●	●	●	●	●						●	●							●
Record unsolicited AEs (Days 0-29)		●[k]	●[k]	●[k]	●[k]	●[k]						●[k]	●[k]							
Record AEs/SAEs leading to withdrawal from further vaccination		●	●	●	●	●						●	●							●
Record SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●						●	●							●
Record SAEs (All, fatal, related to the investigational vaccine) ***[p]***		●	●	●	●	●						●	●							●
Record AEs of specific interest [l]		●	●	●	●	●						●	●							●
Study Conclusion																				●

Epoch	Epoch 001									Epoch 002				Epoch 003				Epoch 004		
Type of contact: Clinic visits	**Visit 1[m] Screening**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5[a]**	**Visit 6[a]**	**Visit 10[b]**	**Visit 11[b]**	**Visit 12[b]**	**Visit 18[c]**	**Visit 19[c]**	**Visit 24[d]**	**Visit 25[e]**	**Visit 28[c]**	**Visit 29[c]**	**Visit 31[f]**	**Visit 32[f]**	**Visit 34[c]**	**Visit 35[c]**	**Visit 39**
Timepoints	**D-28 to ~~D0~~*D-1***	**D0**	**M1**	**M2**	**M2 + 7d**	**M3**	**M7**	**M7 + 7d**	**M8**	**M14**	**M15**	**M20**	**M21**	**M26**	**M27**	**M32**	**M33**	**M38**	**M39**	**M50**
Children age (Months)		**5-17 m**																		
For the reactogenicity sub-cohort only:																				
Blood sampling for assessment of safety (1.0 ml)				●	●	●														
Record solicited local and general AEs (Days 0-3)				●[j]								●[j]								
Groups R012-14-mD and Fx012-14-mFxD																				
Informed consent	●																			
Check inclusion/exclusion criteria	●	O																		
Check the subject's vaccination card	O																			
Check screening lab results (hemoglobin)	●[g]																			
Collect demographic data	●																			
Check medical history	●																			
Physical examination	●	O	O	O	O	O				O	O			O	O			O	O	O
Measure and record length and weight	●																			
Issue subject's identification card	~~O~~	***O***																		
Check subject's identification card		~~O~~	O	O	O	O				O	O			O	O			O	O	O
Randomization		●																		
Distribute ITN [n]	***O***	~~O~~																		
Record if the subject belongs to the reactogenicity sub-cohort		●																		
Check contraindications and warnings and precautions		●[h]	●[h]	●[h]						●[h]				●[h]				●[h]		
Record pre-vaccination body temperature		●	●	●						●				●				●		
Treatment number allocation		O	O	O						O				O				O		
Administer study vaccine		●	●	●						●				●				●		
Recording of administered treatment number		●	●	●						●				●				●		
Blood sampling for assessment of immunogenicity for ALL subjects (2.1~~5~~ ml)		●		●		●				●	●			●	●			●	●	●

Epoch	Epoch 001									Epoch 002				Epoch 003				Epoch 004		
Type of contact: Clinic visits	**Visit 1[m] Screening**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5[a]**	**Visit 6[a]**	**Visit 10[b]**	**Visit 11[b]**	**Visit 12[b]**	**Visit 18[c]**	**Visit 19[c]**	**Visit 24[d]**	**Visit 25[e]**	**Visit 28[c]**	**Visit 29[c]**	**Visit 31[f]**	**Visit 32[f]**	**Visit 34[c]**	**Visit 35[c]**	**Visit 39**
Timepoints	**D-28 to ~~D0~~*D-1***	**D0**	**M1**	**M2**	**M2 + 7d**	**M3**	**M7**	**M7 + 7d**	**M8**	**M14**	**M15**	**M20**	**M21**	**M26**	**M27**	**M32**	**M33**	**M38**	**M39**	**M50**
Children age (Months)		**5-17 m**																		
Blood sampling for assessment of hemoglobin at screening (0.5 ml)	●[i]																			
Blood sampling for assessment of parasitemia for ALL subjects (0.5 ml) [n,o,p]		●	●	●		●				●	●			●				●		●
Record any concomitant medications/vaccinations		●	●	●	●	●				●	●			●	●			●	●	●
Record any intercurrent medical conditions		●	●	●	●	●				●	●			●	●			●	●	●
Record unsolicited AEs (Days 0-29)		●[k]	●[k]	●[k]	●[k]	●[k]				●[k]	●[k]			●[k]	●[k]			●[k]	●[k]	
Record AEs/SAEs leading to withdrawal from further vaccination		●	●	●	●	●				●	●			●	●			●	●	●
Record SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●				●	●			●	●			●	●	●
Record SAEs (All, fatal, related to the investigational vaccine) [p,q]		●	●	●	●	●				●	●			●	●			●	●	●
Record AEs of specific interest [l]		●	●	●	●	●				●	●			●	●			●	●	●
Study Conclusion																				●
For the reactogenicity sub-cohort only:																				
Blood sampling for assessment of safety (1.0 ml)				●	●	●														
Record solicited local and general AEs (Days 0-3)				●[j]						●[j]				●[j]				●[j]		
Group Fx017-mFxD																				
Informed consent	●																			
Check inclusion/exclusion criteria	●	O																		
Check the subject's vaccination card	O																			
Check screening lab results (hemoglobin)	●[g]																			
Collect demographic data	●																			
Check medical history	●																			
Physical examination	●	O	O	O			O	O	O			O	O			O	O			O
Measure and record length and weight	●																			

Epoch	Epoch 001									Epoch 002				Epoch 003				Epoch 004		
Type of contact: Clinic visits	Visit 1[m] Screening	Visit 2	Visit 3	Visit 4	Visit 5[a]	Visit 6[a]	Visit 10[b]	Visit 11[b]	Visit 12[b]	Visit 18[c]	Visit 19[c]	Visit 24[d]	Visit 25[e]	Visit 28[c]	Visit 29[c]	Visit 31[f]	Visit 32[f]	Visit 34[c]	Visit 35[c]	Visit 39
Timepoints	D-28 to ~~D0~~*D-1*	D0	M1	M2	M2 + 7d	M3	M7	M7 + 7d	M8	M14	M15	M20	M21	M26	M27	M32	M33	M38	M39	M50
Children age (Months)		5-17 m																		
Issue subject's identification card	~~O~~	***O***																		
Check subject's identification card		~~O~~	O	O			O	O	O			O	O			O	O			O
Randomization		●																		
Distribute ITN [n]	***O***	~~O~~																		
Record if the subject belongs to the reactogenicity sub-cohort		●																		
Check contraindications and warnings and precautions		●[h]	●[h]				●[h]					●[h]				●[h]				
Record pre-vaccination body temperature		●	●				●					●				●				
Treatment number allocation		O	O				O					O				O				
Administer study vaccine		●	●				●					●				●				
Recording of administered treatment number		●	●				●					●				●				
Blood sampling for assessment of immunogenicity for ALL subjects (2.~~1~~***5*** ml)		●		●			●		●			●	●			●	●			●
Blood sampling for assessment of hemoglobin at screening (0.5 ml)	●[i]																			
Blood sampling for assessment of parasitemia for ALL subjects (0.5 ml) [n,o,~~p~~]		●	●	●			●		●			●	●			●				●
Record any concomitant medications/vaccinations		●	●	●			●	●	●			●	●			●	●			●
Record any intercurrent medical conditions		●	●	●			●	●	●			●	●			●	●			●
Record unsolicited AEs (Days 0-29)		●[k]	●[k]	●[k]			●[k]	●[k]	●[k]			●[k]	●[k]			●[k]	●[k]			
Record AEs/SAEs leading to withdrawal from further vaccination		●	●	●			●	●	●			●	●			●	●			●
Record SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●			●	●	●			●	●			●	●			●
Record SAEs (All, fatal, related to the investigational vaccine) [~~p~~ q]		●	●	●			●	●	●			●	●			●	●			●
Record AEs of specific interest [l]		●	●	●			●	●	●			●	●			●	●			●
Study Conclusion																				●

Epoch	Epoch 001									Epoch 002				Epoch 003				Epoch 004		
Type of contact: Clinic visits	Visit 1[m] Screening	Visit 2	Visit 3	Visit 4	Visit 5[a]	Visit 6[a]	Visit 10[b]	Visit 11[b]	Visit 12[b]	Visit 18[c]	Visit 19[c]	Visit 24[d]	Visit 25[e]	Visit 28[c]	Visit 29[c]	Visit 31[f]	Visit 32[f]	Visit 34[c]	Visit 35[c]	Visit 39
Timepoints	D-28 to ~~D0~~*D-1*	D0	M1	M2	M2 + 7d	M3	M7	M7 + 7d	M8	M14	M15	M20	M21	M26	M27	M32	M33	M38	M39	M50
Children age (Months)		5-17 m																		
For the reactogenicity sub-cohort only:																				
Blood sampling for assessment of safety (1.0 ml)							●	●	●											
Record solicited local and general AEs (Days 0-3)							●[j]					●[j]				●[j]				

Note: The double-line border following Month 21 (Visit 25) indicates the first analysis which will be performed on all data collected up to Month 21 (i.e. data that are as clean as possible). The final analysis will be performed on data collected up to study end (Month 50).

D: Day, M: Month.

● is used to indicate a study procedure that requires documentation in the individual eCRF.

O is used to indicate a study procedure that does not require documentation in the individual eCRF.

a. Clinic visit 5 (Month 2 + 7 days) and clinic visit 6 (Month 3) are only for groups R012-20, R012-14-mD, Fx012-14-mFxD and Control. The group FX017-mFXD has a field worker visit at Month 3 for assessment of parasitemia.

b. Clinic visit 10 (Month 7), clinic visit 11 (Month 7 + 7 days) and clinic visit 12 (Month 8) are only for group Fx017-mFxD. The other groups have field worker visits at Month 7 and Month 8 respectively for assessment of parasitemia.

c. Clinic visit 18 (Month 14), clinic visit 19 (Month 15), clinic visit 28 (Month 26), clinic visit 29 (Month 27), clinic visit 34 (Month 38) and clinic visit 35 (Month 39) are only for groups R012-14-mD and Fx012-14-mFxD. The other groups have field worker visits at Month 14, Month 15, Month 26 and Month 38 respectively for assessment of parasitemia.

d. Clinic visit 24 (Month 20) is only for groups R012-20, Fx017-mFxD and Control. The other groups have a field worker visit at Month 20 for assessment of parasitemia.

e. Clinic visit 25 (Month 21) is only for groups R012-20 and Fx017-mFxD. The other groups have a field worker visit at Month 21 for assessment of parasitemia.

f. Clinic visit 31 (Month 32) and clinic visit 32 (Month 33) are only for group Fx017-mFxD. The other groups have a field worker visit at Month 32 for assessment of parasitemia.

g. The screening laboratory results (hemoglobin) must be checked during the screening activities and before randomization.

h. There is no specific section in the eCRF to record the contraindications, warnings and precautions. The absolute contraindications to further administration of study vaccines have to be recorded in the AE or SAE section of the eCRF.

i. At screening, hemoglobin will be assessed in all subjects screened.

j. Solicited local and general AEs will be collected in the first 50 subjects enrolled in each group (reactogenicity sub-cohort) during four days (day of vaccination and three subsequent days) after vaccination as indicated in the table above. On the day of vaccination the evaluation will be carried out by the study physician at the study center. On Days 1, 2 and 3 after vaccination, trained study personnel will visit the children to record solicited AEs on diary cards.

k. Unsolicited AEs will be collected during 30 days (day of vaccination and 29 subsequent days) after each dose of study vaccine. Unsolicited AEs will be captured through passive surveillance at inpatient and outpatient facilities and during study visits.

l. AEs of specific interest include all seizures occurring within 30 days post-vaccination, meningitis and pIMDs (see Section 9.1.6). pIMDs will be reported via the electronic Expedited Adverse Events Report. Meningitis and seizures will be reported via the electronic Expedited Adverse Events Report and in addition clinical details of each case will be reported in a specific eCRF screen.

m. If a subject is considered momentarily ineligible on the day of the screening visit (i.e. failing to meet one or more eligibility criteria) procedures for screening can be repeated one further time, within the time window allowed for screening (see Table 14). No more than one repeat is allowed.

n. ~~An ITN will be provided to each subject through the national program or where this is not available the ITN will be supplied by the investigators~~Blood for parasitemia (0.5 ml) includes the blood for the slide reading and for the filter paper. The parasitemia assessment by blood slide reading will include blood-stage parasites and gametocytes counts.

o. In addition to the scheduled clinic visits, malaria cases will be captured by PCD throughout the study. All sick children presenting with fever and/or history of fever will have a blood sample taken for the evaluation of vaccine efficacy (for blood slide and filter paper for PCR).

p. Case of severe malaria or cerebral malaria will be reported via the electronic Expedited Adverse Events Report (refer to Section 9.3.1) and in addition clinical details of each case will be reported in a specific eCRF screen.

6.6.9. Issue subject's identification card

At Visit ***2***~~1 (Screening)~~, take a picture of the subject and his/her parent(s)/LAR(s) to make an identification card with subject's picture and number. Give this identification card to the subject's parent(s)/LAR(s).

6.6.16. Blood sampling for all subjects

- **Blood sampling for assessment of immunogenicity**

  A volume of approximately 2.5 ml of whole blood should be drawn from all subjects at each pre-defined timepoint. Out of this, a volume of ~~at least~~ ***approximately*** ~~1.1~~***1.5*** ml of whole blood ***will provide 600 µl of serum*** (~~to provide at least 1~~***3***00 µl of serum for anti-CS enzyme-linked immunosorbent assay [ELISA] + anti-CS avidity and ~~at least~~ 250 µl of serum for anti-HBs) ***and serum from a volume of approximately*** ~~In addition,~~ 1.0 ml of whole blood ***will be stored*** ~~should be drawn from all subjects at each pre-defined timepoint~~ to support potential ancillary studies for the further characterization of the immune response and translational research for correlates of protection.

  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.

- **Blood sampling for assessment of hemoglobin at screening**

  A volume of ***approximately*** ~~at least~~ 0.5 ml of whole blood should be drawn from all subjects screened at Visit 1 (Screening) to measure hemoglobin concentration.

- **Blood sampling for assessment of parasitemia**

  A volume of ***approximately*** ~~at least~~ 0.5 ml of whole blood should be drawn from all subjects at each pre-defined timepoint for the assessment of *P. falciparum* parasitemia (for blood slide and filter paper).

  In addition to the scheduled clinic visits, malaria cases will be captured by PCD throughout the study. All sick children presenting with fever and/or history of fever will have a blood sample taken for the evaluation of vaccine efficacy (for blood slide and filter paper).

6.6.17. Blood sampling for the reactogenicity sub-cohort

- **Blood sampling for assessment of safety**

  A volume of ~~at least~~ ***approximately*** 1.0 ml of whole blood should be drawn at each pre-defined timepoint for the assessment of hematology (hemoglobin, WBC, platelets) biochemistry (ALT, creatinine) parameters.

6.7. Biological sample handling and analysis

6.7.2. Biological samples

Sample type to be collected in the study: whole blood.

Table 15 Biological samples (whole blood)

Timepoint	Assessment	Total volume of blood per visit (ml)				
		R012-20	R012-14-mD	Fx012-14-mFxD	Fx017-mFxD	Control
Visit 1 (Screening)	Safety (hemoglobin)†	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 2 (Day 0)	Immunogenicity Parasitemia **Total:**	2.~~1~~***5*** ml 0.5 ml **~~2.6~~*3.0* ml**	2.~~1~~***5*** ml 0.5 ml **~~2.6~~*3.0* ml**	2.~~1~~***5*** ml 0.5 ml **~~2.6~~*3.0* ml**	2.~~1~~***5*** ml l 0.5 ml **~~2.6~~*3.0* ml**	2.~~1~~***5*** ml 0.5 ml **~~2.6~~*3.0* ml**
Visit 3 (Month 1)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 4 (Month 2)	Safety* Immunogenicity Parasitemia **Total:**	1.0 ml* 2.~~1~~***5*** ml 0.5 ml **~~3.6~~*4.0* or ~~2.6~~*3.0* ml l****	1.0 ml* 2.~~1~~***5*** ml 0.5 ml **~~3.6~~*4.0* or ~~2.6~~*3.0* ml ****	1.0 ml* 2.~~1~~***5*** ml 0.5 ml **~~3.6~~*4.0* or ~~2.6~~*3.0* ml ****	- 2.~~1~~***5*** ml 0.5 ml **~~2.6~~*3.0* ml**	1.0 ml* 2.~~1~~***5*** ml 0.5 ml **~~3.6~~*4.0* or ~~2.6~~*3.0* ml ****
Visit 5 (Month 2 + 7d)	Safety*	1.0 ml*	1.0 ml*	1.0 ml*	-	1.0 ml*
Visit 6 (Month 3)	Safety* Immunogenicity Parasitemia **Total:**	1.0 ml* 2.~~1~~***5*** ml 0.5 ml **~~3.6~~*4.0* or ~~2.6~~*3.0* ml ****	1.0 ml* 2.~~1~~***5*** ml 0.5 ml **~~3.6~~*4.0* or ~~2.6~~*3.0* ml ****	1.0 ml* 2.~~1~~***5*** ml 0.5 ml **~~3.6~~*4.0* or ~~2.6~~*3.0* ml ****	- - 0.5 ml **0.5 ml**	1.0 ml* 2.~~1~~***5*** ml 0.5 ml **~~3.6~~*4.0* or ~~2.6~~*3.0* ml ****
Visit 7 (Month 4)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 8 (Month 5)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 9 (Month 6)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 10 (Month 7)	Safety* Immunogenicity Parasitemia **Total:**	- - 0.5 ml **0.5 ml**	- - 0.5 ml **0.5 ml**	- - 0.5 ml **0.5 ml**	1.0 ml* 2.~~1~~***5*** ml 0.5 ml **~~3.6~~*4.0* or ~~2.6~~*3.0* ml ****	- - 0.5 ml **0.5 ml**
Visit 11 (Month 7 + 7d)	Safety*	-	-	-	1.0 ml*	-
Visit 12 (Month 8)	Safety* Immunogenicity Parasitemia **Total:**	- - 0.5 ml **0.5 ml**	- - 0.5 ml **0.5 ml**	- - 0.5 ml **0.5 ml**	1.0 ml* 2.~~1~~***5*** ml l 0.5 ml **~~3.6~~*4.0* or ~~2.6~~*3.0* ml ****	- - 0.5 ml **0.5 ml**
Visit 13 (Month 9)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 14 (Month 10)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 15 (Month 11)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 16 (Month 12)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 17 (Month 13)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 18 (Month 14)	Immunogenicity Parasitemia **Total:**	- 0.5 ml **0.5 ml**	2.~~1~~***5*** ml 0.5 ml **~~2.6~~*3.0* ml**	2.~~1~~***5*** ml 0.5 ml **~~2.6~~*3.0* ml**	- 0.5 ml **0.5 ml**	- 0.5 ml **0.5 ml**
Visit 19 (Month 15)	Immunogenicity Parasitemia **Total:**	- 0.5 ml **0.5 ml**	2.~~1~~***5*** ml 0.5 ml **~~2.6~~*3.0* ml**	2.~~1~~***5*** ml 0.5 ml **~~2.6~~*3.0* ml**	- 0.5 ml **0.5 ml**	- 0.5 ml **0.5 ml**
Visit 20 (Month 16)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 21 (Month 17)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 22 (Month 18)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 23 (Month 19)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 24 (Month 20)	Immunogenicity Parasitemia **Total:**	2.~~1~~***5*** ml 0.5 ml **~~2.6~~*3.0* ml**	- 0.5 ml **0.5 ml**	- 0.5 ml **0.5 ml**	2.~~1~~***5*** ml 0.5 ml **~~2.6~~*3.0* ml**	2.~~1~~***5*** ml 0.5 ml **~~2.6~~*3.0* ml**

