Module 1.8.2

European Union Risk Management Plan (EU-RMP) for Mosquirix (*Plasmodium falciparum* and hepatitis B vaccine (recombinant, adjuvanted))

RMP version to be assessed as part of this application	
RMP Version number	6.1
Data lock point for this RMP	11/JUN/2024
Date of final sign off	31/JAN/2025

Rationale for submitting an updated RMP

The Company proposes to remove meningitis as important potential risk supported by the availability of the results of the Category 3 studies EPI-MAL-003 and MVPE, and to update the remaining safety concerns with the available EPI-MAL-003 and MVPE data.

Editorial updates of Mosquirix EU-RMP 6.0 following the feedback received by the PRAC in the Request for Supplementary Information.

Summary of significant changes in this RMP:

PART	MODULE	Changes made in the present EU-RMP
II	Module SI Epidemiology of the indication and target population	Update of references
II	Module SIII Clinical trial exposure	Updates to the clinical trial exposure up to the Data lock point
II	Module SV Post-authorization experience	Update of content up to the Data lock point
II	Module SVII - Identified and potential risks	Removal of `meningitis` from the list of important potential risks
II	Module SVIII - Summary of the safety concerns	Removal of `meningitis` from the list of important potential risks
III	Pharmacovigilance Plan (including post authorization safety studies)	Update of the pharmacovigilance plan: • Removal of MVPE and EPI-MAL-002 studies. • Amendment of the timelines of the ongoing GSK Phase IV studies.
V	Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)	Removal of `meningitis` from the routine minimization measures. Inclusion of effectiveness data as part of the routine minimization measures.

VI	Summary of the risk management plan	Removal of `meningitis` from the list of important potential risks. Inclusion of effectiveness data as part of the routine minimization measures.
VII	Annexes	Updated Annexes 2,3,4,7, and 8

Other RMP versions under evaluation Not applicable		
Details of the currently approved RMP		
Version number	**Approved with procedure**	**Date of approval (opinion date)**
5.1	EMEA/H/W/002300/II/0043	16/JAN/2020

QPPV Name	Dr. Jens-Ulrich Stegmann, MD Senior Vice President, Head of Clinical Safety & Pharmacovigilance and EU QPPV
QPPV Signature	Electronic signature on file

ABBREVIATIONS

AAP	American academy of pediatrics
ACT	Artemisinin-combination therapy
ADEM	Acute disseminated encephalomyelitis
ADR	Adverse drug reaction
AE	Adverse event
AEFI	Adverse event following immunization
AS	Active Surveillance
ASEI	Adverse event of special interest
ATC	Anatomical therapeutic classification
AHA	Acute hemolytic anemia
AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral therapy
ATP	According-to-protocol
BCG	Bacillus Calmette–Guérin
BCS	Blantyre coma score
C3C	Control group in Malaria-055 PRI
CDC	Centers for disease control and prevention
CHMI	Controlled human malaria infection
CHMP	Committee for medicinal products for human use
CI	Confidence interval
CPMP	Committee for proprietary medicinal products
CS	Circumsporozoite
eCTD	Electronic common technical document
DDT	Dichlorodiphenyltrichloroethane
DLP	Data lock point
DNA	Deoxyribonucleic acid
DQ	Quenched QS-21
DTPw	Diphtheria tetanus pertussis (whole cell)
eCTD	Electronic Common Technical Document
EEA	European economic area
EHS	Enhanced hospitalization surveillance
EIR	Entomological inoculation rate
ELISA	Enzyme-linked immunosorbent assay
EMA	European medicines agency
EPI	Expanded program on immunization
EU	European union
GBS	Guillain-Barre syndrome
GLP	Good laboratory practice
GMT	Geometric mean titre
GPRD	UK general practice research database
G6PD	Glucose-6-phosphate dehydrogenase
GSK	GlaxoSmithKline
GVP	Good pharmacovigilance practices
HDSS	Health and demographic surveillance system
HEE	Hypotonic hypo-responsive episode
HepB	Hepatitis B vaccine

Hib	Haemophilus influenzae type B
HbAC	Haemoglobin C trait
HbC	Hemoglobin C
HbCC	Haemoglobin C disease
HbAS	Sickle cell trait
HbS	Sickle haemoglobin
HbSS	Sickle cell disease
HIV	Human immunodeficiency virus
HSP	Henoch-Schonlein purpura
IA	Interim Analysis
IDMC	Independent Data Monitoring Committee
IgE	Immunoglobulin E
INN	International non-proprietary name
IPTi	Intermittent preventive treatment in infants
IRR	Incidence rate ratio
IRS	Indoor residual spraying
ITT	Intention-to-treat
ITN	Insecticide-treated nets
JTEG	Joint technical expert group (WHO)
KD	Kawasaki disease
LLIN	Long-lasting insecticide-treated nets
QPPV	Qualified person for pharmacovigilance
MPAC	Malaria Policy Advisory Committee
MedDRA	Medical dictionary for regulatory activities
MenC	Meningococcal C vaccine
MPL	3-O-desacyl-4'- monophosphoryl lipid A
MTI	Malaria transmission intensity
MVPE	Malaria vaccine pilot evaluation
NIH	US national institute of health
OPV	Oral polio vaccine
OR	Odds ratio
PAES	Post-authorisation efficacy study
PB	Purified bulk
PCR	Polymerase chain reaction
PCV	Pneumococcal conjugate vaccine
pIMD	Potential immune-mediated disorder
PMC	Perennial Malaria Chemoprevention
PSUR	Periodic safety update report
PhV	Pharmacovigilance
QS-21	Quillaja Saponaria Molina (fraction 21)
R3C	3-dose Mosquirix group in Malaria-055 PRI
R3R	4-dose Mosquirix group in Malaria-055 PRI
RBM	Roll back malaria
RMM	Risk minimisation measure
aRMM	Additional risk minimisation measure
RMP	Risk management plan
RSI	Reference safety information

RTS	A portion of the *P. falciparum* circumsporozoite protein fused with hepatitis B surface antigen
S	Hepatitis B surface antigen
SAE	Serious adverse event
SAGE	Strategic Advisory Group of Experts on Immunization
SD	Standard deviation
SE	Study end
SJS	Stevens-Johnson syndrome
SMC	Seasonal malaria chemoprevention
SmPC	Summary of product characteristics
SP	Sulfadoxine-pyrimethamine
SP-AQ	Sulfadoxine-pyrimethamine-amodiaquine
SSA	Sub-Saharan Africa
TEN	Toxic epidermal necrolysis
TI	Transmission intensity
TVC	Total vaccinated cohort
VE	Vaccine efficacy
VPL	Virus-like particles
WAZ	Weight-for-age Z score
WHO	World health organization