Timepoint	Assessment	Total volume of blood per visit (ml)				
		R012-20	R012-14-mD	Fx012-14-mFxD	Fx017-mFxD	Control
Visit 25 (Month 21)	Immunogenicity Parasitemia **Total:**	2.~~1~~***5*** ml 0.5 ml **~~2.6~~*3.0* ml**	- 0.5 ml **0.5 ml**	- 0.5 ml **0.5 ml**	2.~~1~~***5*** ml 0.5 ml **~~2.6~~*3.0* ml**	- 0.5 ml **0.5 ml**
Visit 26 (Month 22)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 27 (Month 23)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 28 (Month 26)	Immunogenicity Parasitemia **Total:**	- 0.5 ml **0.5 ml**	2.~~1~~***5*** ml 0.5 ml **~~2.6~~*3.0* ml**	2.~~1~~***5*** ml 0.5 ml **~~2.6~~*3.0* ml**	- 0.5 ml **0.5 ml**	- 0.5 ml **0.5 ml**
Visit 29 (Month 27)	Immunogenicity	-	2.~~1~~***5*** ml	2.~~1~~***5*** ml	-	-
Visit 30 (Month 29)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 31 (Month 32)	Immunogenicity Parasitemia **Total:**	- 0.5 ml **0.5 ml**	- 0.5 ml **0.5 ml**	- 0.5 ml **0.5 ml**	2.~~1~~***5*** ml 0.5 ml **~~2.6~~*3.0* ml**	- 0.5 ml **0.5 ml**
Visit 32 (Month 33)	Immunogenicity	-	-	-	2.~~1~~***5*** ml	-
Visit 33 (Month 35)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 34 (Month 38)	Immunogenicity Parasitemia **Total:**	- 0.5 ml **0.5 ml**	2.~~1~~***5*** ml 0.5 ml **~~2.6~~*3.0* ml**	2.~~1~~***5*** ml 0.5 ml **~~2.6~~*3.0* ml**	- 0.5 ml **0.5 ml**	- 0.5 ml **0.5 ml**
Visit 35 (Month 39)	Immunogenicity	-	2.~~1~~***5*** ml	2.~~1~~***5*** ml	-	-
Visit 36 (Month 41)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 37 (Month 44)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 38 (Month 47)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 39 (Month 50)	Immunogenicity Parasitemia **Total:**	2.~~1~~***5*** ml 0.5 ml **~~2.6~~*3.0* ml**	2.~~1~~***5*** ml 0.5 ml **~~2.6~~*3.0* ml**	2.~~1~~***5*** ml 0.5 ml **~~2.6~~*3.0* ml**	2.~~1~~***5*** ml 0.5 ml **~~2.6~~*3.0* ml**	2.~~1~~***5*** ml 0.5 ml **~~2.6~~*3.0* ml**

† At screening, hemoglobin will be assessed in all subjects screened.

* Blood samples for hematology and biochemistry will be taken only in subjects belonging to the reactogenicity sub-cohort.

** The total volume of blood to be taken depends if the subject belongs to the reactogenicity sub-cohort or not.

d: day

6.7.3. Laboratory assays

Table 17 Assessment of *P. falciparum* infection

System	Component	Method	Unit	Laboratory
Whole Blood*	*Plasmodium falciparum* parasites**	Not applicable***	Not applicable	KEMRI/USAMRU-K, WRP, Malaria Diagnostics Center, Kisumu§

KEMRI/USAMRU-K, WRP: Kenya Medical Research Institute / US Army Medical Research Unit Kenya, Walter Reed Project.

* The incidence of *P. falciparum* infection assessed by PCR and parasite genotyping will be evaluated in an ancillary study, using samples collected as described in the present ~~concept~~ protocol (see Table 20).

** *P. falciparum* parasite count includes blood-stage parasites and gametocytes counts.

*** Method used will be blood slide microscope reading.

§ And/or other GSK designated laboratory.

7.3. Dosage and administration of study vaccines

7.3.1. RTS,S/AS01$_E$

Disinfect the top of the vaccine vial (pellet) and adjuvant vial with alcohol swabs and let dry. Withdraw the content of the adjuvant vial in a syringe and inject the adjuvant into the vial of lyophilized antigen. The pellet is then dissolved by gently shaking the vial. Wait for one minute to ensure the complete dissolution of the vial content before withdrawing one full dose of RTS,S/AS01$_E$ (0.5 ml) or a fractional dose of RTS,S/AS01$_E$ (0.1 ml). For the full dose of RTS,S/AS01$_E$, 0.5 ml should be administered using a fresh 25 gauge needle with a length of one inch (25 mm). For the fractional dose of RTS,S/AS01$_E$, 0.1 ml should be administered using a 1 ml syringe and fresh 25 gauge needle with a length of one inch (25 mm). The reconstituted vaccine should be administered by slow intramuscular injection into the left deltoid. The vaccine should be injected within four hours of reconstitution (storage at +2°C to +8°C). ***Refer to the SPM for full details of how to fill the syringe and inject the fractional dose.***

9.1. Safety definitions

9.1.6.1. Potential immune-mediated diseases

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. ***Tests for further evaluation of pIMDs may be conducted at Clinical Laboratory Sciences (CLS) South Africa if there is an indication for the test (see APPENDIX D for details of tests available at CLS South Africa).***

9.1.6.3. Meningitis

The recommended method for evaluation of meningitis will be through CSF analysis. Lumbar puncture should be performed by qualified medical personnel in subjects when there is an indication for testing. The initial CSF testing to aid in the diagnosis of meningitis including, and not limited to, microscopy and gram staining, differential white cell and red blood cell count, CSF biochemistry, antigen/agglutination tests and culture, amongst others, is to be carried out by the site. For every suspected meningitis case, a CSF sample will be collected and from this approximately 500 µl will be sent to CLS South Africa for CSF polymerase chain reaction (PCR) testing for selected common aetiological pathogens of meningitis (see APPENDIX D for details of additional tests available at CLS South Africa for the evaluation of meningitis).

9.2. Detecting and recording adverse events and serious adverse events

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

An overview of the protocol-required reporting periods for AEs and SAEs is given in Table 27.

Table 27 Reporting periods for collecting safety information

Study visits	1	2			3			4			10			18			24			28			31			34			39
Event	Scr*	Vac 1			Vac 2			Vac 3			Vac 4			Vac 5			Vac 6			Vac 7			Vac 8			Vac 9			Study end
Study timepoint:	D -28 to ~~0~~ -1	D0	D0 + 3d	D0 + 29d	M1	M1 + 3d	M1 + 29d	M2	M2 + 3d	M2 + 29d	M7	M7 + 3d	M7 + 29d	M14	M14 + 3d	M14 + 29d	M20	M20 + 3d	M20 + 29d	M26	M26 + 3d	M26 + 29d	M32	M32 + 3d	M32 + 29d	M38	M38 + 3d	M38 + 29d	M50
For ALL groups																													
AEs/SAEs leading to withdrawal from further vaccination		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
SAEs related to study participation or concurrent GSK medication/vaccine	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
SAEs (All, fatal, related to the investigational vaccine)		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
AEs of specific interest**		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Group R012-20																													
Solicited local and general AEs***								■	■								■	■											
Unsolicited AEs		■	■	■	■	■	■	■	■	■							■	■	■										
Group R012-14-mD and Fx012-14-mFxD																													
Solicited local and general AEs***								■	■					■	■					■	■					■	■		

Study visits	**1**	**2**			**3**			**4**			**10**			**18**			**24**			**28**			**31**			**34**			**39**
Event	**Scr***	**Vac 1**			**Vac 2**			**Vac 3**			**Vac 4**			**Vac 5**			**Vac 6**			**Vac 7**			**Vac 8**			**Vac 9**			**Study end**
Study timepoint:	**D -28 to ~~0~~ *-1***	**D0**	**D0 + 3d**	**D0 + 29d**	**M1**	**M1 + 3d**	**M1 + 29d**	**M2**	**M2 + 3d**	**M2 + 29d**	**M7**	**M7 + 3d**	**M7 + 29d**	**M14**	**M14 + 3d**	**M14 + 29d**	**M20**	**M20 + 3d**	**M20 + 29d**	**M26**	**M26 + 3d**	**M26 + 29d**	**M32**	**M32 + 3d**	**M32 + 29d**	**M38**	**M38 + 3d**	**M38 + 29d**	**M50**
Unsolicited AEs																													
Group Fx017-mFxD																													
Solicited local and general AEs***																													
Unsolicited AEs																													
Control group																													
Solicited local and general AEs***																													
Unsolicited AEs																													

* i.e. consent obtained.
** AEs of specific interest include seizures occurring within 30 days post-vaccination, meningitis and pIMDs.
*** Solicited local and general AEs will be collected in the first 50 subjects enrolled in each group (reactogenicity sub-cohort).
Scr: Screening; Vac: Vaccination; D: Day; M: Month; 3d: 3 days; 29d: 29 days.

9.5. Treatment of adverse events

Cases of suspected malaria will be tested with a rapid diagnostic test (RDT) or blood slide and managed on the basis of their result. These tests are separate to samples taken for determination of efficacy against P. falciparum infection by blood slide reading and filter paper for PCR (see Section 6.7.3).

14. REFERENCES

Regules JA, Cicatelli SB, Bennett JW et al. Fractional third and fourth dose of RTS,S/AS01 malaria candidate vaccine: a phase 2a controlled human malaria parasite infection and immunogenicity study. J Infect Dis. 2016; 214:762–71.

APPENDIX B CLINICAL LABORATORIES

Table 31 GSK Biologicals' laboratories

Laboratory	Address
GSK Biologicals ~~Global Vaccine~~ Clinical Laboratory ***Services***, Rixensart	Biospecimen Reception - B7/44 Rue de l'Institut, 89 - B-1330 Rixensart - Belgium
GSK Biologicals ~~Global Vaccine~~ Clinical Laboratory ***Services***, Rixensart	Avenue Fleming, 20 - B-1300 Wavre - Belgium

Table 32 Outsourced laboratories

Laboratory	Address
Clinical Laboratory Services, South Africa	***4th Floor Spencer Lister Building*** ***Corner of Hospital and de Korte Streets*** ***Braamfontein*** ***Johannesburg 2000, South Africa***
CEVAC - University of Gent	De Pintelaan, 185 Gent Belgium
Kenya Medical Research Institute / US Army Medical Research Unit Kenya, Walter Reed Project.(KEMRI/USAMRU-K, WRP), Malaria Diagnostics Center, Kisumu	PO Box 54, Kisumu 40100, Kenya

<u>Collaborators for filter paper assessment of molecular detection and genotyping of Plasmodium falciparum parasites</u>

This ancillary analysis will be carried out in partnership with the Harvard School of Public Health (Holyoke Center 727, 1350 Massachusetts Avenue, Cambridge, Massachusetts 02138, USA) and the Broad Institute (415 Main St, Cambridge, MA 02142, USA).

APPENDIX D SAFETY LABORATORY TESTING: CLS South Africa

Cerebrospinal fluid (CSF) for meningitis testing

The recommended method for evaluation of meningitis will be through CSF analysis.

For all suspected meningitis cases, a CSF sample will be sent to CLS South Africa for CSF polymerase chain reaction (PCR) testing for selected common aetiological pathogens of meningitis as listed below. An approximate volume of CSF should be 500 µl.

- ***CSF: PCR testing***

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

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

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

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

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

Optionally, if indicated, an additional blood sample of approximately 5 ml whole blood may be taken by the treating clinician to aid in the diagnosis of meningitis through serum PCR or serum serology. The following tests will be available at CLS South Africa.

- ***Serum: PCR***

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

- ***Serum: Serology***

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

<u>Analysis of potential Immune-Mediated Diseases (pIMDs)</u>

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

Optionally, if indicated, an additional blood sample of approximately 5 ml whole blood may be taken by the treating clinician to aid in the diagnosis of pIMDs. A list of potential serum autoimmune tests that can be performed at CLS South Africa is provided below.

- ***Serum: Autoimmune tests***

TEST
Anti-insulin autoantibodies (IA2)*
Anti-glutamic acid decarboxylase autoantibodies (anti-GAD65)
Anti-Tyrosine phosphatase-like IA2 antibodies
Anti-islet cell antibodies
Anti-smooth muscle antibodies (ASMA)
Anti-liver-kidney microsomal antibodies (anti-LKM)
Anti-soluble liver antigens (anti-SLA)
Anti-mitochondrial antibodies (AMA)
Anti-nuclear antibodies (ANA)
Anti-double stranded DNA (anti-dsDNA)

TEST
Rheumatoid factor (RF)
Anti-Glomerular Basement Membrane antibodies (anti-GBM)
Anti-neutrophil cytoplasmic autoantibodies (ANCAs)
Anti-streptolysin O / Anti-DNAse
Serum C3, C4 complement
Anti-cyclic citrullinated peptide antibodies (anti-CCP)
Anti-skin basement membrane protein
IgA endomysial antibodies
Anticardiolipin (ELISA) IgM, IgG
Anti-beta 2 glycoprotein I
Anti-prothrombin

GlaxoSmithKline Biologicals

Vaccine Value & Health Science (VVHS)

Protocol Amendment 2

eTrack study number and Abbreviated Title	204889 (MALARIA-094)
Amendment number:	Amendment 2
Amendment date:	06 April 2017
Co-ordinating author:	PPD, Scientific Writer, Freelance Contractor for GSK Biologicals

Rationale/background for changes:

To align with Malaria-095, the ancillary study to Malaria-094, in which an efficacy analyses will be conducted at Month 32, an additional interim analysis has been added to Malaria-094 at Month 33, 1 month post fractional booster dose (Group Fx017-mFxD). In addition monthly cross-sectional visits will take place up until Month 20 instead of Month 23 and thereafter every 3 months.

At the request of the Ghana Health Service Ethics Review Committee, clarification has been provided that subjects should continue with their routine EPI immunizations as applicable to their age whilst participating in the study.

Following a request by the Ghana FDA, the secondary objectives and endpoints have been simplified.

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

GlaxoSmithKline

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

Primary study vaccine/product and number	• GlaxoSmithKline (GSK) Biologicals' candidate *Plasmodium falciparum* malaria vaccine RTS,S/AS01$_E$ (SB257049).
Other study vaccine/product	• Rabies vaccine (Rabipur™)
eTrack study number and abbreviated title	204889 (MALARIA-094)
EudraCT number	2016-000290-20
Date of protocol	Final Version 1: 16 February 2016

Date of protocol amendment	Amendment 1 Final: 13 September 2016 ***Amendment 2 Final: 06 April 2017***
Title	Efficacy, safety and immunogenicity study of GSK Biologicals' candidate malaria vaccine (SB257049) evaluating schedules with or without fractional doses, early Dose 4 and yearly doses, in children 5-17 months of age.
Detailed title	Phase IIb randomized, open-label, controlled, multi-center study of the efficacy, safety and immunogenicity of GSK Biologicals' candidate malaria vaccine RTS,S/AS01$_E$ evaluating schedules with or without fractional doses, early Dose 4 and yearly doses, in children 5-17 months of age living in sub-Saharan Africa.
Coordinating author	PPD Project Manager Science Writing, Malaria Vaccines
Contributing authors	• PPD, Study Data Manager, TCS, contractor for GSK Biologicals • PPD Study Delivery Lead*s* • PPD Vaccine Supply Coordinator • PPD, Biostatistics • PPD, Safety Physician • PPD, Clinical Laboratory Sciences Lead • PPD, Clinical Laboratory Sciences Study Manager • PPD, Lead Statistician • PPD, Clinical Research and Development Leads • PPD, Senior Local Delivery Lead • PPD, Global Patent representative • PPD Business and Decision Life Sciences, and PPD TCS, Project Data Managers, contractors for GSK Biologicals • PPD ***, Project Statistician*** • PPD, Clinical Regulatory Affairs representative

- ~~PPD , Clinical Research and Development Lead~~
- PPD , Study Delivery Manager
- PPD , Clinical Research & Development, R&D Center Belgium and PPD , Clinical & Epidemiology Project Lead, DDW Vaccines, Belgium

GSK Biologicals' Protocol DS v 14.1.1

SYNOPSIS

Detailed Title

Phase IIb randomized, open-label, controlled, multi-center study of the efficacy, safety and immunogenicity of GSK Biologicals' candidate malaria vaccine RTS,S/AS01$_E$ evaluating schedules with or without fractional doses, early Dose 4 and yearly doses, in children 5-17 months of age living in sub-Saharan Africa.

Rationale for the study and study design

Rationale for the use of a rabies vaccine as a comparator vaccine

.....

The efficacy of cell culture-derived rabies vaccines including human diploid cells vaccine (HDCV), purified Vero cells vaccine (PVRV), purified chick embryo cells vaccine (PCECV), purified hamster kidney cells vaccine (PHKCV) and purified duck embryo cells vaccine (PDEV) has been demonstrated [WHO, 20~~06~~***10***]. In this study, a PCECV (*Rabipur*) will be used as comparator vaccine.

.....

Objectives

Secondary

- **Efficacy**
  - ***To assess the incremental vaccine efficacy against clinical malaria of a schedule with a fractional third dose at Month 2 versus a schedule with 3 full doses (primary and secondary case definitions) over 12 months post-Dose 3.***
  - ***To assess the incremental vaccine efficacy against clinical malaria, over 7 and 12 months post-Dose 3,***

of a schedule with a fractional third dose at Month 7 versus a schedule with a fractional third dose at Month 2.

- ***To assess the incremental vaccine efficacy against clinical malaria, over 7 and 12 months post-Dose 3, of a schedule with a fractional third dose at Month 7 versus a schedule with 3 full doses.***
- ***To assess the incremental vaccine efficacy against clinical malaria, over 12 months post-Dose 4, post-Dose 5 and post-Dose 6 of a schedule with a fractional third dose at Month 2 and yearly fractional doses versus a schedule with full doses at Month 0, Month 1, Month 2 and yearly full doses.***
- ***To assess the incremental vaccine efficacy against clinical malaria, over 12 months post-Dose 4, of a schedule with a fractional third dose at Month 7 versus a standard schedule with 4 full doses at 0,1,2,20 months.***
- ***To assess the vaccine efficacy and impact of each RTS,S/AS01$_E$ schedule over the entire study period by measuring the efficacy against clinical malaria at Months 14, 20, 26, 32, 38 and 50.***
- ***To assess the prevalence of P. falciparum infections (defined by a positive blood slide) of each RTS,S/AS01$_E$ schedule at cross-sectional visits (monthly from Month 0-20 and every three months thereafter till study end).***
- ***To assess the vaccine efficacy against incident P. falciparum infections defined by positive blood slide over the entire study period.***

- ~~**Efficacy: Incremental efficacy of a schedule with a fractional third dose at Month 2 over the standard schedule (primary and secondary case definitions)**~~
  - ~~To assess the incremental vaccine efficacy against clinical malaria (primary and secondary case definitions), over 12 months post-Dose 3, of a schedule with a fractional third dose at Month 2 versus the standard schedule.~~
  - ~~To assess the incremental vaccine efficacy against incident *P. falciparum* infections (defined by a positive blood slide), over 12 months post-Dose 3, of a~~

schedule with a fractional third dose at Month 2 versus the standard schedule.

- **Efficacy: Efficacy of each RTS,S/AS01E schedule up to one year post-Dose 3**

  - To assess the vaccine efficacy against clinical malaria, over seven months post-Dose 3, of a schedule with a fractional third dose at Month 2.

  - To assess the vaccine efficacy against incident *P. falciparum* infections (defined by a positive blood slide), over seven months post-Dose 3, of a schedule with a fractional third dose at Month 2.

  - To assess the vaccine efficacy against clinical malaria, over seven months post-Dose 3, of a schedule with a fractional third dose at Month 7.

  - To assess the vaccine efficacy against incident *P. falciparum* infections (defined by a positive blood slide), over seven months post-Dose 3, of a schedule with a fractional third dose at Month 7.

  - To assess the vaccine efficacy against clinical malaria, over seven months post-Dose 3, of the standard 0, 1, 2-month schedule.

  - To assess the vaccine efficacy against incident *P. falciparum infections* (defined by a positive blood slide), over seven months post-Dose 3, of the standard 0, 1, 2-month schedule.

  - To assess the vaccine efficacy against clinical malaria, over 12 months post-Dose 3, of a schedule with a fractional third dose at Month 2.

  - To assess the vaccine efficacy against incident *P. falciparum* infections (defined by a positive blood slide), over 12 months post-Dose 3, of a schedule with a fractional third dose at Month 2.

  - To assess the vaccine efficacy against clinical malaria, over 12 months post-Dose 3, of a schedule with a fractional third dose at Month 7.

  - To assess the vaccine efficacy against incident *P. falciparum* infections (defined by a positive blood slide), over 12 months post-Dose 3, of a schedule with a fractional third dose at Month 7.

- To assess the vaccine efficacy against clinical malaria, over 12 months post-Dose 3, of the standard 0, 1, 2-month schedule.

- To assess the vaccine efficacy against incident *P. falciparum* infections (defined by a positive blood slide), over 12 months post-Dose 3, of the standard 0, 1, 2-month schedule.

- **Efficacy: Timing of the fractional third dose**

  - To assess the incremental vaccine efficacy against clinical malaria, over seven months post-Dose 3, of a schedule with a fractional third dose at Month 7 versus a schedule with a fractional third dose at Month 2.

  - To assess the incremental vaccine efficacy against incident *P. falciparum* infections (defined by a positive blood slide), over seven months post-Dose 3, of a schedule with a fractional third dose at Month 7 versus a schedule with a fractional third dose at Month 2.

  - To assess the incremental vaccine efficacy against clinical malaria, over seven months post-Dose 3, of a schedule with a fractional third dose at Month 7 versus the standard schedule.

  - To assess the incremental vaccine efficacy against incident *P. falciparum* infections (defined by a positive blood slide), over seven months post-Dose 3, of a schedule with a fractional third dose at Month 7 versus the standard schedule.

  - To assess the incremental vaccine efficacy against clinical malaria, over 12 months post-Dose 3, of a schedule with a fractional third dose at Month 7 versus a schedule with a fractional third dose at Month 2.

  - To assess the incremental vaccine efficacy against incident *P. falciparum* infections (defined by a positive blood slide), over 12 months post-Dose 3, of a schedule with a fractional third dose at Month 7 versus a schedule with a fractional third dose at Month 2.

  - To assess the incremental vaccine efficacy against clinical malaria, over 12 months post-Dose 3, of a schedule with a fractional third dose at Month 7 versus the standard schedule.

  - To assess the incremental vaccine efficacy against incident *P. falciparum* infections (defined by a

positive blood slide), over 12 months post-Dose 3, of a schedule with a fractional third dose at Month 7 versus the standard schedule.

- **Efficacy: Incremental efficacy of fractional Dose 4, Dose 5 and Dose 6 versus full doses**
  - To assess the incremental vaccine efficacy against clinical malaria, over 12 months post-Dose 4, of a schedule with a fractional third dose at Month 7 versus the standard schedule.
  - To assess the incremental vaccine efficacy against incident *P. falciparum* infections (defined by a positive blood slide), over 12 months post-Dose 4, of a schedule with a fractional third dose at Month 7 versus the standard schedule.
  - To assess the incremental vaccine efficacy against clinical malaria, over 12 months post-Dose 4, post-Dose 5 and post-Dose 6 of a schedule with a fractional third dose at Month 2 and yearly fractional doses versus a schedule with full doses at Month 0, Month 1, Month 2 and yearly full doses.
  - To assess the incremental vaccine efficacy against incident *P. falciparum* infections (defined by a positive blood slide), over 12 months post-Dose 4, post-Dose 5 and post-Dose 6 of a schedule with a fractional third dose at Month 2 and yearly fractional doses versus a schedule with full doses at Month 0, Month 1, Month 2 and yearly full doses.

- **Efficacy: Efficacy and impact of each RTS,S/AS01$_E$ schedule over the entire study period**
  - To assess the vaccine efficacy against clinical malaria of each RTS,S/AS01$_E$ schedule up to Month 14.
  - To assess the vaccine efficacy and impact against clinical malaria of each RTS,S/AS01$_E$ schedule up to Month 20, Month 26, Month 38 and up to study end (Month 50).
  - To assess the vaccine efficacy against incident *P. falciparum* infections (defined by a positive blood slide) of each RTS,S/AS01$_E$ schedule up to Month 14, Month 20, Month 26, Month 38 and up to study end (Month 50).

- ~~**Efficacy: Efficacy against prevalent *P. falciparum* infections**~~

  ~~To assess the occurrence of prevalent *P. falciparum* infections (defined by a positive blood slide) of each RTS,S/AS01$_E$ schedule at Month 14, Month 20, Month 26, Month 38 and up to study end (Month 50).~~

Study design

- **.....**.
- **Duration of the study:** Approximately 50 months, with ~~an~~ ***two*** interim ~~analysis~~ ***analyses*** and option for conditional continuation (see next bullet point).
  - Epoch 001: Starting at Visit 1 (Screening) and ending at Visit 17 (Month 13). Note: the data up to Visit 18 (Month 14) pertains to Epoch 001.
  - Epoch 002: Starting at Visit 18 (Month 14) and ending at Visit 2~~7~~***6*** (Month 23). Note: the data up to Visit 2~~8~~***7*** (Month 26) pertains to Epoch 002.
  - Epoch 003: Starting at Visit 2~~8~~***7*** (Month 26) and ending at Visit 3~~3~~***2*** (Month 35). Note: the data up to Visit 34***3*** (Month 38) pertains to Epoch 003.
  - Epoch 004: Starting at Visit 34***3*** (Month 38) and ending at Visit 3~~9~~***8*** (Month 50).
- **Sequence of analyses and conditional continuation:**
  - A first analysis will be performed on data collected up to Month 21 (Visit 25) to evaluate the primary objective and relevant secondary objectives.
  - ***A second analysis will be performed on data collected up to Month 33 (Visit 31) to evaluate relevant secondary objectives.***
  - A ~~second~~ ***final*** analysis will be performed at study end (Month 50) on data collected up to Month 50. An integrated study report presenting all results until Month 50 will be produced.

After the ~~first~~ ***interim*** ~~analysis~~***analyses***, the Independent Data Monitoring Committee (IDMC) will have the possibility to recommend the suspension of further vaccinations and termination of specific study group(s) upon consideration of the study results. In the event that the IDMC recommend the suspension of further vaccinations, the group(s) impacted will be followed up for 12 months after their last study vaccination.

- **Sampling schedule:**
  - .....
  - In addition to the blood samples listed in Synopsis Table 4, a small amount of blood (for blood smear and filter paper) will be taken every month from Day 0 until Month ~~23~~ ***20*** and ~~then~~ ***thereafter*** every three months ~~from Month 23~~ until Month 50 in all subjects for the evaluation of *P. falciparum* infections.

Synopsis Table 4 Blood sampling timepoints

		Visit 1	Visit 2	Visit 4	Visit 5	Visit 6	Visit 10	Visit 11	Visit 12	Visit 18	Visit 19	Visit 24	Visit 25	Visit 287	Visit 298	Visit 310	Visit 321	Visit 343	Visit 354	Visit 398
Study group	**Type of blood sampling**	**Scr**	**D0**	**M2**	**M2 + 7d**	**M3**	**M7**	**M7 + 7d**	**M8**	**M14**	**M15**	**M20**	**M21**	**M26**	**M27**	**M32**	**M33**	**M38**	**M39**	**M50**
R012-20	Safety	x*		x**	x**	x**														
	Immunogenicity§		x	x		x						x	x							x
R012-14-mD	Safety	x*		x**	x**	x**														
	Immunogenicity§		x	x		x				x	x			x	x			x	x	x
Fx012-14-mFxD	Safety	x*		x**	x**	x**														
	Immunogenicity§		x	x		x				x	x			x	x			x	x	x
Fx017-mFxD	Safety	x*					x**	x**	x**											
	Immunogenicity§		x	x			x		x			x	x			x	x			x
Control	Safety	x*		x**	x**	x**														
	Immunogenicity§		x	x		x						x								x

* At screening, hemoglobin will be assessed in all subjects screened.
** Blood samples for hematology and biochemistry will be taken in a sub-cohort consisting of the first 50 subjects enrolled in each group.
§ Blood samples for immunogenicity will be taken in all subjects enrolled.
Scr: Screening
M: Month
D: Day

- **Efficacy surveillance:**
  - .....
  - Cross-sectional surveys: to evaluate the vaccine efficacy against incident and prevalent *P. falciparum* infections, monthly cross-sectional surveys will be performed from Day 0 until Month ~~23~~ ***20*** to measure *P. falciparum* parasitemia. ~~From Month 23~~ ***Thereafter*** until study end (Month 50) parasitemia will be measured every three months. Blood slides from cross-sectional surveys will not be read in real time.
- **Safety monitoring:**
  - .....
  - ***Where possible autopsies will be performed.*** Verbal autopsy will be performed on all cases of mortality occurring outside hospital ***if autopsies cannot be performed***.

Synopsis Table 6 Case definition of incident P. falciparum infection*

Case definition 1	A documented *P. falciparum* asexual parasite density > 0 detected by blood slide reading at a cross-sectional survey or as captured by the secondary case definition of clinical malaria (active a ***detection of infection*** and passive ***case*** detection ~~of infection~~).

***** Note, the incidence of *P. falciparum* infection defined by positive PCR and parasite genotyping will be evaluated in the context of an ancillary study, using samples collected as described in the present protocol.

Endpoints

Primary

- **Efficacy: ~~Incremental efficacy of a schedule with a fractional third dose at Month 2 over the standard schedule~~**
  - The occurrence of clinical malaria meeting the primary case definition from Month 2.5 up to Month 14 ~~in group Fx012-14-mFxD and groups R012-20 + R012-14-mD~~.

Secondary

- **Efficacy~~: Incremental efficacy of a schedule with a fractional third dose at Month 2 over the standard schedule (primary and secondary case definitions)~~**

- ***The occurrence of clinical malaria meeting the primary and secondary case definitions from Day 0 up to Month 50.***
- ***The occurrence of incident P. falciparum infections from Day 0 to Month 50.***
- ***The prevalence of P. falciparum infections defined by positive blood slide at each cross-sectional survey.***

- ~~**Efficacy: Efficacy of each RTS,S/AS01$_E$ schedule up to one year post-Dose 3**~~
  - ~~The occurrence of clinical malaria meeting the primary and secondary case definitions from Month 2.5 up to Month 9 in group Fx012-14-mFxD and Control group.~~
  - ~~The occurrence of incident *P. falciparum* infections from Month 2.5 up to Month 9 in group Fx012-14-mFxD and Control group.~~
  - ~~The occurrence of clinical malaria meeting the primary and secondary case definitions from Month 7.5 up to Month 14 in group Fx017-mFxD and Control group.~~
  - ~~The occurrence of incident *P. falciparum* infections from Month 7.5 up to Month 14 in group Fx017-mFxD and Control group.~~
  - ~~The occurrence of clinical malaria meeting the primary and secondary case definitions from Month 2.5 up to Month 9 in groups R012-20 + R012-14-mD and Control group.~~
  - ~~The occurrence of incident *P. falciparum* infections from Month 2.5 up to Month 9 in groups R012-20 + R012-14-mD and Control group.~~
  - ~~The occurrence of clinical malaria meeting the primary and secondary case definitions from Month 2.5 up to Month 14 in group Fx012-14-mFxD and Control group.~~
  - ~~The occurrence of incident *P. falciparum* infections from Month 2.5 up to Month 14 in group Fx012-14-mFxD and Control group.~~
  - ~~The occurrence of clinical malaria meeting the primary and secondary case definitions from Month 7.5 up to Month 19 in group Fx017-mFxD and Control group.~~
  - ~~The occurrence of incident *P. falciparum* infections from Month 7.5 up to Month 19 in group Fx017-mFxD and Control group.~~

- ~~The occurrence of clinical malaria meeting the primary and secondary case definition from Month 2.5 up to Month 14 in groups R012-20 + R012-14-mD and Control group.~~
- ~~The occurrence of incident *P. falciparum* infections from Month 2.5 up to Month 14 in groups R012-20 + R012-14-mD and Control group.~~

- **~~Efficacy: Timing of the fractional third dose~~**
  - ~~The occurrence of clinical malaria meeting the primary and secondary case definitions, from Month 7.5 up to Month 14 in group Fx017-mFxD and from Month 2.5 up to Month 9 in group Fx012-14-mFxD.~~
  - ~~The occurrence of incident *P. falciparum* infections, from Month 7.5 up to Month 14 in group Fx017-mFxD and from Month 2.5 up to Month 9 in group Fx012-14-mFxD.~~
  - ~~The occurrence of clinical malaria meeting the primary and secondary case definitions, from Month 7.5 up to Month 14 in group Fx017-mFxD and from Month 2.5 up to Month 9 in groups R012-20 + R012-14-mD.~~
  - ~~The occurrence of incident *P. falciparum* infections, from Month 7.5 up to Month 14 in group Fx017-mFxD and from Month 2.5 up to Month 9 in groups R012-20 + R012-14-mD.~~
  - ~~The occurrence of clinical malaria meeting the primary and secondary case definitions, from Month 7.5 up to Month 19 in group Fx017-mFxD and from Month 2.5 up to Month 14 in group Fx012-14-mFxD.~~
  - ~~The occurrence of incident *P. falciparum* infections, from Month 7.5 up to Month 19 in group Fx017-mFxD and from Month 2.5 up to Month 14 in group Fx012-14-mFxD.~~
  - ~~The occurrence of clinical malaria meeting the primary and secondary case definitions, from Month 7.5 up to Month 19 in group Fx017-mFxD and from Month 2.5 up to Month 14 in groups R012-20 + R012-14-mD.~~
  - ~~The occurrence of incident *P. falciparum* infections, from Month 7.5 up to Month 19 in group Fx017-mFxD and from Month 2.5 up to Month 14 in groups R012-20 + R012-14-mD.~~

- ~~**Efficacy: Incremental efficacy of fractional Dose 4, Dose 5 and Dose 6 versus full doses**~~

  - ~~The occurrence of clinical malaria meeting the primary and secondary case definitions, from Month 20 up to Month 32 in groups Fx017-mFxD and R012-20.~~

  - ~~The occurrence of incident *P. falciparum* infections, from Month 20 up to Month 32 in groups Fx017-mFxD and R012-20.~~

  - ~~The occurrence of clinical malaria meeting the primary and secondary case definitions, from Month 14 up to Month 26, from Month 26 up to Month 38 and from Month 38 up to Month 50 in groups Fx012-14-mFxD and R012-14-mD.~~

  - ~~The occurrence of incident *P. falciparum* infections, from Month 14 up to Month 26, from Month 26 up to Month 38 and from Month 38 up to Month 50 in groups Fx012-14-mFxD and R012-14-mD.~~

- ~~**Efficacy: Efficacy and impact of each RTS,S/AS01$_E$ schedule over the entire study period**~~

  - ~~The occurrence of clinical malaria meeting the primary and secondary case definitions from Day 0 up to Month 14, Day 0 up to Month 20, Day 0 up to Month 26, Day 0 up to Month 38 and Day 0 up to Month 50 in each group.~~

  - ~~The occurrence of incident *P. falciparum* infections from Day 0 up to Month 14, Day 0 up to Month 20, Day 0 up to Month 26, Day 0 up to Month 38 and Day 0 up to Month 50 in each group.~~

- ~~**Efficacy: Efficacy against prevalent *P. falciparum* infections**~~

- ~~The occurrence of prevalent *P. falciparum* infections at each cross sectional survey.~~

- **Immunogenicity: Immune response to the CS and HBs antigens *(immunogenicity subset)***
  - .....