Trademark Information

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PART I: PRODUCT(S) OVERVIEW

Table 1 Product Overview

Active substance(s) **(INN or common name)**	*Plasmodium falciparum* and hepatitis B vaccine (recombinant, adjuvanted)
Pharmacotherapeutic group(s) (ATC Code)	J07XA01
Marketing Authorization Holder/ Applicant	GlaxoSmithKline Biologicals S.A.
Medicinal products to which this RMP refers	Plasmodium falciparum and hepatitis B vaccine (recombinant, adjuvanted)
Invented name(s) in the European Economic Area (EEA)	Mosquirix
Marketing authorization procedure	European procedure through Article 58 of Regulation (EC) No 726/2004.
Brief description of the product	Chemical class Mosquirix is an inactivated malaria vaccine intended for use in *Plasmodium falciparum* endemic regions. It is a pre-erythrocytic vaccine designed to help the immune system to limit the ability of the *P. falciparum* parasite to infect, mature and multiply in the liver
	Summary of mode of action The circumsporozoite (CS) protein is abundantly present on the surface of the sporozoite. Mosquirix induces the production of anti-CS antibodies and CS-specific activated T cells. Although no correlate of protection has currently been established, both humoral and cellular immune responses are considered to contribute to protection against P. falciparum infection. Mosquirix induces antibodies against hepatitis B surface antigen (anti-HBs antibodies). An anti-HBs antibody titre ≥10 mIU/mL correlates with protection against hepatitis B virus infection.
	Important information about its composition The RTS,S antigen consists of a portion of the P. falciparum circumsporozoite protein fused with hepatitis B surface antigen (RTS), and combined with hepatitis B surface antigen (S) and is in the

	form of non-infectious virus-like particles (VLPs) produced in yeast cells (Saccharomyces cerevisiae) by recombinant DNA technology. The GlaxoSmithKline proprietary AS01E adjuvant system is composed of Quillaja saponaria Molina, fraction 21 (QS-21) (25 µg) and 3-O-desacyl-4'-monophosphoryl lipid A (MPL) (25 µg) in a liposomes suspension.
Reference to the Product Information	Please refer to Module 1.3.1 of eCTD for the proposed update of the currently approved product information.
Indication(s) in the EEA	Mosquirix is indicated for the active immunization against malaria caused by *P. falciparum* and hepatitis B in infants and children aged 6 weeks to 17 months. **Note**: The use of Mosquirix should be based on official recommendations considering Plasmodium falciparum malaria epidemiology in different geographical areas
Dosage in the EEA	Three doses, each consisting of 0.5 mL, should be given at monthly intervals. A fourth dose is recommended 18 months after the third dose.
Pharmaceutical form(s) and strengths	Powder and suspension for suspension for injection. Following reconstitution, one dose (*i.e.* 0.5 mL) contains 25 µg of RTS,$S^{1,2}$ adjuvanted with $AS01_E$[3]. 1. portion of *P. falciparum* circumsporozoite protein fused with hepatitis B surface antigen (RTS) and combined with hepatitis B surface antigen (S). 2. in the form of non-infectious virus-like particles (VLPs) produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology. 3. $AS01_E$ is composed of *Quillaja saponaria Molina*, fraction 21 (QS-21) (25 µg) and 3-O-desacyl-4'- monophosphoryl lipid A (MPL) (25 µg).
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 Malaria caused by Plasmodium falciparum

Incidence/ Prevalence

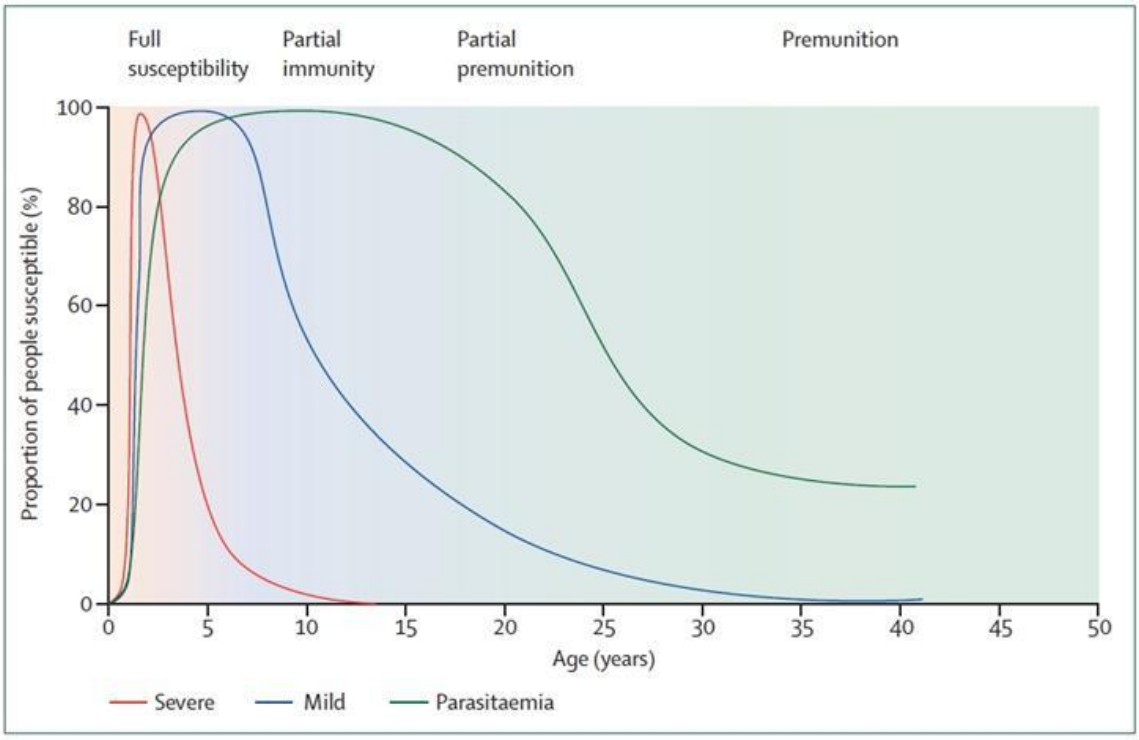
Malaria is a life-threatening disease caused in humans by 5 species of the genus Plasmodium: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*. Of these 5, *P. falciparum* is recognised as being the major cause of severe morbidity and mortality.

P. falciparum is present predominantly in SSA, where it accounts for 98% of plasmodium-causing malaria in humans. Most (88%) malaria cases occur in the WHO African Region. Globally in 2022, there were an estimated 249 million malaria cases, an increase of 5 million cases compared with 2021. Malaria case incidence declined from 81 per 1000 population at risk in 2000 to 57 in 2019. Following a small increase of 3% in 2020, incidence rates have remained stable over the past 3 years. In 2022, malaria case incidence was 58 per 1000 population at risk [WHO 2023a]

Between 2000 and 2019, malaria deaths declined steadily, from 864 000 in 2000 to 576 000 in 2019. In 2020, there was an increase of 55 000 malaria deaths to an estimated 631 000, partly as a result of the disruptions in access to malaria prevention and case management tools due to the COVID-19 pandemic; this increase was followed by a marginal decline in 2021 and 2022, to 610 000 and 608 000, respectively.

The WHO African Region continues to carry a disproportionately high share of the global malaria burden [WHO 2023a]. In SSA, the vast majority of malaria cases are due to *P. falciparum*. Transmission intensities may be very high, with EIR as high as 1,000/year recorded. In this context, most malaria infections in adults are asymptomatic, due to partial natural immunity, and the greatest burden of malaria morbidity and mortality is therefore observed during early childhood (Figure 1) [White 2014, Sarda 2009].

Figure 1 Relation between age and malaria severity in an area of moderate transmission intensity [Directly from White, Lancet 2014, as adapted from Sarda, Infect Immun 2009].



With repeated exposure, protection is acquired, first against severe malaria, then against clinical malaria, and, much more slowly, against microscopy-detectable parasitaemia [Sarda 2009]. The malaria burden, as defined by three outcomes (general clinical malaria, hospitalisations with parasitaemia and death), shifts towards younger ages with increasing transmission intensity, although marked seasonality moderates this effect. These trends, reported in published studies, persist despite known limitations in reporting systems [Griffin 2014; Hay 2010; Abdullah 2007].

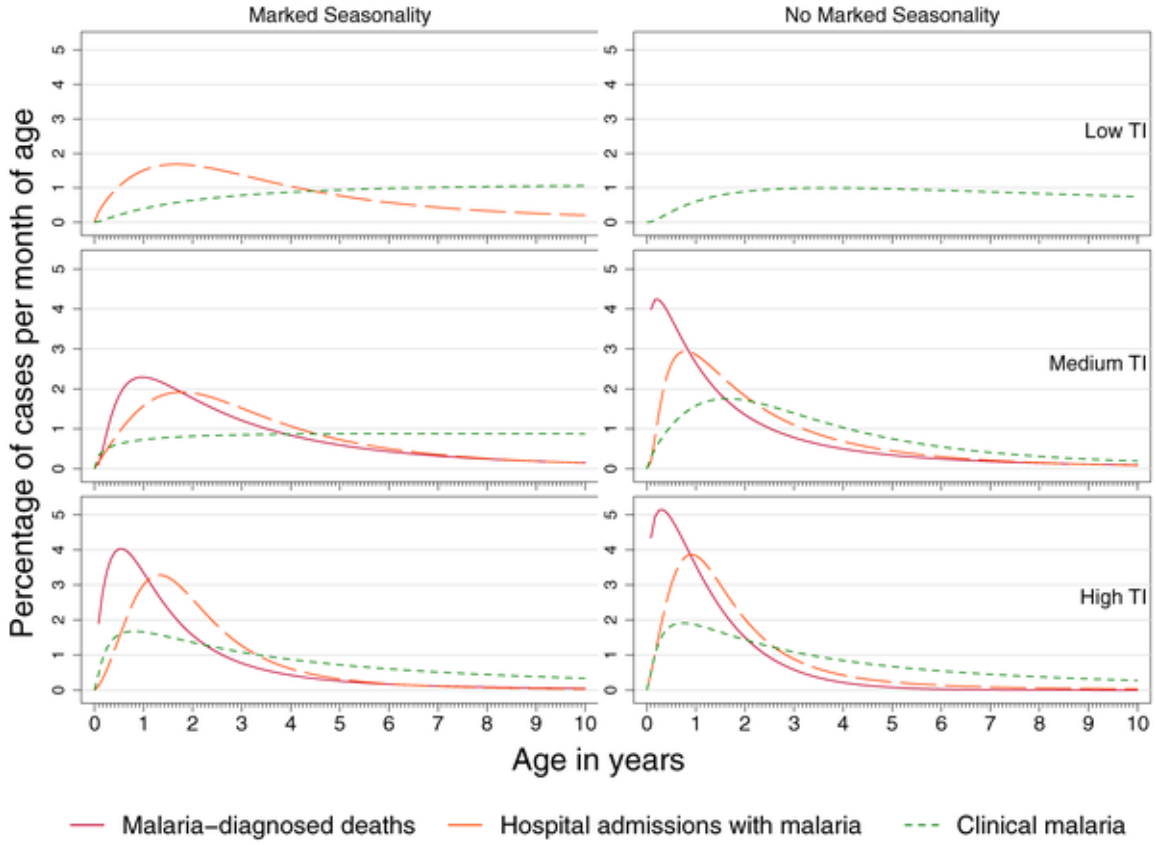
This shift suggests that natural immunity develops over time, depending upon the frequency and duration of parasite exposure from birth [Okiro 2009a; Carneiro 2010; Mawili-Mboumba 2013].

Carneiro et al (2010) conducted a systematic review of the literature published over a 25-year period (1980 through 2005) to examine the influence of *P. falciparum* transmission intensity on age patterns and severity of outcomes. Maximum likelihood methods were used to demonstrate that uncomplicated clinical malaria was relatively evenly distributed across the first 10 years-of-life for all transmission levels/settings; however, the burden tended to shift toward younger children in higher transmission intensity settings, regardless of seasonality characteristics. The authors noted that, due to study methods, the burden in younger children was probably underestimated, especially in areas with marked seasonality (Figure 2) [Carneiro 2010].

Hospitalisations with parasitaemia, a marker of severe malaria, were more commonly reported in the younger age groups than outpatient clinical malaria cases in all settings. This phenomenon (*i.e.,* of more severe disease manifestations in younger children) became more pronounced with increasing malaria transmission intensity and decreasing seasonality.

Similarly, a distinctive shift in the peak age towards younger children was more pronounced for mortality, especially as transmission becomes more intense [Carneiro 2010].