- **Safety**

  - The occurrence of SAEs (all, fatal and related) ***during the whole study period*** ~~from Dose 1 (Day 0) up to Month 20 and from Day 0 up to Month 50~~ according to

the Medical Dictionary for Regulatory Activities (MedDRA) classification.

~~The occurrence of SAEs (all, fatal and related) within 30 days (day of vaccination and 29 subsequent days) after each dose of study vaccine, according to the MedDRA classification.~~

- The occurrence of AEs and SAEs leading to withdrawal from further vaccination from Dose 1 (Day 0) up to Month 50, according to the MedDRA classification.
- The occurrence of severe malaria cases and cerebral malaria cases ~~from Day 0 up to Month 20, Day 0 up to Month 50 and over successive years within the study~~***during the whole study period***.
- The occurrence of pIMDs from Day 0 ~~up to Month 20 and from Day 0~~ up to Month 50, according to the MedDRA classification.
- The occurrence of meningitis from Day 0 up to ~~Month 20 and from Day 0 up to~~ Month 50, according to the MedDRA classification.
- .....

- **Reactogenicity** ***(reactogenicity sub-cohort)***
  - The occurrence of solicited local and general AEs in a the first 50 subjects enrolled in each group ~~(reactogenicity sub-cohort)~~ within four days (day of vaccination and three subsequent days) after Dose 3 of study vaccine (all groups including controls), after Dose 4 (groups R012-20, R012-14-mD, Fx012-14-mFxD and Fx017-mFxD), after Dose 5 (groups R012-14-mD, Fx012-14-mFxD and Fx017-mFxD) and after Dose 6 (groups R012-14-mD and Fx012-14-mFxD).

1.2.3. Rationale for the use of a rabies vaccine as a comparator vaccine

.....

The efficacy of cell culture-derived rabies vaccines including human diploid cells vaccine (HDCV), purified Vero cell rabies vaccine (PVRV), purified chick embryo cells vaccine (PCECV), purified chick embryo cells vaccine (PHKCV) and purified duck embryo cells vaccine (PDEV) has been demonstrated [WHO, 20~~06~~***10***]. In this study, a PCECV (*Rabipur*) will be used as comparator vaccine.

.....

2.2. Secondary objectives

See synopsis for changes in secondary objectives.

3. STUDY DESIGN OVERVIEW

Figure 1 Study design: clinic visits

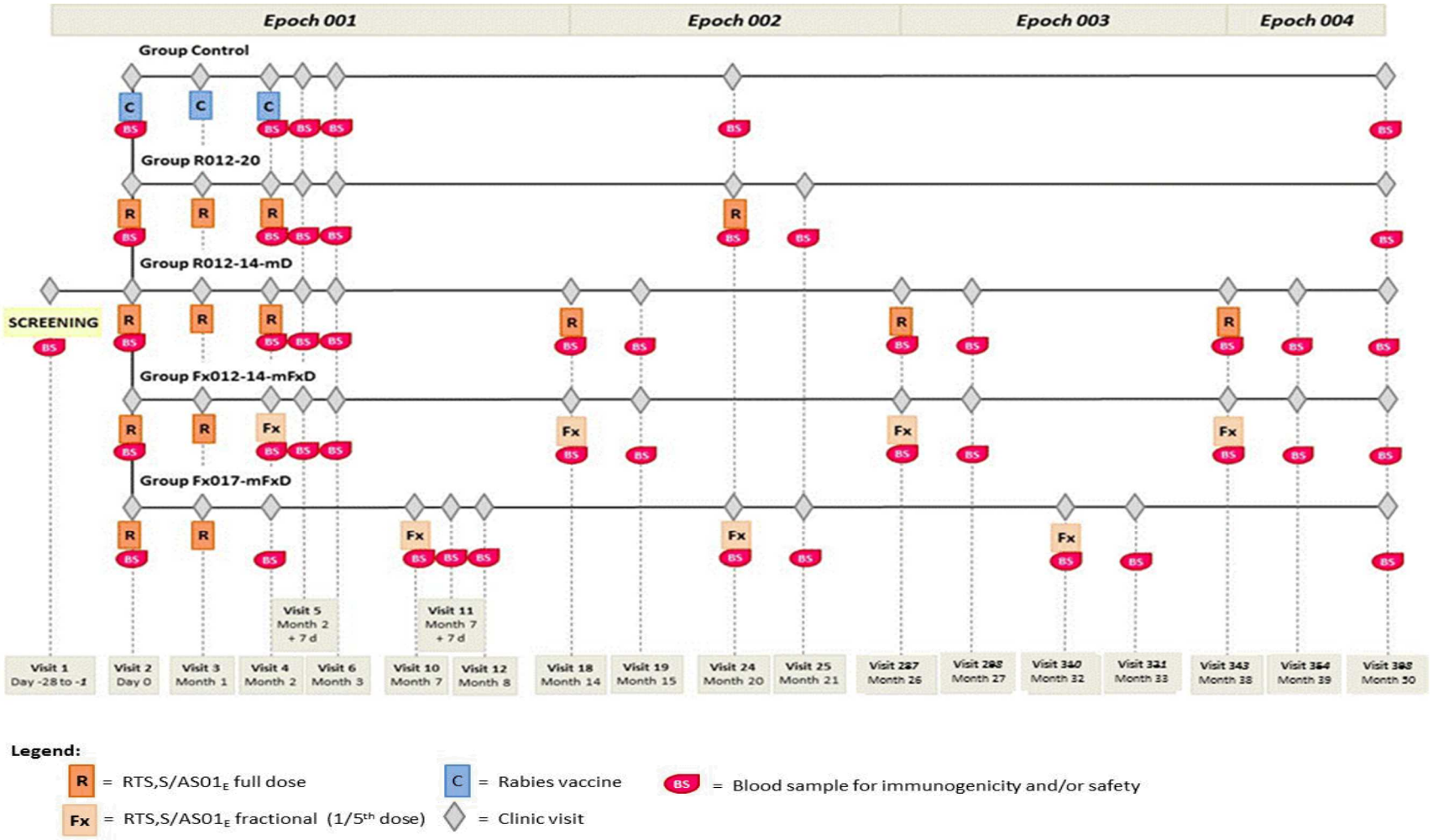


Figure 2 Study design: visits for assessment of parasite prevalence

Visits for parasite prevalence													
Year 1	Visit 2 Day 0	Visit 3 Month 1	Visit 4 Month 2	Visit 6 Month 3	Visit 7 Month 4	Visit 8 Month 5	Visit 9 Month 6	Visit 10 Month 7	Visit 12 Month 8	Visit 13 Month 9	Visit 14 Month 10	Visit 15 Month 11	Visit 16 Month 12
Year 2		Visit 17 Month 13	Visit 18 Month 14	Visit 19 Month 15	Visit 20 Month 16	Visit 21 Month 17	Visit 22 Month 18	Visit 23 Month 19	Visit 24 Month 20			Visit 2***6*** Month 23	
Year 3			Visit 2***7*** Month 26			Visit ***29*** Month 29			Visit 3***0*** Month 32			Visit 3***2*** Month 35	
Year 4			Visit 3***3*** Month 38			Visit 3***5*** Month 41			Visit 3***6*** Month 44			Visit 3***7*** Month 47	
Year 5			Visit 3***8*** Month 50										

- **.....**.

- **Duration of the study:** Approximately 50 months, with ~~an~~ ***two*** interim ~~analysis~~ ***analyses*** and option for conditional continuation (see next bullet point).

  – Epoch 001: Starting at Visit 1 (Screening) and ending at Visit 17 (Month 13). Note: the data up to Visit 18 (Month 14) pertains to Epoch 001.

  – Epoch 002: Starting at Visit 18 (Month 14) and ending at Visit 2~~7~~***6*** (Month 23). Note: the data up to Visit 2~~8~~***7*** (Month 26) pertains to Epoch 002.

  – Epoch 003: Starting at Visit 2~~8~~***7*** (Month 26) and ending at Visit 3~~3~~***2*** (Month 35). Note: the data up to Visit 3***4*** (Month 38) pertains to Epoch 003.

  – Epoch 004: Starting at Visit 3***4*** (Month 38) and ending at Visit 3~~9~~***8*** (Month 50).

- **Sequence of analyses and conditional continuation:**

  – A first analysis will be performed on data collected up to Month 21 (Visit 25) to evaluate the primary objective and relevant secondary objectives.

  – ***A second analysis will be performed on data collected up to Month 33 (Visit 31) to evaluate relevant secondary objectives.***

  – A ~~second~~ ***final*** analysis will be performed at study end (Month 50) on data collected up to Month 50. An integrated study report presenting all results until Month 50 will be produced.

After the ***interim***~~first analysis~~***analyses***, the Independent Data Monitoring Committee (IDMC) will have the possibility to recommend the suspension of further vaccinations and termination of specific study group(s) upon consideration of the study results. In the event that the IDMC recommend the suspension of further vaccinations, the group(s) impacted will be followed up for 12 months after their last study vaccination.

- **Sampling schedule:**

  – .....

  – In addition to the blood samples listed in Table 5, a small amount of blood (for blood smear and filter paper) will be taken every month from Day 0 until Month ~~23~~ ***20*** and ~~then~~ ***thereafter*** every three months ~~from Month 23~~ until Month 50 in all subjects for the evaluation of *P. falciparum* infections (see Section 6.7.4.2).

  – .....

Table 5 Blood sampling timepoints

		Visit 1	Visit 2	Visit 4	Visit 5	Visit 6	Visit 10	Visit 11	Visit 12	Visit 18	Visit 19	Visit 24	Visit 25	Visit 287	Visit 298	Visit 310	Visit 321	Visit 343	Visit 354	Visit 398
Study group	**Type of blood sampling**	**Scr**	**D0**	**M2**	**M2 + 7d**	**M3**	**M7**	**M7 + 7d**	**M8**	**M14**	**M15**	**M20**	**M21**	**M26**	**M27**	**M32**	**M33**	**M38**	**M39**	**M50**
R012-20	Safety	x*		x**	x**	x**														
	Immunogenicity§		x	x		x						x	x							x
R012-14-mD	Safety	x*		x**	x**	x**														
	Immunogenicity§		x	x		x				x	x			x	x			x	x	x
Fx012-14-mFxD	Safety	x*		x**	x**	x**														
	Immunogenicity§		x	x		x				x	x			x	x			x	x	x
Fx017-mFxD	Safety	x*					x**	x**	x**											
	Immunogenicity§		x	x			x		x			x	x			x	x			x
Control	Safety	x*		x**	x**	x**														
	Immunogenicity§		x	x		x						x								x

* At screening, hemoglobin will be assessed in all subjects screened.
** Blood samples for hematology and biochemistry will be taken in a sub-cohort consisting of the first 50 subjects enrolled in each group.
§ Blood samples for immunogenicity will be taken in all subjects enrolled.
Scr: Screening
M: Month
D: Day

- **Efficacy surveillance:**
  - .....
  - Cross-sectional surveys: to evaluate the vaccine efficacy against incident and prevalent *P. falciparum* infections, monthly cross-sectional surveys will be performed from Day 0 until Month ~~23~~ ***20*** to measure *P. falciparum* parasitemia. ~~From Month 23~~ ***Thereafter*** until study end (Month 50) parasitemia will be measured every three months. Blood slides from cross-sectional surveys will not be read in real time.
  - .....
- **Safety monitoring:**
  - .....
  - ***Where possible autopsies will be performed.*** Verbal autopsy will be performed on all cases of mortality occurring outside hospital ***if autopsies cannot be performed.***

4.2. Case definitions of *P. falciparum* infection

Table 7 Case definition of incident *P. falciparum* infection*

Case definition 1	A documented *P. falciparum* asexual parasite density > 0 detected by blood slide reading at a cross-sectional survey or as captured by the secondary case definition of clinical malaria (active ***detection of infection*** and passive ***case*** detection~~ of infection~~).

***Note, the incidence of *P. falciparum* infection defined by positive PCR and parasite genotyping will be evaluated in the context of an ancillary study, using samples collected as described in the present protocol (see Section 6.7.4.2).

6.2.3. Allocation of subjects to assay subsets

Blood samples for immunogenicity will be taken in all subjects at timepoints described in Table 5. Not all samples will be used for testing:

- Anti-CS and anti-HBs immune responses will be tested in a subset ***which includes***~~ing~~ ***the same subjects as in the reactogenicity sub-cohort***~~corresponding to~~ ***(***the first 50 subjects enrolled in each group***)***.
- .....

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

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

Subjects should continue with their routine EPI immunizations as applicable to their age whilst participating in the study.

Clinical malaria episodes are detected by PCD and treatment will be guided by rapid diagnostic test (RDT)/clinical evaluation at the discretion of the investigator. Blood slides will also be collected, however, these will not be read in real time but sent to a central laboratory (see Table 17) where all blood samples will be read according to a standardized method. Case definitions of clinical malaria will be based on final parasite density obtained from this process.

Malaria infections will be detected through active detection of infections through cross-sectional blood sampling. Blood slides obtained will not be read in real time and will follow the same process as described above. As a result, non-febrile parasite positive children with no symptoms will not be treated for malaria at the time of cross-sectional visits.

6.5. Outline of study procedures

Table 11 List of study procedures for clinic visits

Epoch	Epoch 001									Epoch 002				Epoch 003				Epoch 004		
Type of contact: Clinic visits	Visit 1[m] Screening	Visit 2	Visit 3	Visit 4	Visit 5[a]	Visit 6[a]	Visit 10[b]	Visit 11[b]	Visit 12[b]	Visit 18[c]	Visit 19[c]	Visit 24[d]	Visit 25[e]	Visit 287[c]	Visit 298[c]	Visit 310[f]	Visit 321[f]	Visit 343[c]	Visit 354[c]	Visit 398
Timepoints	D-28 to D-1	D0	M1	M2	M2 + 7d	M3	M7	M7 + 7d	M8	M14	M15	M20	M21	M26	M27	M32	M33	M38	M39	M50
Children age (Months)		5-17 m																		
Control group																				
Informed consent	●																			
Check inclusion/exclusion criteria	●	O																		
Check the subject's vaccination card	O																			
Check screening lab results (hemoglobin)	●[g]																			
Collect demographic data	●																			
Check medical history	●																			
Physical examination	●	O	O	O	O	O						O								O
Measure and record length and weight	●																			
Issue subject's identification card		O																		
Check subject's identification card			O	O	O	O						O								O
Randomization		●																		
Distribute ITN	O																			
Record if the subject belongs to the reactogenicity sub-cohort		●																		
Check contraindications and warnings and precautions		●[h]	●[h]	●[h]																
Record pre-vaccination body temperature		●	●	●																
Treatment number allocation		O	O	O																
Administer study vaccine		●	●	●																
Recording of administered treatment number		●	●	●																
Blood sampling for assessment of immunogenicity for ALL subjects (2.5 ml)		●		●		●						●								●

Epoch	Epoch 001									Epoch 002				Epoch 003				Epoch 004		
Type of contact: Clinic visits	Visit 1[m] Screening	Visit 2	Visit 3	Visit 4	Visit 5[a]	Visit 6[a]	Visit 10[b]	Visit 11[b]	Visit 12[b]	Visit 18[c]	Visit 19[c]	Visit 24[d]	Visit 25[e]	Visit ~~28~~ 27[c]	Visit ~~29~~ 28[c]	Visit ~~31~~ 0[f]	Visit ~~32~~ 1[f]	Visit ~~34~~ 3[c]	Visit ~~35~~ 4[c]	Visit ~~39~~ 8
Timepoints	D-28 to D-1	D0	M1	M2	M2 + 7d	M3	M7	M7 + 7d	M8	M14	M15	M20	M21	M26	M27	M32	M33	M38	M39	M50
Children age (Months)		5-17 m																		
Blood sampling for assessment of hemoglobin at screening (0.5 ml)	●[i]																			
Blood sampling for assessment of parasitemia for ALL subjects (0.5 ml) [n,o]		●	●	●		●						●								●
Record any concomitant medications/vaccinations		●	●	●	●	●						●								●
Record any intercurrent medical conditions		●	●	●	●	●						●								●
Record unsolicited AEs (Days 0-29)		●[k]	●[k]	●[k]	●[k]	●[k]														
Record AEs/SAEs leading to withdrawal from further vaccination		●	●	●	●	●						●								●
Record SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●						●								●
Record SAEs (All, fatal, related to the investigational vaccine) [p]		●	●	●	●	●						●								●
Record AEs of specific interest [l]		●	●	●	●	●						●								●
Study Conclusion																				●
For the reactogenicity sub-cohort only:																				
Blood sampling for assessment of safety (1.0 ml)				●	●	●														
Record solicited local and general AEs (Days 0-3)				●[j]																
Group R012-20																				
Informed consent	●																			
Check inclusion/exclusion criteria	●	O																		
Check the subject's vaccination card	O																			
Check screening lab results (hemoglobin)	●[g]																			
Collect demographic data	●																			
Check medical history	●																			
Physical examination	●	O	O	O	O	O						O	O							O
Measure and record length and weight	●																			

Epoch	Epoch 001									Epoch 002				Epoch 003				Epoch 004		
Type of contact: Clinic visits	Visit 1[m] Screening	Visit 2	Visit 3	Visit 4	Visit 5[a]	Visit 6[a]	Visit 10[b]	Visit 11[b]	Visit 12[b]	Visit 18[c]	Visit 19[c]	Visit 24[d]	Visit 25[e]	Visit 2~~8~~7[c]	Visit 2~~9~~8[c]	Visit 3~~1~~0[f]	Visit 3~~2~~1[f]	Visit 3~~4~~3[c]	Visit 3~~5~~4[c]	Visit 3~~9~~8[c]
Timepoints	D-28 to D-1	D0	M1	M2	M2 + 7d	M3	M7	M7 + 7d	M8	M14	M15	M20	M21	M26	M27	M32	M33	M38	M39	M50
Children age (Months)		5-17 m																		
Issue subject's identification card		O																		
Check subject's identification card			O	O	O	O						O	O							O
Randomization		●																		
Distribute ITN	O																			
Record if the subject belongs to the reactogenicity sub-cohort		●																		
Check contraindications and warnings and precautions		●[h]	●[h]	●[h]								●[h]								
Record pre-vaccination body temperature		●	●	●								●								
Treatment number allocation		O	O	O								O								
Administer study vaccine		●	●	●								●								
Recording of administered treatment number		●	●	●								●								
Blood sampling for assessment of immunogenicity for ALL subjects (2.5 ml)		●		●		●						●	●							●
Blood sampling for assessment of hemoglobin at screening (0.5 ml)	●[i]																			
Blood sampling for assessment of parasitemia for ALL subjects (0.5 ml) [n, o]		●	●	●		●						●	●							●
Record any concomitant medications/vaccinations		●	●	●	●	●						●	●							●
Record any intercurrent medical conditions		●	●	●	●	●						●	●							●
Record unsolicited AEs (Days 0-29)		●[k]	●[k]	●[k]	●[k]	●[k]						●[k]	●[k]							
Record AEs/SAEs leading to withdrawal from further vaccination		●	●	●	●	●						●	●							●
Record SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●						●	●							●
Record SAEs (All, fatal, related to the investigational vaccine) [p]		●	●	●	●	●						●	●							●
Record AEs of specific interest [l]		●	●	●	●	●						●	●							●
Study Conclusion																				●

Epoch	Epoch 001									Epoch 002				Epoch 003				Epoch 004		
Type of contact: Clinic visits	Visit 1[m] Screening	Visit 2	Visit 3	Visit 4	Visit 5[a]	Visit 6[a]	Visit 10[b]	Visit 11[b]	Visit 12[b]	Visit 18[c]	Visit 19[c]	Visit 24[d]	Visit 25[e]	Visit ~~28~~ 27[c]	Visit ~~29~~ 28[c]	Visit ~~31~~ 0[f]	Visit ~~32~~ 1[f]	Visit ~~34~~ 3[c]	Visit ~~35~~ 4[c]	Visit ~~39~~ 8
Timepoints	D-28 to D-1	D0	M1	M2	M2 + 7d	M3	M7	M7 + 7d	M8	M14	M15	M20	M21	M26	M27	M32	M33	M38	M39	M50
Children age (Months)		5-17 m																		
For the reactogenicity sub-cohort only:																				
Blood sampling for assessment of safety (1.0 ml)				●	●	●														
Record solicited local and general AEs (Days 0-3)				●[j]								●[j]								
Groups R012-14-mD and Fx012-14-mFxD																				
Informed consent	●																			
Check inclusion/exclusion criteria	●	O																		
Check the subject's vaccination card	O																			
Check screening lab results (hemoglobin)	●[g]																			
Collect demographic data	●																			
Check medical history	●																			
Physical examination	●	O	O	O	O	O				O	O			O	O			O	O	O
Measure and record length and weight	●																			
Issue subject's identification card		O																		
Check subject's identification card			O	O	O	O				O	O			O	O			O	O	O
Randomization		●																		
Distribute ITN	O																			
Record if the subject belongs to the reactogenicity sub-cohort		●																		
Check contraindications and warnings and precautions		●[h]	●[h]	●[h]						●[h]				●[h]				●[h]		
Record pre-vaccination body temperature		●	●	●						●				●				●		
Treatment number allocation		O	O	O						O				O				O		
Administer study vaccine		●	●	●						●				●				●		
Recording of administered treatment number		●	●	●						●				●				●		
Blood sampling for assessment of immunogenicity for ALL subjects (2.5 ml)		●		●		●				●	●			●	●			●	●	●

Epoch	Epoch 001									Epoch 002				Epoch 003				Epoch 004		
Type of contact: Clinic visits	**Visit 1[m] Screening**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5[a]**	**Visit 6[a]**	**Visit 10[b]**	**Visit 11[b]**	**Visit 12[b]**	**Visit 18[c]**	**Visit 19[c]**	**Visit 24[d]**	**Visit 25[e]**	**Visit ~~28~~ 27[c]**	**Visit ~~29~~ 28[c]**	**Visit ~~31~~ 0[f]**	**Visit ~~32~~ 1[f]**	**Visit ~~34~~ 3[c]**	**Visit ~~35~~ 4[c]**	**Visit ~~39~~ 8**
Timepoints	**D-28 to D-1**	**D0**	**M1**	**M2**	**M2 + 7d**	**M3**	**M7**	**M7 + 7d**	**M8**	**M14**	**M15**	**M20**	**M21**	**M26**	**M27**	**M32**	**M33**	**M38**	**M39**	**M50**
Children age (Months)		**5-17 m**																		
Blood sampling for assessment of hemoglobin at screening (0.5 ml)	●[i]																			
Blood sampling for assessment of parasitemia for ALL subjects (0.5 ml) [n, 0]		●	●	●		●				●	●			●				●		●
Record any concomitant medications/vaccinations		●	●	●	●	●				●	●			●	●			●	●	●
Record any intercurrent medical conditions		●	●	●	●	●				●	●			●	●			●	●	●
Record unsolicited AEs (Days 0-29)		●[k]	●[k]	●[k]	●[k]	●[k]				●[k]	●[k]			●[k]	●[k]			●[k]	●[k]	
Record AEs/SAEs leading to withdrawal from further vaccination		●	●	●	●	●				●	●			●	●			●	●	●
Record SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	●				●	●			●	●			●	●	●
Record SAEs (All, fatal, related to the investigational vaccine) [p]		●	●	●	●	●				●	●			●	●			●	●	●
Record AEs of specific interest [l]		●	●	●	●	●				●	●			●	●			●	●	●
Study Conclusion																				●
For the reactogenicity sub-cohort only:																				
Blood sampling for assessment of safety (1.0 ml)				●	●	●														
Record solicited local and general AEs (Days 0-3)				●[j]						●[j]				●[j]				●[j]		
Group Fx017-mFxD																				
Informed consent	●																			
Check inclusion/exclusion criteria	●	O																		
Check the subject's vaccination card	O																			
Check screening lab results (hemoglobin)	●[g]																			
Collect demographic data	●																			
Check medical history	●																			
Physical examination	●	O	O	O			O	O	O			O	O			O	O			O
Measure and record length and weight	●																			

Epoch	Epoch 001									Epoch 002				Epoch 003				Epoch 004		
Type of contact: Clinic visits	Visit 1[m] Screening	Visit 2	Visit 3	Visit 4	Visit 5[a]	Visit 6[a]	Visit 10[b]	Visit 11[b]	Visit 12[b]	Visit 18[c]	Visit 19[c]	Visit 24[d]	Visit 25[e]	Visit ~~28~~7[c]	Visit ~~29~~8[c]	Visit ~~31~~0[f]	Visit ~~32~~1[f]	Visit ~~34~~3[c]	Visit ~~35~~4[c]	Visit ~~39~~8
Timepoints	D-28 to D-1	D0	M1	M2	M2 + 7d	M3	M7	M7 + 7d	M8	M14	M15	M20	M21	M26	M27	M32	M33	M38	M39	M50
Children age (Months)		5-17 m																		
Issue subject's identification card		O																		
Check subject's identification card			O	O			O	O	O			O	O			O	O			O
Randomization		●																		
Distribute ITN	O																			
Record if the subject belongs to the reactogenicity sub-cohort		●																		
Check contraindications and warnings and precautions		●[h]	●[h]				●[h]					●[h]				●[h]				
Record pre-vaccination body temperature		●	●				●					●				●				
Treatment number allocation		O	O				O					O				O				
Administer study vaccine		●	●				●					●				●				
Recording of administered treatment number		●	●				●					●				●				
Blood sampling for assessment of immunogenicity for ALL subjects (2.5 ml)		●		●			●		●			●	●			●	●			●
Blood sampling for assessment of hemoglobin at screening (0.5 ml)	●[i]																			
Blood sampling for assessment of parasitemia for ALL subjects (0.5 ml) [n, o]		●	●	●			●		●			●	●			●				●
Record any concomitant medications/vaccinations		●	●	●			●	●	●			●	●			●	●			●
Record any intercurrent medical conditions		●	●	●			●	●	●			●	●			●	●			●
Record unsolicited AEs (Days 0-29)		●[k]	●[k]	●[k]			●[k]	●[k]	●[k]			●[k]	●[k]			●[k]	●[k]			
Record AEs/SAEs leading to withdrawal from further vaccination		●	●	●			●	●	●			●	●			●	●			●
Record SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●			●	●	●			●	●			●	●			●
Record SAEs (All, fatal, related to the investigational vaccine) [p]		●	●	●			●	●	●			●	●			●	●			●
Record AEs of specific interest [l]		●	●	●			●	●	●			●	●			●	●			●
Study Conclusion																				●

Epoch	Epoch 001									Epoch 002				Epoch 003				Epoch 004		
Type of contact: Clinic visits	**Visit 1[m] Screening**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5[a]**	**Visit 6[a]**	**Visit 10[b]**	**Visit 11[b]**	**Visit 12[b]**	**Visit 18[c]**	**Visit 19[c]**	**Visit 24[d]**	**Visit 25[e]**	**Visit 2~~8~~7[c]**	**Visit 2~~9~~8[c]**	**Visit 3~~1~~0[f]**	**Visit 3~~2~~1[f]**	**Visit 3~~3~~4[c]**	**Visit 3~~5~~4[c]**	**Visit 3~~9~~8**
Timepoints	**D-28 to D-1**	**D0**	**M1**	**M2**	**M2 + 7d**	**M3**	**M7**	**M7 + 7d**	**M8**	**M14**	**M15**	**M20**	**M21**	**M26**	**M27**	**M32**	**M33**	**M38**	**M39**	**M50**
Children age (Months)		**5-17 m**																		
For the reactogenicity sub-cohort only:																				
Blood sampling for assessment of safety (1.0 ml)							●	●	●											
Record solicited local and general AEs (Days 0-3)							● j					● j				● j				

Note: The double-line border following Month 21 (Visit 25) ***and Month 33 (Visit 31)*** indicates the ***two interim*** ~~first~~ analys~~e~~is which will be performed on all data collected up to ***respectively*** Month 21 ***and up to Month 33*** (i.e. data that are as clean as possible***, except clinical malaria fully cleaned up to Month 14***). The final analysis will be performed on ***fully cleaned*** data collected up to study end (Month 50).

D: Day, M: Month.

● is used to indicate a study procedure that requires documentation in the individual eCRF.

O is used to indicate a study procedure that does not require documentation in the individual eCRF.

a. Clinic visit 5 (Month 2 + 7 days) and clinic visit 6 (Month 3) are only for groups R012-20, R012-14-mD, Fx012-14-mFxD and Control. The group FX017-mFXD has a field worker visit at Month 3 for assessment of parasitemia.
b. Clinic visit 10 (Month 7), clinic visit 11 (Month 7 + 7 days) and clinic visit 12 (Month 8) are only for group Fx017-mFxD. The other groups have field worker visits at Month 7 and Month 8 respectively for assessment of parasitemia.
c. Clinic visit 18 (Month 14), clinic visit 19 (Month 15), clinic visit 2~~8~~***7*** (Month 26), clinic visit 2~~9~~***8*** (Month 27), clinic visit 3~~4~~***3*** (Month 38) and clinic visit 3~~5~~***4*** (Month 39) are only for groups R012-14-mD and Fx012-14-mFxD. The other groups have field worker visits at Month 14, Month 15, Month 26 and Month 38 respectively for assessment of parasitemia.
d. Clinic visit 24 (Month 20) is only for groups R012-20, Fx017-mFxD and Control. The other groups have a field worker visit at Month 20 for assessment of parasitemia.
e. Clinic visit 25 (Month 21) is only for groups R012-20 and Fx017-mFxD. ~~The other groups have a field worker visit at Month 21 for assessment of parasitemia.~~
f. Clinic visit 3~~1~~***0*** (Month 32) and clinic visit 3~~2~~***1*** (Month 33) are only for group Fx017-mFxD. The other groups have a field worker visit at Month 32 for assessment of parasitemia.
g. The screening laboratory results (hemoglobin) must be checked during the screening activities and before randomization.
h. There is no specific section in the eCRF to record the contraindications, warnings and precautions. The absolute contraindications to further administration of study vaccines have to be recorded in the AE or SAE section of the eCRF.
i. At screening, hemoglobin will be assessed in all subjects screened.
j. Solicited local and general AEs will be collected in the first 50 subjects enrolled in each group (reactogenicity sub-cohort) during four days (day of vaccination and three subsequent days) after vaccination as indicated in the table above. On the day of vaccination the evaluation will be carried out by the study physician at the study center. On Days 1, 2 and 3 after vaccination, trained study personnel will visit the children to record solicited AEs on diary cards.
k. Unsolicited AEs will be collected during 30 days (day of vaccination and 29 subsequent days) after each dose of study vaccine. Unsolicited AEs will be captured through passive surveillance at inpatient and outpatient facilities and during study visits.

l. AEs of specific interest include all seizures occurring within 30 days post-vaccination, meningitis and pIMDs (see Section 9.1.6). pIMDs will be reported via the electronic Expedited Adverse Events Report. Meningitis and seizures will be reported via the electronic Expedited Adverse Events Report and in addition clinical details of each case will be reported in a specific eCRF screen.

m. If a subject is considered momentarily ineligible on the day of the screening visit (i.e. failing to meet one or more eligibility criteria) procedures for screening can be repeated one further time, within the time window allowed for screening (see Table 14). No more than one repeat is allowed.

n. Blood for parasitemia (0.5 ml) includes the blood for the slide reading and for the filter paper. The parasitemia assessment by blood slide reading will include blood-stage parasites and gametocytes counts.

o. In addition to the scheduled clinic visits, malaria cases will be captured by PCD throughout the study. All sick children presenting with fever and/or history of fever will have a blood sample taken for the evaluation of vaccine efficacy (for blood slide and filter paper for PCR).

p. Case of severe malaria or cerebral malaria will be reported via the electronic Expedited Adverse Events Report (refer to Section 9.3.1) and in addition clinical details of each case will be reported in a specific eCRF screen.