Figure 2 Age-patterns of *P. falciparum* malaria in Sub-Saharan Africa



Age distribution of uncomplicated clinical malaria, hospital admissions with malaria and malaria-diagnosed deaths per month of age in children under ten years of age, by transmission intensity (TI) and seasonality of malaria transmission [Carneiro 2010]

The declining risk of severe malaria with increasing age, and the trend for severe malaria to be concentrated in younger children, both suggest that either limited parasite exposure might be sufficient to confer some degree of immunity, or that age itself modifies risks for severe malaria [Okiro 2009b; Carneiro 2010].

The trend for decreasing age of malaria burden as malaria transmission intensity increases was reflected in cross-sectional studies conducted in Gabon in 2005, 2008 and 2011.The objective of the studies was to describe malaria burden among febrile

children less than 11 years-of-age, and 6 years after control strategies were implemented in 2005. After a uniform drop in prevalence from 2005 to 2008, some sites followed with an increase in 2011. The risk in 2008 was highest in children >5 years, although this risk decreased in the 2011 survey. The authors concluded that the epidemiology, with respect to prevalence and age is changing, tending to toward the >5 age group being at greatest risk [Mawili-Mboumba 2013].

Achieving the 2015 Millennium Development Goals, updated by RBM, to reduce global malaria deaths to near zero; reduce global malaria cases by 75% (from the levels in 2000) and to eliminate malaria in 10 new countries were not achieved.

The barriers that prevented the achievement of these goals included limited access to, and the capabilities of, local health care services (and hence access to timely, good quality diagnostic and treatment services) and the dramatic increase in recent years of the spread and level of resistance to the insecticides commonly used to control the mosquito malaria vector, which threatens the success of control programmes [Ranson 2016].

Additional challenges in malaria control include the availability and use of artemisinin monotherapy, insufficient coverage of recommended control tools in the populations at risk, and the limitations inherent in recommended control tools such as IRS, ITN, and LLIN.

An ongoing burden of the most severe manifestations of malaria persists in the youngest age groups in much of SSA. In this context, the addition of a vaccine that can prevent malaria cases and deaths due to *P. falciparum* has the potential to significantly reduce the malaria burden in areas of greatest need.

SI.1.1 Demographics of the population in the authorized indication and risk factors for the disease

Risk factors for malaria include age, HIV/AIDS status and sickle cell disease.

In 2022, in the WHO African region about 94% of all malaria cases and 95% of deaths were recorded. Children under 5 years of age accounted for about 78% of all malaria deaths in the Region [WHO2023a]. Four African countries accounted for approximately half of all malaria deaths worldwide: Nigeria (26.8%), the Democratic Republic of the Congo (12.3%), Uganda (5.1%) and Mozambique (4.2%) [WHO 2023].

In SSA, the vast majority of malaria cases are due to *P. falciparum, w*ith transmission intensities varying from low to very high, and EIR as high as 1,000/year recorded. In this context, most malaria infections in adults are asymptomatic, due to build up of (partial) natural immunity after multiple exposures – premunition [Obi 2010]. This protective immunity to clinical malaria rather than infection may be of long duration and is characterized by a low parasitemia which mostly persists in the presence of circulating antibodies to the various malaria stages and in the absence of clinical disease. The greatest burden of malaria morbidity and mortality is therefore observed during early childhood in the context of initial infections [White 2014, Sarda 2009].

Between 2010 and 2022, reported cases in children aged under 5 years, represented 38.9% (2010), 37.0% (2015), 36.6% (2022) percentage of total cases in West Africa WHO Africa subregion, 44.9% (2010), 42.6% (2015), 43.8% (2022) in Central Africa, 40.5% (2010), 29.9% (2015), 35.1% (2022) in high transmission areas of East and Southern Africa, and 27.5% (2010), 13.7% (2015), 10.8% (2022) in low transmission areas of East and Southern Africa. Reported deaths in children aged under 5 years in 2022, per WHO Africa subregions, were: 20 600 (West Africa), 28 700 (Central Africa), 7207 (in high and low transmission areas of East and Southern Africa) [WHO 2023].

HIV infection, through immunosuppression, affects the acquisition and persistence of immune response to malaria. Theoretically, HIV infection could increase morbidity and mortality attributable to malaria in two ways. First, immunosuppression might increase susceptibility to malaria, with an increased occurrence of clinical and severe malaria. Second, because immunosuppressed patients have more frequent malaria infections and higher parasite density or delayed clearance of parasitaemia, these individuals might contribute to increasing the parasite biomass and transmission. Yet, interactions between the two diseases might be limited by differences in geographic distribution (when HIV is more prevalent in urban areas and malaria is more prevalent in rural areas) and in age patterns (HIV mainly affects adults, whereas the prevalence of malaria is higher in children in areas of high malaria transmission) [Flateau 2011].

Data from prospective cohort studies indicate a higher prevalence of clinical malaria in HIV-infected children than in children without HIV, increasing with the severity of immunosuppression, [Kamya 2007; Mermin 2004; Colebunders 1990] whereas parasite density was similar for HIV-infected and HIV-uninfected children [Otieno 2006; Grimwade 2003] Moreover, HIV infection was significantly associated with severe Plasmodium falciparum malaria in children older than 1 year in Kenya (odds ratio [OR] 12) [Berkley 2009].

The WHO estimates that 300,000 children are born with SCD each year, 75% of whom are in sub-Saharan Africa [Roucher 2012; Silva-Nunes 2007]. The gene does not protect against infection by the malaria parasite, but it prevents establishment of disease following infection [Sabeti 2006]. As SCT offers relative protection against malaria, one might expect the protection to be at least as effective in the homozygous state (SS) [Ashley-Koch 2000]. However, clinical experiences have shown it to be more dangerous since malaria does not only worsen the preexisting anemia in patients with SCD, to the point of becoming life threatening but also, the abnormal splenic function in SCD patients hinders clearance of parasitized RBCs [Luzzatto 2012].

SI.1.2 The main existing treatment options

In the last century, chloroquine was the most successful treatment against malaria, but by the 1980s, widespread resistance had developed, and the world was left without an effective treatment for malaria.

Since around 2003, countries have shifted their national drug policies towards the use of ACTs and the WHO recommends ACTs for the treatment of uncomplicated malaria caused by the *P. falciparum* parasite. By combining 2 active ingredients with

different mechanisms of action, ACTs are the most effective antimalarial medicines available today.