Table 13 List of study procedures for field worker visits - Part 2 (Month 20 to Month 50)

Epochs	**Epoch 002**							**Epoch 003**											**Epoch 004**						
Type of contact: Field worker visits	**Visit 24**	Visit j*	Visit k*	Visit l*	**Visit 25**	~~**Visit 26**~~	~~**Visit 27**~~ **6**	**Visit 28**~~**7**~~	Visit m*	Visit n*	Visit o*	**Visit 29**~~**8**~~	**Visit 30**~~**29**~~	**Visit 31**~~**0**~~	Visit p*	Visit q*	Visit r*	**Visit 33**~~**2**~~	**Visit 34**~~**3**~~	Visit s*	Visit t*	Visit u*	**Visit 36**~~**5**~~	**Visit 37**~~**6**~~	**Visit 38**~~**7**~~
Timepoints	**M20**	M20 + 1d	M20 + 2d	M20 + 3d	**M21**	~~**M22**~~	**M23**	**M26**	M26 + 1d	M26 + 2d	M26 + 3d	**M27**	**M29**	**M32**	M32 + 1d	M32 + 2d	M32 + 3d	**M35**	**M38**	M38 + 1d	M38 + 2d	M38 + 3d	**M41**	**M44**	**M47**
Control group																									
Check subject's identification card					O	~~O~~	O	O					O	O				O	O				O	O	O
Blood sampling for assessment of parasitemia for ALL subjects (0.5 ml) †, §	●				~~●~~	~~●~~	●	●					●	●				●	●				●	●	●
For the reactogenicity sub-cohort only: Record solicited local and general AEs (Days 0-3)																									
Group R012-20																									
Check subject's identification card		O	O	O		~~O~~	O	O					O	O				O	O				O	O	O
Blood sampling for assessment of parasitemia for ALL subjects (0.5 ml) †, §	●					~~●~~	●	●					●	●				●	●				●	●	●
For the reactogenicity sub-cohort only: Record solicited local and general AEs (Days 0-3)		●	●	●																					

Epochs	Epoch 002							Epoch 003											Epoch 004						
Type of contact: Field worker visits	**Visit 24**	Visit j*	Visit k*	Visit l*	**Visit 25**	~~**Visit 26**~~	**Visit ~~27~~6**	**Visit ~~28~~7**	Visit m*	Visit n*	Visit o*	**Visit ~~29~~8**	**Visit ~~30~~29**	**Visit ~~31~~0**	Visit p*	Visit q*	Visit r*	**Visit ~~32~~2**	**Visit ~~34~~3**	Visit s*	Visit t*	Visit u*	**Visit ~~36~~5**	**Visit ~~37~~6**	**Visit ~~38~~7**
Timepoints	**M20**	M20 + 1d	M20 + 2d	M20 + 3d	**M21**	~~**M22**~~	**M23**	**M26**	M26 + 1d	M26 + 2d	M26 + 3d	**M27**	**M29**	**M32**	M32 + 1d	M32 + 2d	M32 + 3d	**M35**	**M38**	M38 + 1d	M38 + 2d	M38 + 3d	**M41**	**M44**	**M47**
Groups R012-14-mD and Fx012-14-mFxD																									
Check subject's identification card	O				O	~~O~~	O		O	O	O		O	O				O		O	O	O	O	O	O
Blood sampling for assessment of parasitemia for ALL subjects (0.5 ml) †, §	●				~~●~~	~~●~~	●						●	●				●					●	●	●
For the reactogenicity sub-cohort only: Record solicited local and general AEs (Days 0-3)									●	●	●									●	●	●			
Group Fx017-mFxD																									
Check subject's identification card		O	O	O		~~O~~	O	O					O		O	O	O	O	O				O	O	O
Blood sampling for assessment of parasitemia for ALL subjects (0.5 ml) †, §	●					~~●~~	●	●					●					●	●				●	●	●
For the reactogenicity sub-cohort only: Record solicited local and general AEs (Days 0-3)		●	●	●											●	●	●								

M: Month, d: day.

● is used to indicate a study procedure that requires documentation in the individual eCRF.

O is used to indicate a study procedure that does not require documentation in the individual eCRF.

* Visits a-u are restricted to the subjects in the reactogenicity sub-cohort; these visits are for the recording of solicited local and general AEs in the three days following each vaccination.

† Blood for parasitemia (0.5 ml) includes the blood for the slide reading and for the filter paper. The parasitemia assessment by blood slide reading will include blood-stage parasites and gametocytes counts.

§ In addition to the scheduled clinic visits, malaria cases will be captured by PCD throughout the study. All sick children presenting with fever and/or history of fever will have a blood sample taken for the evaluation of vaccine efficacy (for blood slide and filter paper for PCR).

Table 14 Intervals between study visits

Interval	Optimal length of interval [1]	Allowed interval[2]
Visit 1→Visit 2 (Vacc)	0 to 28 days	0 - 28 days
Visit 2→Visit 3 (Vacc)	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 3→Visit 4 (Vacc)	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 4→Visit 5	7 days	Minimum 6 days - Maximum 8 days
Visit 4→Visit 6	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 6→Visit 7	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 7→Visit 8	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 8→Visit 9	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 3→Visit 10 (Vacc)	6 months	Minimum 161 days (23 weeks) - Maximum 203 days (29 weeks)
Visit 10→Visit 11	7 days	Minimum 6 days - Maximum 8 days
Visit 10→Visit 12	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 12→Visit 13	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 13→Visit 14	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 14→Visit 15	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 15→Visit 16	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 16→Visit 17	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 4→Visit 18 (Vacc)	12 months	Minimum 336 days (48 weeks) - Maximum 392 days (56 weeks)
Visit 18→Visit 19	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 19→Visit 20	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 20→Visit 21	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 21→Visit 22	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 22→Visit 23	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 4→Visit 24 (Vacc)*	18 months	Minimum 518 days (74 weeks) - Maximum 574 days (82 weeks)
Visit 10→Visit 24 (Vacc)**	13 months	Minimum 364 days (52 weeks) - Maximum420 days (60 weeks)
Visit 24→Visit 25	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 25~~4~~→Visit 26	~~1~~***3*** month***s***	Minimum ~~21~~***77*** days (~~3~~***11*** weeks***) -*** Maximum ~~35~~***105*** days (~~5~~***15*** weeks)
~~Visit 26→Visit 27~~	~~1 month~~	~~Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)~~
Visit 18→Visit 2~~8~~***7*** (Vacc)	12 months	Minimum 336 days (48 weeks) - Maximum 392 days (56 weeks)
Visit 2~~8~~***7***→Visit 2~~9~~***8***	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 2~~8~~***7***→Visit ~~30~~***29***	3 months	Minimum 77 days (11 weeks) - Maximum 105 days (15 weeks)
Visit 24→Visit 3~~1~~***0*** (Vacc)	12 months	Minimum 336 days (48 weeks) - Maximum 392 days (56 weeks)
Visit 3~~1~~***0***→Visit 3~~2~~***1***	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 3~~1~~***0***→Visit 3~~3~~***2***	3 months	Minimum 77 days (11 weeks) - Maximum 105 days (15 weeks)
Visit 2~~8~~***7***→Visit 3~~4~~***3*** (Vacc)	12 months	Minimum 336 days (48 weeks) - Maximum 392 days (56 weeks)
Visit 3~~4~~***3***→Visit 3~~5~~***4***	1 month	Minimum 21 days (3 weeks) - Maximum 35 days (5 weeks)
Visit 3~~4~~***3***→Visit 3~~6~~***5***	3 months	Minimum 77 days (11 weeks) - Maximum 105 days (15 weeks)
Visit 3~~6~~***5***→Visit 3~~7~~***6***	3 months	Minimum 77 days (11 weeks) - Maximum 105 days (15 weeks)
Visit 3~~7~~***6***→Visit 3~~8~~***7***	3 months	Minimum 77 days (11 weeks) - Maximum 105 days (15 weeks)
Visit 3~~8~~***7***→Visit 3~~9~~***8***	3 months	Minimum 77 days (11 weeks) - Maximum 105 days (15 weeks)

[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) cohorts if they make the study visit outside this interval: to be included in the ATP cohort for efficacy, subjects should receive all vaccinations within the protocol specified intervals; to be included in the ATP cohort for immunogenicity, subjects should receive all vaccinations within the protocol specified intervals and perform all blood samplings for immunogenicity within the protocol specified intervals.

* Interval between Visit 4 and Visit 24 is for groups Control and R012-20.

** Interval between Visit 10 and Visit 24 is for group Fx017-mFxD.

Vacc: vaccination in at least one group.

6.6.19. Recording of unsolicited AEs, SAEs and AEs of specific interest

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Where possible autopsies will be performed. Verbal autopsy will be performed on all cases of mortality occurring outside hospital ***if it is not possible to perform the autopsies*** (Refer to Section 9.2.3.6).

6.7.2. Biological samples

Table 15 Biological samples (whole blood)

Timepoint	Assessment	Total volume of blood per visit (ml)				
		R012-20	R012-14-mD	Fx012-14-mFxD	Fx017-mFxD	Control
Visit 1 (Screening)	Safety (hemoglobin)†	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 2 (Day 0)	Immunogenicity	2.5 ml	2.5 ml	2.5 ml	2.5 ml l	2.5 ml
	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**3.0 ml**	**3.0 ml**	**3.0 ml**	**3.0 ml**	**3.0 ml**
Visit 3 (Month 1)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 4 (Month 2)	Safety*	1.0 ml*	1.0 ml*	1.0 ml*	-	1.0 ml*
	Immunogenicity	2.5 ml	2.5 ml	2.5 ml	2.5 ml	2.5 ml
	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**4.0 or 3.0 ml****	**4.0 or 3.0 ml****	**4.0 or 3.0 ml****	**3.0 ml**	**4.0 or 3.0 ml****
Visit 5 (Month 2 + 7d)	Safety*	1.0 ml*	1.0 ml*	1.0 ml*	-	1.0 ml*
Visit 6 (Month 3)	Safety*	1.0 ml*	1.0 ml*	1.0 ml*	-	1.0 ml*
	Immunogenicity	2.5 ml	2.5 ml	2.5 ml	-	2.5 ml
	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**4.0 or 3.0 ml****	**4.0 or 3.0 ml****	**4.0 or 3.0 ml****	**0.5 ml**	**4.0 or 3.0 ml****
Visit 7 (Month 4)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 8 (Month 5)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 9 (Month 6)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 10 (Month 7)	Safety*	-	-	-	1.0 ml*	-
	Immunogenicity	-	-	-	2.5 ml	-
	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**0.5 ml**	**0.5 ml**	**0.5 ml**	**4.0 or 3.0 ml****	**0.5 ml**
Visit 11 (Month 7 + 7d)	Safety*	-	-	-	1.0 ml*	-
Visit 12 (Month 8)	Safety*	-	-	-	1.0 ml*	-
	Immunogenicity	-	-	-	2.5 ml	-
	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**0.5 ml**	**0.5 ml**	**0.5 ml**	**4.0 or 3.0 ml****	**0.5 ml**
Visit 13 (Month 9)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 14 (Month 10)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 15 (Month 11)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 16 (Month 12)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 17 (Month 13)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 18 (Month 14)	Immunogenicity	-	2.5 ml	2.5 ml	-	-
	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**0.5 ml**	**3.0 ml**	**3.0 ml**	**0.5 ml**	**0.5 ml**

Timepoint	Assessment	Total volume of blood per visit (ml)				
		R012-20	R012-14-mD	Fx012-14-mFxD	Fx017-mFxD	Control
Visit 19 (Month 15)	Immunogenicity	-	2.5 ml	2.5 ml	-	-
	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**0.5 ml**	**3.0 ml**	**3.0 ml**	**0.5 ml**	**0.5 ml**
Visit 20 (Month 16)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 21 (Month 17)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 22 (Month 18)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 23 (Month 19)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 24 (Month 20)	Immunogenicity	2.5 ml	-	-	2.5 ml	2.5 ml
	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**3.0 ml**	**0.5 ml**	**0.5 ml**	**3.0 ml**	**3.0 ml**
Visit 25 (Month 21)	Immunogenicity	2.5 ml	-	-	2.5 ml	-
	~~Parasitemia~~	~~0.5 ml~~	~~0.5 ml~~	~~0.5 ml~~	~~0.5 ml~~	~~0.5 ml~~
	~~**Total:**~~	~~**3.0 ml**~~	~~**0.5 ml**~~	~~**0.5 ml**~~	~~**3.0 ml**~~	~~**0.5 ml**~~
~~Visit 26 (Month 22)~~	~~Parasitemia~~	~~0.5 ml~~	~~0.5 ml~~	~~0.5 ml~~	~~0.5 ml~~	~~0.5 ml~~
Visit 2~~7~~***6*** (Month 23)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 2~~8~~***7*** (Month 26)	Immunogenicity	-	2.5 ml	2.5 ml	-	-
	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**0.5 ml**	**3.0 ml**	**3.0 ml**	**0.5 ml**	**0.5 ml**
Visit 2~~9~~***8*** (Month 27)	Immunogenicity	-	2.5 ml	2.5 ml	-	-
Visit ~~30~~***29*** (Month 29)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 3~~1~~***0*** (Month 32)	Immunogenicity	-	-	-	2.5 ml	-
	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**0.5 ml**	**0.5 ml**	**0.5 ml**	**3.0 ml**	**0.5 ml**
Visit 3~~2~~***1*** (Month 33)	Immunogenicity	-	-	-	2.5 ml	-
Visit 3~~3~~***2*** (Month 35)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 3~~4~~***3*** (Month 38)	Immunogenicity	-	2.5 ml	2.5 ml	-	-
	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**0.5 ml**	**3.0 ml**	**3.0 ml**	**0.5 ml**	**0.5 ml**
Visit 3~~5~~***4*** (Month 39)	Immunogenicity	-	2.5 ml	2.5 ml	-	-
Visit 3~~6~~***5*** (Month 41)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 3~~7~~***6*** (Month 44)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 3~~8~~***7*** (Month 47)	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 3~~9~~***8*** (Month 50)	Immunogenicity	2.5 ml	2.5 ml	2.5 ml	2.5 ml	2.5 ml
	Parasitemia	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**3.0 ml**	**3.0 ml**	**3.0 ml**	**3.0 ml**	**3.0 ml**

† At screening, hemoglobin will be assessed in all subjects screened.

* Blood samples for hematology and biochemistry will be taken only in subjects belonging to the reactogenicity sub-cohort.

** The total volume of blood to be taken depends if the subject belongs to the reactogenicity sub-cohort or not.

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6.7.4. Biological samples evaluation

6.7.4.1. Immunological read-outs

Table 19 Immunological read-outs

Blood sampling timepoint		Study groups	Subset name	No. subjects	Component	Components priority rank
Type of contact and timepoint	**Sampling timepoint**					
Visit 2 (Day 0)	Pre-Vacc	All groups	Immunogenicity	250	Anti- CS	1
		All groups	Immunogenicity	250	Anti-CS avidity	2
		All groups	Immunogenicity	250	Anti-HBs	3
Visit 4 (Month 2)	Post-Dose 2 (Fx017-mFxD) / Pre-Dose 3 (other groups)	All groups	Immunogenicity	250	Anti-CS	1
		All groups	Immunogenicity	250	Anti-CS avidity	2
		All groups	Immunogenicity	250	Anti-HBs	3
Visit 6 (Month 3)	Post-Dose 3	R012-20 R012-14-mD Fx012-14-mFxD Control	Immunogenicity	200	Anti-CS	1
		R012-20 R012-14-mD Fx012-14-mFxD Control	Immunogenicity	200	Anti-CS avidity	2
		R012-20 R012-14-mD Fx012-14-mFxD Control	Immunogenicity	200	Anti-HBs	3
Visit 10 (Month 7)	Pre-Dose 3	Fx017-mFxD	Immunogenicity	50	Anti-CS	1
		Fx017-mFxD	Immunogenicity	50	Anti-CS avidity	2
		Fx017-mFxD	Immunogenicity	50	Anti-HBs	3
Visit 12 (Month 8)	Post-Dose 3	Fx017-mFxD	Immunogenicity	50	Anti-CS	1
		Fx017-mFxD	Immunogenicity	50	Anti-CS avidity	2
		Fx017-mFxD	Immunogenicity	50	Anti-HBs	3
Visit 18 (Month 14)	Pre-Dose 4	R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-CS	1
		R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-CS avidity	2
		R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-HBs	3
Visit 19 (Month 15)	Post-Dose 4	R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-CS	1
		R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-CS avidity	2
		R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-HBs	3
Visit 24 (Month 20)	Pre-Dose 4	R012-20 Fx017-mFxD Control	Immunogenicity	150	Anti-CS	1
		R012-20 Fx017-mFxD Control	Immunogenicity	150	Anti-CS avidity	2
		R012-20 Fx017-mFxD Control	Immunogenicity	150	Anti-HBs	3

Blood sampling timepoint		Study groups	Subset name	No. subjects	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint					
Visit 25 (Month 21)	Post-Dose 4	R012-20 Fx017-mFxD	Immunogenicity	100	Anti-CS	1
		R012-20 Fx017-mFxD	Immunogenicity	100	Anti-CS avidity	2
		R012-20 Fx017-mFxD	Immunogenicity	100	Anti-HBs	3
Visit ~~28~~**7** (Month 26)	Pre-Dose 5	R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-CS	1
		R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-CS avidity	2
		R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-HBs	3
Visit ~~29~~**8** (Month 27)	Post-Dose 5	R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-CS	1
		R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-CS avidity	2
		R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-HBs	3
Visit ~~31~~**0** (Month 32)	Pre-Dose 5	Fx017-mFxD	Immunogenicity	50	Anti-CS	1
		Fx017-mFxD	Immunogenicity	50	Anti-CS avidity	2
		Fx017-mFxD	Immunogenicity	50	Anti-HBs	3
Visit ~~32~~**1** (Month 33)	Post-Dose 5	Fx017-mFxD	Immunogenicity	50	Anti-CS	1
		Fx017-mFxD	Immunogenicity	50	Anti-CS avidity	2
		Fx017-mFxD	Immunogenicity	50	Anti-HBs	3
Visit ~~34~~**3** (Month 38)	Pre-Dose 6	R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-CS	1
		R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-CS avidity	2
		R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-HBs	3
Visit ~~35~~**4** (Month 39)	Post-Dose 6	R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-CS	1
		R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-CS avidity	2
		R012-14-mD Fx012-14-mFxD	Immunogenicity	100	Anti-HBs	3
Visit ~~39~~**8** (Month 50)	Study end	All groups	Immunogenicity	250	Anti-CS	1
		All groups	Immunogenicity	250	Anti-CS avidity	2
		All groups	Immunogenicity	250	Anti-HBs	3

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6.7.4.2. Parasitemia

Table 20 Parasitemia (blood smear)

Blood sampling timepoint	Study groups	No. subjects	Component	Components priority rank
Visit 2 (Day 0)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 3 (Month 1)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 4 (Month 2)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 6 (Month 3)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 7 (Month 4)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 8 (Month 5)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 9 (Month 6)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 10 (Month 7)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 12 (Month 8)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 13 (Month 9)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 14 (Month 10)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 15 (Month 11)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 16 (Month 12)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 17 (Month 13)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 18 (Month 14)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 19 (Month 15)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 20 (Month 16)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 21 (Month 17)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 22 (Month 18)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 23 (Month 19)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 24 (Month 20)	All groups	1500	Blood smear + blood for ancillary study*	1
~~Visit 25 (Month 21)~~	~~All groups~~	~~1500~~	~~Blood smear + blood for ancillary study*~~	~~1~~
~~Visit 26 (Month 22)~~	~~All groups~~	~~1500~~	~~Blood smear + blood for ancillary study*~~	~~1~~
Visit 2~~7~~***6*** (Month 23)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 2~~8~~***7*** (Month 26)	All groups	1500	Blood smear + blood for ancillary study*	1

Blood sampling timepoint	Study groups	No. subjects	Component	Components priority rank
Visit ~~30~~***29*** (Month 29)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 3~~1~~***0*** (Month 32)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 3~~3~~***2*** (Month 35)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 3~~4~~***3*** (Month 38)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 3~~6~~***5*** (Month 41)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 3~~7~~***6*** (Month 44)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 3~~8~~***7*** (Month 47)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 3~~9~~***8*** (Month 50)	All groups	1500	Blood smear + blood for ancillary study*	1

* The incidence of *P. falciparum* infection assessed by PCR and parasite genotyping will be evaluated in an ancillary study, using samples collected as described in the present protocol. The blood for the ancillary study will be collected on filter paper.

7.3.2. Rabies vaccine

Table 23 Dosage and administration

Type of contact and timepoint	Volume to be administered	Study group	Treatment name	Route [1]	Site	Side
Visit 2 (Day 0)	0.5 ml	R012-20 R012-14-mD Fx012-14-mFxD Fx017-mFxD	RTS,S/AS01$_E$ (Full dose)	IM	Deltoid	Left
	1.0 ml	Control	Rabies vaccine	IM	Deltoid	Left
Visit 3 (Month 1)	0.5 ml	R012-20 R012-14-mD Fx012-14-mFxD Fx017-mFxD	RTS,S/AS01$_E$ (Full dose)	IM	Deltoid	Left
	1.0 ml	Control	Rabies vaccine	IM	Deltoid	Left
Visit 4 (Month 2)	0.5 ml	R012-20 R012-14-mD	RTS,S/AS01$_E$ (Full dose)	IM	Deltoid	Left
	0.1 ml	Fx012-14-mFxD	RTS,S/AS01$_E$ (1/5th dose)	IM	Deltoid	Left
	1.0 ml	Control	Rabies vaccine	IM	Deltoid	Left
Visit 10 (Month 7)	0.1 ml	Fx017-mFxD	RTS,S/AS01$_E$ (1/5th dose)	IM	Deltoid	Left
Visit 18 (Month 14)	0.5 ml	R012-14-mD	RTS,S/AS01$_E$ (Full dose)	IM	Deltoid	Left
	0.1 ml	Fx012-14-mFxD	RTS,S/AS01$_E$ (1/5th dose)	IM	Deltoid	Left
Visit 24 (Month 20)	0.5 ml	R012-20	RTS,S/AS01$_E$ (Full dose)	IM	Deltoid	Left
	0.1 ml	Fx017-mFxD	RTS,S/AS01$_E$ (1/5th dose)	IM	Deltoid	Left
Visit 2~~8~~***7*** (Month 26)	0.5 ml	R012-14-mD	RTS,S/AS01$_E$ (Full dose)	IM	Deltoid	Left
	0.1 ml	Fx012-14-mFxD	RTS,S/AS01$_E$ (1/5th dose)	IM	Deltoid	Left
Visit 3~~1~~***0*** (Month 32)	0.1 ml	Fx017-mFxD	RTS,S/AS01$_E$ (1/5th dose)	IM	Deltoid	Left
Visit 3~~4~~***3*** (Month 38)	0.5 ml	R012-14-mD	RTS,S/AS01$_E$ (Full dose)	IM	Deltoid	Left
	0.1 ml	Fx012-14-mFxD	RTS,S/AS01$_E$ (1/5th dose)	IM	Deltoid	Left

[1] Intramuscular (IM)

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

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Table 27 Reporting periods for collecting safety information

Study visits	1	2			3			4			10			18			24			~~28~~7			~~31~~0			~~34~~3			~~39~~8
Event	Scr*	Vac 1			Vac 2			Vac 3			Vac 4			Vac 5			Vac 6			Vac 7			Vac 8			Vac 9			Study end
Study timepoint:	D -28 to -1	D0	D0 + 3d	D0 + 29d	M1	M1 + 3d	M1 + 29d	M2	M2 + 3d	M2 + 29d	M7	M7 + 3d	M7 + 29d	M14	M14 + 3d	M14 + 29d	M20	M20 + 3d	M20 + 29d	M26	M26 + 3d	M26 + 29d	M32	M32 + 3d	M32 + 29d	M38	M38 + 3d	M38 + 29d	M50
For ALL groups																													
AEs/SAEs leading to withdrawal from further vaccination		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
SAEs related to study participation or concurrent GSK medication/vaccine	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
SAEs (All, fatal, related to the investigational vaccine)		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
AEs of specific interest**		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Group R012-20																													
Solicited local and general AEs***								■	■								■	■											
Unsolicited AEs		■	■	■	■	■	■	■	■	■							■	■	■										
Group R012-14-mD and Fx012-14-mFxD																													
Solicited local and general AEs***								■	■					■	■					■	■					■	■		

Study visits	1	2			3			4			10			18			24			287			310			343			398
Event	Scr*	Vac 1			Vac 2			Vac 3			Vac 4			Vac 5			Vac 6			Vac 7			Vac 8			Vac 9			Study end
Study timepoint:	D -28 to -1	D0	D0 + 3d	D0 + 29d	M1	M1 + 3d	M1 + 29d	M2	M2 + 3d	M2 + 29d	M7	M7 + 3d	M7 + 29d	M14	M14 + 3d	M14 + 29d	M20	M20 + 3d	M20 + 29d	M26	M26 + 3d	M26 + 29d	M32	M32 + 3d	M32 + 29d	M38	M38 + 3d	M38 + 29d	M50
Unsolicited AEs																													
Group Fx017-mFxD																													
Solicited local and general AEs***																													
Unsolicited AEs																													
Control group																													
Solicited local and general AEs***																													
Unsolicited AEs																													

* i.e. consent obtained.
** AEs of specific interest include seizures occurring within 30 days post-vaccination, meningitis and pIMDs.
*** Solicited local and general AEs will be collected in the first 50 subjects enrolled in each group (reactogenicity sub-cohort).
Scr: Screening; Vac: Vaccination; D: Day; M: Month; 3d: 3 days; 29d: 29 days.

9.2.3.6. Verbal autopsy process

Where possible autopsies will be performed. Verbal autopsies will be carried out on all children who die outside a health facility to ascribe the cause of death ***if it is not possible to perform the autopsies***. The questionnaire used will be based on the INDEPTH standard and adapted to be locally appropriate [WHO, 2007].

11. Statistical methods

11.1. Primary endpoint

See synopsis for changes in Primary endpoint.

11.2. Secondary endpoint

See synopsis for changes in Secondary endpoints.

11.7.6. Secondary analyses of efficacy

A) Clinical malaria:

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Analysis performed at Month 33:

- ***Vaccine efficacy and impact of R012-20 versus Control group over D0-M26 (all episodes, TVC).***
- ***Vaccine efficacy and impact of R012-14-mD versus Control group over D0-M26 (all episodes, TVC).***
- ***Vaccine efficacy and impact of Fx012-14-mFxD versus Control group over D0-M26 (all episodes, TVC).***
- ***Vaccine efficacy and impact of Fx017-mFxD versus Control group over D0-M26 (all episodes, TVC).***
- ***Incremental efficacy of Fx017-mFxD versus R012-20 over M20-M32 (all episodes, ATP).***
- ***Incremental efficacy of Fx012-14-mFxD versus R012-14-mD over M14-M26 (all episodes, ATP).***

Analysis performed at Month 50:

- ~~Vaccine efficacy and impact of R012-20 versus Control group over D0-M26 (all episodes, TVC).~~
- Vaccine efficacy and impact of R012-20 versus Control group over D0-M38 (all episodes, TVC).
- Vaccine efficacy and impact of R012-20 versus Control group over D0-M50 (all episodes, TVC).

- ~~Vaccine efficacy and impact of R012-14-mD versus Control group over D0-M26 (all episodes, TVC).~~
- Vaccine efficacy and impact of R012-14-mD versus Control group over D0-M38 (all episodes, TVC).
- Vaccine efficacy and impact of R012-14-mD versus Control group over D0-M50 (all episodes, TVC).
- ~~Vaccine efficacy and impact of Fx012-14-mFxD versus Control group over D0-M26 (all episodes, TVC).~~
- Vaccine efficacy and impact of Fx012-14-mFxD versus Control group over D0-M38 (all episodes, TVC).
- Vaccine efficacy and impact of Fx012-14-mFxD versus Control group over D0-M50 (all episodes, TVC).
- ~~Vaccine efficacy and impact of Fx017-mFxD versus Control group over D0-M26 (all episodes, TVC).~~
- Vaccine efficacy and impact of Fx017-mFxD versus Control group over D0-M38 (all episodes, TVC).
- Vaccine efficacy and impact of Fx017-mFxD versus Control group over D0-M50 (all episodes, TVC).
- ~~Incremental efficacy of Fx017-mFxD versus R012-20 over M20-M32 (all episodes, ATP).~~
- ~~Incremental efficacy of Fx012-14-mFxD versus R012-14-mD over M14-M26 (all episodes, ATP).~~
- Incremental efficacy of Fx012-14-mFxD versus R012-14-mD over M26-M38 (all episodes, ATP).
- Incremental efficacy of Fx012-14-mFxD versus R012-14-mD over M38-M50 (all episodes, ATP).

B) Incident *P. falciparum* infections

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Analysis performed at Month 33:

- ***Vaccine efficacy of R012-20 versus Control group over D0-M26 (all episodes, TVC).***
- ***Vaccine efficacy of R012-14-mD versus Control group over D0-M26 (all episodes, TVC).***
- ***Vaccine efficacy of Fx012-14-mFxD versus Control group over D0-M26 (all episodes, TVC).***
- ***Vaccine efficacy of Fx017-mFxD versus Control group over D0-M26 (all episodes, TVC).***

- ***Incremental efficacy of Fx017-mFxD versus R012-20 over M20-M32 (all episodes, ATP).***
- ***Incremental efficacy of Fx012-14-mFxD versus R012-14-mD over M14-M26 (all episodes, ATP).***

Analysis performed at Month 50:

- ~~Vaccine efficacy of R012-20 versus Control group over D0-M26 (all episodes, TVC).~~
- Vaccine efficacy of R012-20 versus Control group over D0-M38 (all episodes, TVC).
- Vaccine efficacy of R012-20 versus Control group over D0-M50 (all episodes, TVC).
- ~~Vaccine efficacy of R012-14-mD versus Control group over D0-M26 (all episodes, TVC).~~
- Vaccine efficacy of R012-14-mD versus Control group over D0-M38 (all episodes, TVC).
- Vaccine efficacy of R012-14-mD versus Control group over D0-M50 (all episodes, TVC).
- ~~Vaccine efficacy of Fx012-14-mFxD versus Control group over D0-M26 (all episodes, TVC).~~
- Vaccine efficacy of Fx012-14-mFxD versus Control group over D0-M38 (all episodes, TVC).
- Vaccine efficacy of Fx012-14-mFxD versus Control group over D0-M50 (all episodes, TVC).
- ~~Vaccine efficacy of Fx017-mFxD versus Control group over D0-M26 (all episodes, TVC).~~
- Vaccine efficacy of Fx017-mFxD versus Control group over D0-M38 (all episodes, TVC).
- Vaccine efficacy of Fx017-mFxD versus Control group over D0-M50 (all episodes, TVC).
- ~~Incremental efficacy of Fx017-mFxD versus R012-20 over M20-M32 (all episodes, ATP).~~
- ~~Incremental efficacy of Fx012-14-mFxD versus R012-14-mD over M14-M26 (all episodes, ATP).~~
- Incremental efficacy of Fx012-14-mFxD versus R012-14-mD over M26-M38 (all episodes, ATP).
- Incremental efficacy of Fx012-14-mFxD versus R012-14-mD over M38-M50 (all episodes, ATP).

C) Prevalent *P. falciparum* infections

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Analysis performed at Month 33:

- ***Prevalent P. falciparum infections at each cross-sectional survey at Month 26 (TVC).***

Analysis performed at Month 50:

- ~~Prevalent *P. falciparum* infections at each cross-sectional survey at Month 26 (TVC).~~
- Prevalent *P. falciparum* infections at each cross-sectional survey at Month 38 (TVC).
- Prevalent *P. falciparum* infections at each cross-sectional survey at Month 50 (TVC).

11.12.1. Sequence of analyses

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

- **Sequence of analyses and conditional continuation:**
  - A first analysis will be performed on data collected up to Month 21 (Visit 25) to evaluate the primary objective ***(cleaned data)*** and relevant secondary objectives.
  - ***A second analysis will be performed on data collected up to Month 33 (Visit 31) to evaluate relevant secondary objectives.***
  - A ~~second~~ ***final*** analysis will be performed at study end (Month 50) on data collected up to Month 50. An integrated study report presenting all results until Month 50 will be produced.
- After the ***interim*** ~~first analysis~~***analyses***, the IDMC will have the possibility to recommend the suspension of further vaccinations and termination of specific study group(s) upon consideration of the study results. In the event that the IDMC recommend the suspension of further vaccinations, the group(s) impacted will be followed up for 12 months after their last study vaccination.

11.12.2. Statistical considerations for interim analyses

~~The analysis of the primary endpoint will be performed on data collected up to Month 14. No alpha adjustment is foreseen because the primary endpoint will be analyzed at the time of the first interim analysis.~~***The analysis of the primary endpoint will be performed after Month 21 (Visit 25) on cleaned data collected up to Month 14. No alpha adjustment is foreseen because final analysis of the primary endpoint will occur at the time of the first interim analysis after Month 21 (Visit 25) on cleaned data collected up to Month 14.***

14. REFERENCES

~~WHO Child Growth Standards (2006):~~
~~http://www.who.int/childgrowth/standards/cht_wfa_girls_p_0_2.pdf and~~
~~http://www.who.int/childgrowth/standards/cht_wfa_boys_p_0_2.pdf. Accessed: 25 January 2016.~~

GlaxoSmithKline Biologicals

Vaccine Value & Health Science (VVHS)

Protocol Amendment 3

eTrack study number and Abbreviated Title	204889 (MALARIA-094)
Amendment number:	Amendment 3
Amendment date:	14 November 2019
Co-ordinating author:	PPD Scientific Writer, Freelance Contractor for GSK Biologicals

Rationale/background for changes:

Case definition of severe *P. falciparum* malaria: Per protocol, impaired consciousness was to be evaluated using the Glasgow coma score for children ≥ 2 years and using the Blantyre coma score for children < 2 years (Appendix C: Case definition of severe *P. falciparum* malaria). However, local practice is to use the Blantyre coma score for children. After discussion with the Independent Data Monitoring Committee (IDMC), only the Blantyre coma score is to be used for assessment of impaired consciousness in all age groups in the study.

Per protocol, filter paper blood spots were to be collected for use in the ancillary study, MALARIA-095, to look at vaccine efficacy against clinical and asymptomatic malaria infection using ultra-sensitive molecular amplification and sequencing methodology. However, the MALARIA-095 protocol will use samples only up to Month 32. The MALARIA-094 protocol has been amended to reflect filter paper sampling up until the Month 32 timepoint.

In the assessment of vaccine efficacy against all episodes of malaria (Section 11.7.2), an estimated seven days for drug clearance (half-life) following an episode meeting the case definition under evaluation was to be subtracted from the follow-up time. This has been changed to 14 days to be in line with actual clearance and also to allow for comparison with previous Phase III efficacy data in the same population (MALARIA-055 data).

The anti-CS immunogenicity endpoint for the immunogenicity secondary objective 'Immune response to the CS antigen' was inadvertently omitted between protocol amendment 1 and protocol amendment 2 and has been reinstated.

According to EU regulation, the definition of end of study (EoS) must be included in the clinical protocol, and the study report submitted in a predefined timeframe based on the EoS milestone. Per GSK policies, a summary of the study results have to be publicly disclosed, the reference milestone for which is based on the primary completion date. The definitions for the EoS and primary completion date have been clarified. Details for the disclosure of protocol information and study results have been updated (Section 12.5).

APPENDIX D Safety Laboratory Testing: CLS South Africa: the number of tests that can be performed by polymerase chain reaction (PCR) on cerebrospinal fluid (CSF) and serum samples has increased. The Appendix has been amended to show the breadth of analyses available.