For many years, national malaria control programmes recommended treating children <5 years-of-age presenting with the signs/symptoms of clinical malaria because of the lack of laboratory equipment and trained personnel to perform blood smear testing; however, in 2010, WHO recommended that all suspected cases of malaria should be confirmed with a diagnostic test prior to treatment [WHO 2010], with the aim of targeting the use of ACTs to those who actually have malaria and to reduce the emergence and spread of drug resistance.

WHO currently recommends five ACTs to treat *P. falciparum* malaria. The choice of ACT should be based on the results of therapeutic efficacy studies against local strains of *P. falciparum*. ACTs are efficacious drugs that act rapidly leading to a marked reduction in parasite load and a rapid reduction in temperature. ACTs are however more expensive compared to previous treatments and coverage remains very low in most African countries.

Parasite resistance to artemisinin has recently been detected in Asia in 4 countries of the Greater Mekong sub-region. Despite the observed changes in parasite sensitivity to artemisinin's, ACTs continue to cure patients, provided that the partner drug is still efficacious. In one province in Cambodia, resistance has been found to both components of multiple ACTs. In April 2013, the WHO released their emergency response to artemisinin resistance in the greater Mekong sub-region [WHO 2013]. The WHO Q&A on artemisinin resistance, updated in April 2014, stresses that, given the ever-increasing levels of population movement in Asia and the Pacific, the geographic scope of the problem could widen quickly, posing a health security risk for many countries in the region with ongoing malaria transmission. If resistance were to spread to, or emerge in, India or SSA, the public health consequences could be very serious, as no alternative antimalarial medicine is available at present with the same level of efficacy and tolerability as ACTs [White 2010b].

In addition to treatment options, there are also existing preventive measures, which include vector (*i.e,.* Mosquito) control interventions such as ITNs or LLINs and IRS. Also available are preventive chemotherapies such as IPT and SMC.

It is estimated that malaria control interventions accounted for 663 million (70%) malaria cases averted in SSA since 2001, of which 69% were estimated to have been averted through the use of ITNs, 21% due to ACTs and 10% due to IRS. The percentage of the population at risk protected by IRS has declined slightly since 2016, with less than 6% of the population protected in each WHO region. In 2022, 47 countries implemented IRS to prevent malaria [WHO 2023a].

- **ITNs**

ITNs have been associated with substantial reductions in malaria risk. On the basis of four community-randomized trials using no nets as control, a Cochrane review concluded that, when full coverage is achieved, ITNs reduce all-cause child mortality by an average of 17% (range 10–24%) in SSA [Lengeler 2004].

The general implication of this is that 5.5 lives could be saved per year for every 1,000 children under 5 years-of-age sleeping under a bednet. The protective efficacy against uncomplicated malaria was estimated at around 50%. In one trial evaluating severe malaria disease as an endpoint, a 44% reduction in the frequency of severe malaria episodes was observed during 2 years following the introduction of ITNs [Nevill 1996].

Accumulated evidence of the effectiveness of ITNs in reducing the burden of malaria has led to WHO and national recommendations of their use in many SSA countries.

It has been hypothesized that sustained use of ITNs for young children may increase malaria morbidity and mortality rates in older children, as a result of a delayed acquisition of natural immunity to malaria, especially within areas of intense, perennial malaria transmission; however, 3 long-term follow-up ITN studies showed no evidence of increased mortality in older children following sustained use of ITNs for up to 7.5 years [Binka 2002; Diallo 2004, Eisele 2005]. Another trial, by Müller et al (2006), came to the same conclusion.

- **IRS**

IRS has become an increasingly popular method of insecticide use for malaria control, and many recent studies have reported on its effectiveness in reducing malaria burden in a single community or region.

A meta-regression analysis on IRS, based on 13 published studies, revealed a summary relative risk for reducing malaria prevalence of 0.38 (95% confidence interval 0.31–0.46), which indicated a risk reduction of 62%. While an excessive degree of heterogeneity was found between the studies selected, the results indicate that IRS is more effective with high initial prevalence, multiple rounds of spraying, use of DDT), and in regions with a combination of *P. falciparum* and *P. vivax* malaria [Dohyeong 2012].

- **Preventative chemotherapy**

Preventive chemotherapy involves the use of complete treatment courses of effective antimalarial medicines with the goal of preventing malaria infection and thereby reducing morbidity and mortality due to malaria. The 2 main strategies currently recommended by WHO are PMC and SMC.

PMC, previously known as IPTi, is the administration of a full treatment course of an antimalarial medicine at predefined intervals, regardless of whether the child is infected with malaria, in order to prevent illness in moderate to high perennial malaria transmission settings. The goal of PMC is to protect young children by establishing preventive antimalarial drug concentrations in the blood that clear existing infections and prevent new ones during the age of greatest risk of severe malaria. Previously, this recommendation referred to IPTi. Since the initial recommendation, additional data have documented the value of malaria chemoprevention in children aged 12 to 24 months. The name has been changed to PMC because the updated recommendation no

longer limits the intervention specifically to infants and reflects the malaria transmission settings in which the intervention should be considered. [WHO 2023]

A meta-analysis on the administration of IPTi (currently named as PMC) through the standard EPI showed 30% efficacy against clinical malaria and 23% efficacy against all-cause hospitalization [Aponte 2007].

Since 2009, WHO has recommended that "all infants at risk of *P. falciparum* infection in SSA with moderate-to-high malaria transmission intensity and low levels of parasite resistance to the recommended agent SP should receive preventive malaria treatment through immunization services at defined intervals that correspond to routine vaccination schedules".

Previously, PMC was recommended in infants (<12 months of age as IPTi) Since the initial recommendation, additional data have documented the value of malaria chemoprevention in children aged 12 to 24 months [WHO 2023a].

2. SMC, previously called IPTc, was recommended by the WHO in 2012 and is the intermittent administration of full treatment courses of an effective antimalarial medicine during the malaria season to prevent malarial illness in children aged 3 to 59 months with the objective of maintaining therapeutic antimalarial drug concentrations in the blood throughout the season with the highest malaria risk. WHO recommends the use of SMC in areas of highly seasonal malaria transmission in Africa [WHO 2015].A meta-analysis of SMC studies in which a therapeutic course of SP plus amodiaquine (SP-AQ) was given once per month to children under 5 years-of-age during the peak malaria transmission season showed an 82% reduction in the incidence of clinical malaria episodes and a protective effect of 57% against all-cause mortality during the malaria transmission season [Wilson 2011].Combining several interventions such as vector control, prophylactic vaccination, and mass drug administration, thus targeting different stages of the parasite cycle, may offer the best control of malaria transmission as shown in a double-blind, randomized, controlled trial involving children aged 5 to 17 months in Burkina Faso and Mali. This study showed that seasonal vaccination with RTS,S/AS01$_E$ is non-inferior to SMC in preventing uncomplicated clinical malaria [Chandramohan, 2020; Chandramohan, 2021]. The combination of RTS,S/AS01$_E$ and chemoprevention was superior to RTS,S/AS01$_E$ and to SMC alone with respect to reducing the incidence of uncomplicated clinical malaria, hospital admissions with severe malaria, and deaths from malaria. In addition, a review by Greenwood et al. also showed that the combination of Mosquirix and SMC were important to prevent malaria in children at increased risk of AEs of clinical malaria, such as those with sickle cell disease, and during the final stages of a malaria elimination programme when vaccination could be combined with repeated rounds of mass drug administration [Greenwood, 2021].

As of 2014, 6 of the 15 countries suitable for seasonal malaria chemoprevention, and 2 outside the Sahel sub-region (Congo and Togo), had adopted the policy. One country has adopted IPTi [WHO 2015]. Twelve countries in the subregion implemented SMC; the number of rounds varied, but about 43.1 million children were provided with at

least one dose of SMC per cycle. Mauritania implemented SMC for the first time in 2022 [WHO 2023a].

SI.1.3 Natural history of the indicated condition in the (untreated) population, including mortality and morbidity

Globally, the number of malaria deaths fell from an estimated 864,000 in 2000 (range: 835,000 , 905,000), to 608,000 in 2022 (range: 566,000 738,000), a decline of % . In 2020, there was an increase of 55 000 malaria deaths to an estimated 631 000, partly as a result of the disruptions in access to malaria prevention and case management tools due to the COVID-19 pandemic; this increase was followed by a marginal decline in 2021 and 2022, to 610 000 and 608 000, respectively. Most deaths in 2022 were in the WHO African Region (94%), followed by the WHO South-East Asia Region (3%) The percentage of total malaria deaths among children aged under 5 years declined from 86.8% in 2000 to 76.0% in 2022. [WHO 2023]

Reductions in malaria deaths contributed substantially towards achieving the Millennium Development Goal 4 target of reducing the under-5's mortality rate by two thirds between 1990 and 2015. However, serious bottlenecks remain in providing full access to malaria prevention, diagnostic testing, and treatment. Progress has been uneven, with some countries carrying a disproportionately high share of the global malaria burden. Fifteen countries – mainly in SSA – account for 80% of malaria cases and 78% of deaths globally., [WHO 2015].

SI.1.4 Important co-morbidities

Following the WHO Policy recommendation, published in May 2024 [WHO 2024a Mosquirix is currently intended for the paediatric population in SSA aged from 5-17 months. In SSA, some important comorbidities, such as HIV infection, malnutrition, and haemoglobinopathies, including G6PD and sickle cell disease, are frequent in the target population.

- **HIV infection**

Malaria and HIV are two of the most important infectious diseases in SSA and co-infection is common in this region.

There is growing evidence of biological interaction between HIV and malaria in co-infected people [Reithinger 2009; Slutsker 2007]. Reviews indicate that these 2 infections interact bi-directionally and synergistically with each other. HIV infection increases the burden, clinical severity and transmission of malaria [Achan 2008; Ned 2005].

Malaria is associated with increased viral loads by different mechanisms [Alemu 2013], including strong CD4+ cell activation and up-regulation of pro-inflammatory cytokines, thereby providing an ideal microenvironment for viral replication [Iliyasu 2013].

HIV and malaria co-morbidity results in worse outcomes for both diseases: clinical malaria episodes adversely affect HIV infection by transiently increasing viral load, whereas HIV infection increases the risk for, and the severity of, malaria infection [Whitworth 2005; Whitworth 2000 and Otieno 2006]; however, when the prevalence of both diseases is either very high or very low, the epidemiological impact of the interaction will be minimal. The latter has been confirmed by a review evaluating multiple cross-sectional surveys in western SSA [Van Geertruyden 2014; Van Eijk 2002; Cuadros 2011].

Although the Malaria-058 trial, performed in HIV-positive subjects, was not powered to show efficacy, Mosquirix showed a trend for protection against clinical malaria above that provided by the antimalarial effects of daily co-trimoxazole, used to prevent opportunistic infections in this HIV-infected population.

HIV infection has been associated with a higher prevalence of clinical malaria, increasing with the severity of immunosuppression and with a higher risk of severe malaria, severe anemia, coma and death, in children [Flateau 2011]. A prospective study in Uganda, for instance, demonstrated that HIV-positive children had a nearly 2-fold increased risk of clinical malaria compared to HIV-negative children (IRR=1.77, 95%CI 1.1-2.5) [Mermin 2004]. In Kenya, HIV-positive children had a 12-fold increased risk of severe malaria (OR=12, 95%CI 5.7-25) and a 15-fold increased mortality risk (OR=15, 95%CI 6.5-33) [Otieno 2006].

HIV infection does not impair clinical and parasitological responses to treatment in uncomplicated malaria, even in immunocompromised children, and does not increase the risk of malaria recurrence [Flateau 2011].

In areas with stable malaria, HIV infection increases the risk of malaria infection and clinical malaria in adults, and the risk is inversely correlated with the CD4 cell count, as has been demonstrated in several longitudinal studies [Flateau 2011].

There is no clear evidence yet whether HIV infection increases the risk of severe malaria and of malaria-related mortality. In areas with unstable malaria transmission on the other hand, HIV-infected adults are at increased risk of developing severe malaria and of malaria-related death [Grimwade 2004]. HIV-infected adults with low CD4 counts may be more susceptible to antimalarial treatment failure compared to those not infected with HIV [Flateau 2011].

- **Haemoglobinopathies**

Haemoglobinopathies are genetic disorders whereby haemoglobin, normally composed of 2 alpha and 2 beta globin chains, is altered by genetic polymorphisms that encode single amino acid substitutions in beta-globin (as in HbS and HbC) or reduce production of alpha- and beta-globin chains (alpha- and beta-thalassemia).

In populations in which malaria is (or was) endemic, the prevalence of haemoglobin disorders ranges from 0.3 to 25 per 1,000 live births. The correlation between the distribution of these genetic disorders and the distribution of malaria is explained by

natural selection following a protective effect against malaria caused by *P. falciparum* [Modell 2008].

- ***HbS***

Worldwide, there are an estimated 20-25 million individuals with sickle cell disease (HbSS), of which 12-15 million are in SSA. In some African regions, the prevalence rate exceeds 25%. The prevalence of the heterozygous form (sickle cell trait; HbAS) ranges between 10% and 40% in SSA. In countries where the trait prevalence is above 20% the disease affects about 2% of the population.