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

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

Primary study vaccine/product and number	• GlaxoSmithKline (GSK) Biologicals' candidate *Plasmodium falciparum* malaria vaccine RTS,S/AS01$_E$ (SB257049).
Other study vaccine/product	• Rabies vaccine (Rabipur™)
eTrack study number and abbreviated title	204889 (MALARIA-094)
EudraCT number	2016-000290-20
Date of protocol	Final ~~Version 1~~: 16 February 2016
Date of protocol amendment	Amendment 1 Final: 13 September 2016 Amendment 2 Final: 06 April 2017 ***Amendment 3 Final: 14 November 2019***
Coordinating author	PPD Project Manager Science Writing, Malaria Vaccines
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- PPD , Lead Statistician*s*
- PPD Clinical Research and Development Leads
- PPD , Senior Local Delivery Lead*s*
- PPD Global Patent representative
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SYNOPSIS

Rationale for the study and study design	**Rationale for the use of a rabies vaccine as a comparator vaccine** …… The efficacy of cell culture-derived rabies vaccines including human diploid cells vaccine (HDCV), purified Vero cell~~s~~ ***rabies*** vaccine (PVRV), purified chick embryo cells vaccine (PCECV), purified hamster kidney cells vaccine (PHKCV) and purified duck embryo cells vaccine (PDEV) has been demonstrated [WHO, 2010]. In this study, a PCECV (Rabipur) will be used as comparator vaccine. ……..
Study design	• ***Primary completion date: Visit 18 (Month 14) or last visit of Epoch 001.*** ***Refer to the GLOSSARY OF TERMS for the definition of primary completion date.***

- ***End of Study (EoS): Last testing results released of samples collected at Visit 38 (Month 50). Refer to the GLOSSARY OF TERMS for the definition of EoS.***
- **Sampling schedule:**
  - …….
  - In addition to the blood samples listed in Synopsis Table 4, a small amount of blood (for blood smear and filter paper) will be taken every month from Day 0 until Month 20**,** and thereafter every three months until Month 50 ***for blood smear and until Month 32 for filter paper*** in all subjects for the evaluation of *P. falciparum* infections.
  - ……..
- **Efficacy surveillance:**
  - ….. All children with fever and/or history of fever will have a blood sample taken for the evaluation of vaccine efficacy (blood slide ***throughout the study*** and filter paper for polymerase chain reaction [PCR] ***up until month 32***). All anti-malaria treatments administered during the study should be recorded in the subject's eCRF.

Endpoints **Secondary**

- **Immunogenicity: Immune response to the CS and HBs antigens (immunogenicity subset)**
  - ***Anti-CS antibody concentrations and seropositivity measured before Dose 1, one month post-Dose 2 (group Fx017-mFxD only), before and one month post-Dose 3, before and one month after Dose 4, before and one month after each yearly dose and at study end (Month 50).***
  - ……

LIST OF ABBREVIATIONS

EoS: ***End of study***

GLOSSARY OF TERMS

End of Study (EoS): ***(Synonym of End of Trial)***	***For studies without collection of human biologicals samples or imaging data EoS is the Last Subject Last Visit (LSLV).*** ***For studies with collection of Human Biologicals Samples or imaging data, EoS is defined as the date of the last testing/reading released of the Human Biologicals Samples or imaging data, related to primary and secondary endpoints. EoS must be achieved no later than 8 months after LSLV.***

TRADEMARKS

The following trademarks are used in the present protocol.

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

Trademark of the GlaxoSmithKline group of companies	**Generic description**
Rabipur™	Purified chick embryo cell culture rabies vaccine

~~**Trademark not owned by the GlaxoSmithKline group of companies**~~	~~**Generic description**~~
~~QS-21 (*Quillaja saponaria Molina*, fraction 21) (Licensed by GSK from Antigenics Inc., a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)~~	~~Triterpene glycoside immune enhancer~~

1.2.1 Rationale for the study design

A recent CHMI study (MALARIA-071) ***demonstrated superior protection against malaria infection***~~6~~ associated with the use of a fractional third dose in a 0, 1, 7-month schedule with a vaccine efficacy against infection of 86.7% (95% CI: 66.8; 94.6; p<0.0001) versus 62.5% (95% CI: 29.4; 80.1; p=0.0009) in the standard 0, 1, 2-month schedule. ……

1.2.3. Rationale for the use of a rabies vaccine as a comparator vaccine

……

The efficacy of cell culture-derived rabies vaccines including human diploid cells vaccine (HDCV), purified Vero cell rabies vaccine (PVRV), purified chick embryo cells vaccine (PCECV), purified ***hamster kidney***~~chick embryo~~ cells vaccine (PHKCV) and purified duck embryo cells vaccine (PDEV) has been demonstrated [WHO, 2010]. In this study, a PCECV (*Rabipur*) will be used as comparator vaccine.

3. STUDY DESIGN OVERVIEW

- ***Primary completion date: Visit 18 (Month 14) or last visit of Epoch 001. Refer to the GLOSSARY OF TERMS for the definition of primary completion date.***
- ***End of Study (EoS): Last testing results released of samples collected at Visit 38 (Month 50). Refer to the GLOSSARY OF TERMS for the definition of EoS.***

- **Sampling schedule:**
  - …….
  - In addition to the blood samples listed in Table 5, a small amount of blood (for blood smear and filter paper) will be taken every month from Day 0 until Month 20**,** and thereafter every three months until Month 50 ***for blood smear and until Month 32 for filter paper*** in all subjects for the evaluation of *P. falciparum* infections (see Section 6.7.4.2).

- **Efficacy surveillance:**
  - …… All children with fever and/or history of fever will have a blood sample taken for the evaluation of vaccine efficacy (blood slide ***throughout the study*** and filter paper for polymerase chain reaction [PCR] ***up until month 32***). …….

6.5. Outline of study procedures

Table 11 List of study procedures for clinic visits

Footnotes to Table 11:
n. Blood for parasitemia (0.5 ml) includes the blood for the slide reading ***(to Month 50)*** and for the filter paper ***(to Month 32)***. The parasitemia assessment by blood slide reading will include blood-stage parasites and gametocytes counts.
o. In addition to the scheduled clinic visits, malaria cases will be captured by PCD throughout the study. All sick children presenting with fever and/or history of fever will have a blood sample taken for the evaluation of vaccine efficacy (for blood slide ***to Month 50*** and filter paper for PCR ***to Month 32***).

Table 13 List of study procedures for field worker visits - Part 2 (Month 20 to Month 50)

Footnotes to Table 13:
† Blood for parasitemia (0.5 ml) includes the blood for the slide reading ***(to Month 50)*** and for the filter paper ***(to Month 32)***. The parasitemia assessment by blood slide reading will include blood-stage parasites and gametocytes counts.
§ In addition to the scheduled clinic visits, malaria cases will be captured by PCD throughout the study. All sick children presenting with fever and/or history of fever will have a blood sample taken for the evaluation of vaccine efficacy (for blood slide ***to Month 50*** and filter paper for PCR ***to Month 32***).

6.6.16. Blood sampling for all subjects

- **Blood sampling for assessment of parasitemia**

  A volume of approximately 0.5 ml of whole blood should be drawn from all subjects at each pre-defined timepoint for the assessment of *P. falciparum* parasitemia (***until Month 50*** for blood slide and ***until Month 32 for*** filter paper).

  In addition to the scheduled clinic visits, malaria cases will be captured by PCD throughout the study. All sick children presenting with fever and/or history of fever will have a blood sample taken for the evaluation of vaccine efficacy (***until Month 50*** for blood slide and ***until Month 32 for*** filter paper).

6.7.2. Biological samples

Table 15 Biological samples (whole blood)

Timepoint	Assessment	Total volume of blood per visit (ml)				
		R012-20	R012-14-mD	Fx012-14-mFxD	Fx017-mFxD	Control
Visit 1 (Screening)	Safety (hemoglobin)†	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 2 (Day 0)	Immunogenicity	2.5 ml	2.5 ml	2.5 ml	2.5 ml l	2.5 ml
	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**3.0 ml**	**3.0 ml**	**3.0 ml**	**3.0 ml**	**3.0 ml**
Visit 3 (Month 1)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 4 (Month 2)	Safety*	1.0 ml*	1.0 ml*	1.0 ml*	-	1.0 ml*
	Immunogenicity	2.5 ml	2.5 ml	2.5 ml	2.5 ml	2.5 ml
	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**4.0 or 3.0 ml****	**4.0 or 3.0 ml****	**4.0 or 3.0 ml****	**3.0 ml**	**4.0 or 3.0 ml****
Visit 5 (Month 2 + 7d)	Safety*	1.0 ml*	1.0 ml*	1.0 ml*	-	1.0 ml*
Visit 6 (Month 3)	Safety*	1.0 ml*	1.0 ml*	1.0 ml*	-	1.0 ml*
	Immunogenicity	2.5 ml	2.5 ml	2.5 ml	-	2.5 ml
	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**4.0 or 3.0 ml****	**4.0 or 3.0 ml****	**4.0 or 3.0 ml****	**0.5 ml**	**4.0 or 3.0 ml****
Visit 7 (Month 4)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 8 (Month 5)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 9 (Month 6)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 10 (Month 7)	Safety*	-	-	-	1.0 ml*	-
	Immunogenicity	-	-	-	2.5 ml	-
	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**0.5 ml**	**0.5 ml**	**0.5 ml**	**4.0 or 3.0 ml****	**0.5 ml**

Timepoint	Assessment	Total volume of blood per visit (ml)				
		R012-20	R012-14-mD	Fx012-14-mFxD	Fx017-mFxD	Control
Visit 11 (Month 7 + 7d)	Safety*	-	-	-	1.0 ml*	-
Visit 12 (Month 8)	Safety*	-	-	-	1.0 ml*	-
	Immunogenicity	-	-	-	2.5 ml	-
	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**0.5 ml**	**0.5 ml**	**0.5 ml**	**4.0 or 3.0 ml****	**0.5 ml**
Visit 13 (Month 9)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 14 (Month 10)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 15 (Month 11)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 16 (Month 12)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 17 (Month 13)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 18 (Month 14)	Immunogenicity	-	2.5 ml	2.5 ml	-	-
	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**0.5 ml**	**3.0 ml**	**3.0 ml**	**0.5 ml**	**0.5 ml**
Visit 19 (Month 15)	Immunogenicity	-	2.5 ml	2.5 ml	-	-
	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**0.5 ml**	**3.0 ml**	**3.0 ml**	**0.5 ml**	**0.5 ml**
Visit 20 (Month 16)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 21 (Month 17)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 22 (Month 18)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 23 (Month 19)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 24 (Month 20)	Immunogenicity	2.5 ml	-	-	2.5 ml	2.5 ml
	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**3.0 ml**	**0.5 ml**	**0.5 ml**	**3.0 ml**	**3.0 ml**
Visit 25 (Month 21)	Immunogenicity	2.5 ml	-	-	2.5 ml	-
Visit 26 (Month 23)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 27 (Month 26)	Immunogenicity	-	2.5 ml	2.5 ml	-	-
	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**0.5 ml**	**3.0 ml**	**3.0 ml**	**0.5 ml**	**0.5 ml**
Visit 28 (Month 27)	Immunogenicity	-	2.5 ml	2.5 ml	-	-
Visit 29 (Month 29)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 30 (Month 32)	Immunogenicity	-	-	-	2.5 ml	-
	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**0.5 ml**	**0.5 ml**	**0.5 ml**	**3.0 ml**	**0.5 ml**
Visit 31 (Month 33)	Immunogenicity	-	-	-	2.5 ml	-
Visit 32 (Month 35)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 33 (Month 38)	Immunogenicity	-	2.5 ml	2.5 ml	-	-
	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**0.5 ml**	**3.0 ml**	**3.0 ml**	**0.5 ml**	**0.5 ml**
Visit 34 (Month 39)	Immunogenicity	-	2.5 ml	2.5 ml	-	-
Visit 35 (Month 41)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 36 (Month 44)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 37 (Month 47)	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Visit 38 (Month 50)	Immunogenicity	2.5 ml	2.5 ml	2.5 ml	2.5 ml	2.5 ml
	Parasitemia‡	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml
	Total:	**3.0 ml**	**3.0 ml**	**3.0 ml**	**3.0 ml**	**3.0 ml**

† At screening, hemoglobin will be assessed in all subjects screened.

* Blood samples for hematology and biochemistry will be taken only in subjects belonging to the reactogenicity sub-cohort.

** The total volume of blood to be taken depends if the subject belongs to the reactogenicity sub-cohort or not.

d: day.

‡ Blood for parasitemia (0.5 ml) includes the blood for the slide reading (to Month 50) and for the filter paper (to Month 32).

~~† At screening, hemoglobin will be assessed in all subjects screened.~~
~~* Blood samples for hematology and biochemistry will be taken only in subjects belonging to the reactogenicity sub-cohort.~~
~~** The total volume of blood to be taken depends if the subject belongs to the reactogenicity sub-cohort or not.~~
~~d: day~~

6.7.4.2. Parasitemia

Table 20 Parasitemia (blood smear *and blood for ancillary study*)

Blood sampling timepoint	Study groups	No. subjects	Component	Components priority rank
Visit 2 (Day 0)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 3 (Month 1)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 4 (Month 2)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 6 (Month 3)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 7 (Month 4)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 8 (Month 5)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 9 (Month 6)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 10 (Month 7)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 12 (Month 8)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 13 (Month 9)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 14 (Month 10)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 15 (Month 11)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 16 (Month 12)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 17 (Month 13)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 18 (Month 14)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 19 (Month 15)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 20 (Month 16)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 21 (Month 17)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 22 (Month 18)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 23 (Month 19)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 24 (Month 20)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 26 (Month 23)	All groups	1500	Blood smear + blood for ancillary study*	1

Blood sampling timepoint	Study groups	No. subjects	Component	Components priority rank
Visit 27 (Month 26)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 29 (Month 29)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 30 (Month 32)	All groups	1500	Blood smear + blood for ancillary study*	1
Visit 32 (Month 35)	All groups	1500	Blood smear ~~+ blood for ancillary study*~~	1
Visit 33 (Month 38)	All groups	1500	Blood smear ~~+ blood for ancillary study*~~	1
Visit 35 (Month 41)	All groups	1500	Blood smear ~~+ blood for ancillary study*~~	1
Visit 36 (Month 44)	All groups	1500	Blood smear ~~+ blood for ancillary study*~~	1
Visit 37 (Month 47)	All groups	1500	Blood smear ~~+ blood for ancillary study*~~	1
Visit 38 (Month 50)	All groups	1500	Blood smear ~~+ blood for ancillary study*~~	1

* The incidence of *P. falciparum* infection assessed by PCR and parasite genotyping will be evaluated in an ancillary study, using samples collected ***until Month 32*** as described in the present protocol. The blood for the ancillary study will be collected on filter paper.

11.2. Secondary endpoints

- **Immunogenicity: Immune response to the CS and HBs antigens (immunogenicity subset)**
  - ***Anti-CS antibody concentrations and seropositivity measured before Dose 1, one month post-Dose 2 (group Fx017-mFxD only), before and one month post-Dose 3, before and one month after Dose 4, before and one month after each yearly dose and at study end (Month 50).***
  - ……..

11.7.2. Measures of incidence (*P. falciparum* infection and clinical malaria)

- **All episodes**

…….. ~~Seven~~ ***Fourteen*** days following an episode meeting the case definition under evaluation will be subtracted from the follow-up time. The distribution of the total number of events per subject will be tabulated by group.

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 six months of the primary completion date for studies of authorized vaccines and 18 months for studies of non-authorized vaccines.~~

~~GSK also aims to publish the results of these studies in the searchable, peer reviewed scientific literature. Manuscripts are submitted for publication within 24 months of the last subject's last visit. At the time of publication, this protocol will be fully disclosed.~~***GSK assures that the key design elements of this protocol will be posted on the GSK website and in publicly accessible database(s) such as clinicaltrials.gov, in compliance with the current regulations.***

GSK also assures that results of this study will be posted on the GSK website and in publicly accessible regulatory registry(ies) within the required time-frame, in compliance with the current regulations. The minimal requirement is to have primary endpoint summary results disclosed at latest 12 months post primary completion date and to have secondary endpoint disclosed at latest 12 months after the Last Subject Last Visit (LSLV) as described in the protocol.

GSK also aims to publish the results of these studies in searchable, peer reviewed scientific literature and follows the guidance from the International Committee of Medical Journal Editors.

APPENDIX C CASE DEFINITIONS OF SEVERE MALARIA AND CEREBRAL MALARIA

Table 33 Case definition of severe *P. falciparum* malaria

Adapted from [WHO, 2015].

P. falciparum parasitemia > 0 detected by microscopy and/or rapid diagnostic test (RDT)

AND one or more of the following, occurring in the absence of an identified alternative cause:

- Impaired consciousness: ~~a Glasgow coma score < 11 in children two years of age or older (≥ 2 years) or~~ a Blantyre coma score < 3 ~~in children less than two years of age (< 2 years)~~;
- .....

Table 34 Case definition of cerebral *P. falciparum* malaria

Adapted from [WHO, 2015].

Severe *P. falciparum* malaria with coma (~~Glasgow coma score < 11 in children two years of age or older [≥ 2 years] or~~ Blantyre coma score < 3 ~~in children less than two years of age [(< 2 years]~~);

AND

If malaria with seizure: coma persisting for > 30 min after the seizure.
Other treatable causes of coma should be excluded before diagnosing cerebral malaria (e.g. hypoglycaemia, bacterial meningitis).

APPENDIX D SAFETY LABORATORY TESTING: CLS SOUTH AFRICA

- **CSF: PCR testing**

	TEST
Bacteria	Haemophilus influenzae**
	Streptococcus pneumoniae**
	Neisseria meningitidis**
	Salmonella enterica
	Mytobacterium tuberculosis
Viruses	Adenovirus*
	Cytomegalovirus*
	Enterovirus*
	Epstein Bar virus*
	Herpes simplex virus 1 & 2*
	HHV 6 ***& 7****
	Rabies
	Mumps virus*
	Parechovirus*
	Parvovirus B19*
	Varicella Zoster Virus*
Parasite	*Plasmodium* spp

These tests are currently available as a single multiplex PCR.
****These tests are currently available as a single multiplex PCR***.

- **CSF: Other possible PCR testing**

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

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

- **Serum: PCR**

	TEST
Bacteria	***Rickettsia****
Viruses	Cytomegalovirus*
	Enterovirus*
	Haemophilus Influenza
	Parvovirus
	Varicella*
Parasite	Toxoplasmosis

***These tests are currently available as a single multiplex PCR**.

- **Serum: Autoimmune tests**

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