Sickle cell disease is associated with increased susceptibility to malaria, which may be partly explained by the impaired splenic function common in these patients; however, in its heterozygous form (sickle cell trait), the gene provides substantial protection against clinical malaria.

A meta-analysis of 5 large case-control studies showed that HbAS reduced the risk of severe malaria by 90% (summary OR 0.09, 95% CI 0.06-0.12) [Taylor 2012], and 2 Kenyan cohort studies found that HbAS reduced the risk of incident severe malaria by more than 70% [Williams 2005a; Williams 2005b].

HbAS was associated with a lower, but still significant, risk reduction in uncomplicated malaria of 30% in another meta-analysis of five longitudinal studies (summary IRR 0.69, 95%CI 0.61-0.79). Protection against acquiring asymptomatic malaria infections (parasitaemia) has not been demonstrated [Taylor 2012].

- **HbC**

HbC is common on the African continent, but the highest prevalence (>20%) is found in West-Africa [Piel 2003]. Patients with the haemoglobin C trait (HbAC) are phenotypically normal with no clinically evident limitations or symptoms, while those with haemoglobin C disease (HbCC) may have a mild degree of haemolytic anaemia, splenomegaly, and borderline anaemia.

HbC appears to protect against severe malaria to a lesser extent than HbS: a meta-analysis of four African case-control studies estimated a summary OR for severe malaria of 0.27 (95%CI 0.11-0.63) for children with homozygous HbCC and of 0.83 (95%CI 0.74-0.92) for those with heterozygous HbAC. Protection against uncomplicated and asymptomatic malaria has not been established [Taylor 2012].

- **Alpha- and beta- thalassemia**

Beta-thalassemia results from changes in beta-globin gene(s). Although the disorder widely occurs in areas where malaria is or has been endemic, lower prevalence has been measured in SSA, which may be the result of the competition with the strongly protective sickle cell gene.

There are few epidemiological data from SSA; 1 case-control study, conducted in Liberia, found that the prevalence of beta-thalassemia was lower in cases of uncomplicated malaria compared to community controls [Willcox 1983].

Alpha-thalassemia results from defects in the 4 alpha-globin genes and comprises a wide clinical spectrum from asymptomatic individuals (only one alpha-globin gene affected) to the absence of all 4 genes, which is incompatible with life and results in stillbirths.

Case-control studies have shown that in children with homozygote alpha-thalassemia, the risk of severe malaria is reduced by 30%, and in heterozygotes by 20%; there was no protective effect against uncomplicated malaria and findings on asymptomatic malaria remain inconclusive [Taylor 2012].

- **G6PD deficiency**

G6PD is an essential enzyme for the metabolism of the erythrocyte and is important in the control of oxidative damage in erythrocytes. The gene for G6PD is located on the X-chromosome so the deficiency is inherited in a sex-linked fashion, with full expression in homozygous males and homozygous females and only in a proportion of female heterozygotes.

G6PD- deficiency affects an estimated 400 million people worldwide and in some parts of SSA the prevalence reaches 35% [WHO 1989]. Clinical manifestations include AHA, jaundice and renal failure, which may lead to death. Most G6PD-deficient people are asymptomatic, unless they are exposed to exogenous oxidative stress, which causes hemolysis.

The anti-malarial drug primaquine, recommended for the treatment of *P. vivax*, *P. malariae* and *P. ovale*, is an oxidant and may cause mild to life-threatening AHA in G6PD-deficient people.

Studies from SSA have demonstrated a protective effect of 50%-70% against severe malaria in hemizygous males with G6PD [WHO 1989, Ruwende 1995].

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

In accordance with the CPMP note for guidance on pre-clinical pharmacological and toxicological testing of vaccines (CPMP/SWP/465/95), the guideline on adjuvants in vaccines for human use (EMEA/CHMP/VEG/134716/2004) and the WHO guidelines on non-clinical evaluation of vaccines [WHO 2005], non-clinical studies for a vaccine intended for prophylactic and paediatric use were performed for RTS,S/AS01$_B$.

The results from these studies support the final paediatric formulation RTS,S/AS01$_E$ (Mosquirix) and therefore, only these were included in the EU "Article 58" application. The RTS,S/AS01$_B$ formulation contains twice the amount of RTS,S antigen, MPL and QS-21 immunoenhancers and liposomes compared to the final paediatric formulation selected, RTS,S/AS01$_E$ (Mosquirix).

Non-clinical toxicology and pharmacology studies were also performed with MPL and QS-21 immunoenhancers alone, as well as on the AS01$_B$ adjuvant system alone, as recommended in the EMA "guideline on adjuvants in vaccines for human use" (EMEA/CHMP/VEG/134716/2004).

An overview of the GLP toxicology studies performed with RTS,S/AS01$_B$; AS01$_B$, QS-21/DQ and MPL and other non-clinical studies performed with RTS,S/AS01$_E$ or AS01$_B$ that are relevant from a safety perspective, are provided in the table below. The GLP toxicology package was generated in adult animals, in accordance with available regulatory guidance.

KEY SAFETY FINDINGS FROM NON-CLINICAL STUDIES AND RELEVANCE TO HUMAN USAGE:

Table 2 Key Safety findings (from non-clinical studies)

Key Safety findings (from non-clinical studies)	Relevance to human usage
RTS,S/AS01 non-clinical program One repeat-dose toxicity study** Two local tolerance studies One safety pharmacology study One immunology study assessing the anti-catalase response to a 1600L-scale RTS,S lot containing a small amount of catalase **No key safety findings**	There are no limitations for human usage based on the results of these non-clinical studies. **In the repeat-dose toxicity study, there were no treatment-related clinical or histological signs of meningitis, encephalitis, convulsion, neurotoxicity and/or inflammation of the brain in any of the animals examined. The only observation related to the brain was a slight inflammatory infiltration of the choroid plexus in some rabbits, but these observations were considered unlikely to be a direct effect of treatment and therefore of no toxicological significance.

Key Safety findings (from non-clinical studies)	Relevance to human usage
QS-21/DQ non-clinical program Two repeat-dose toxicity studies Two local tolerance studies Two in vitro and one in vivo genotoxicity studies **No key safety findings**	There are no limitations for human usage based on the results of these non-clinical studies.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

SIII.1 Brief overview of development

In early studies, the RTS,S antigen was formulated with the AS02 adjuvant system. AS02 contains the same immunoenhancers (*i.e.* QS-21and MPL), as the current AS01 adjuvant system but uses a proprietary oil-in-water emulsion as vehicle *in lieu* of a liposomal suspension. The RTS,S/AS01 formulation was developed in parallel with the RTS,S/AS02 formulation with the aim of improving immune response and vaccine efficacy.

Three studies conducted in *naïve* or semi-immune adult populations were instrumental for final adjuvant system selection: Malaria-027, Malaria-044 and Malaria-048. Of note, the RTS,S/AS02 and RTS,S/AS01 formulations tested in adult populations contained twice the amounts of RTS,S antigen and immunoenhancers compared to the final paediatric formulation selected, RTS,S/AS01$_E$ (*i.e.* Mosquirix). The paediatric dosage was selected based on dose-ranging studies performed with RTS,S/AS02, which showed that half of the adult dosage provided adequate immunogenicity with an acceptable safety profile.

Upon evaluation of the AS01 adjuvant system, the RTS,S/AS01 candidate vaccine was selected for further development based on: superiority over RTS,S/AS02 in terms of humoral and cell-mediated immune responses in both non-clinical and clinical studies and an acceptable safety profile. The clinical development of RTS,S/AS02 has been stopped.

Fourteen Phase II studies evaluated either immunogenicity alone or efficacy and immunogenicity of the RTS,S/AS02 and RTS,S/AS01 paediatric dosage formulations in the paediatric population of diverse malaria endemic areas of the following SSA countries: The Gambia, Mozambique, Gabon, Ghana, Tanzania and Kenya. One of these paediatric studies (Malaria-050) provided data on the suitability for administration of RTS,S/AS01 with other WHO EPI vaccines such as diphtheria, tetanus, whole cell pertussis, polio (oral), *Haemophilus influenzae* type b, measles and yellow fever vaccines. Other studies were conducted with RTS,S/AS02 alone and are not detailed in the RMP.

The Phase III development program of Mosquirix included 6 studies:

- A large efficacy and safety trial (Malaria-055 PRI) conducted in 7 African countries (Kenya, Tanzania, Ghana, Gabon, Burkina Faso, Mozambique and Malawi) in 2 age categories (6 to 12 weeks and 5 to17 months at the time of the first dose) using a 0, 1, 2, 20-month schedule for the 4 doses.
- **Malaria-076** was an open extension to Malaria-055 conducted at 3 study sites (Kombewa in Kenya, Korogwe in Tanzania, Nanoro in Burkina Faso) evaluating long term efficacy, safety and immunogenicity of RTS,S/AS01$_E$. In total, follow-up was for 6-7 years post Dose 1. The primary objective was to describe the incidence of severe malaria in the long term over a 3 year period of follow-up pooled across transmission settings, in both age categories.

- A study (Malaria-058) in HIV infected children from 6 weeks to 17 months-of-age using a 0, 1, 2-month schedule in Kenya.
- A study (Malaria-061) documenting lot-to-lot consistency in terms of anti-CS immunogenicity of three lots of Mosquirix (formulated with 1600L commercial scale RTS,S purified bulk) conducted in Nigeria and the non-inferiority of the immune response of these vaccine lots compared to a Mosquirix lot formulated from a 20L pilot scale RTS,S purified bulk lot. This study was conducted in children from 5 to 17 months-old using a 0, 1, 2-month schedule.
- A study (Malaria-063) supporting the hepatitis B indication, lot-to-lot consistency in terms of anti-HBs immunogenicity of three commercial scale lots of Mosquirix and the suitability of co-administration with rotavirus and pneumococcal conjugate vaccines, the more recently implemented vaccines in WHO EPI in SSA, in children from 8 to 12 weeks-of-age using a 0, 1, 2-month schedule conducted in Ghana and Burkina Faso.
- A study (**Malaria-073**) supporting co-administration of RTS,S/AS01$_E$ with yellow fever, measles and rubella vaccines using alternative schedules thereby allowing for flexibility within EPI conducted in Ghana.

SIII.2 Clinical Trial exposure

The majority of subjects enrolled were <18 months-of-age at the time of the first dose, which corresponds to the target population. Furthermore, all subjects enrolled in the Phase III trials were from SSA countries, which is also representative of the target population. In total 14,998 subjects have received RTS,S/AS01 in clinical studies (see repartition in Table 2 and Table 3).

Table 2 Cumulative Subject Exposure to RTS,S/AS01 in Completed GSK-Sponsored Interventional Studies by Age, Sex and Racial Group for Primary Vaccination (At Least One of the First Three Full/ Standard Doses) for Completed Studies (Total Vaccinated Cohort, Primary Vaccination)

	RTS S/AS01 N=14998		Control N=7118		Total N=22116	
	Value or n	%	Value or n	%	Value or n	%
Status						
Completed	14998	100.0	7118	100.0	22116	100.0
Ongoing*	0	0.0	0	0.0	0	0.0
Study ID						
MALARIA-027 (257049_027)	52	0.3	50	0.7	102	0.5
MALARIA-044 (104743)	85	0.6	170	2.4	255	1.2
MALARIA-046 (105874)	90	0.6	90	1.3	180	0.8
MALARIA-047 (106367)	270	1.8	270	3.8	540	2.4
MALARIA-048 (107731)	12	0.1	24	0.3	36	0.2

	RTS S/AS01 N=14998		Control N=7118		Total N=22116	
	Value or n	**%**	**Value or n**	**%**	**Value or n**	**%**
MALARIA-049 (106464)	447	3.0	447	6.3	894	4.0
MALARIA-050 (106369)	340	2.3	171	2.4	511	2.3
MALARIA-055 PRI (110021)	10306	68.7	5153	72.4	15459	69.9
MALARIA-057 PRI (111315)	419	2.8	60	0.8	479	2.2
MALARIA-058 (112745)	99	0.7	101	1.4	200	0.9
MALARIA-061 (113398)	320	2.1	0	0.0	320	1.4
MALARIA-063 (113681)	425	2.8	280	3.9	705	3.2
MALARIA-068 (114460)	55	0.4	0	0.0	55	0.2
MALARIA-071 (117014)	51	0.3	0	0.0	51	0.2
MALARIA-073 (200596)	690	4.6	9	0.1	699	3.2
MALARIA-092 (205081)	130	0.9	0	0.0	130	0.6
MALARIA-094 (204889)	1207	8.0	293	4.1	1500	6.8
Adjuvant* **						
AS01B	333	2.2	0	0.0	333	1.5
AS01E	14665	97.8	0	0.0	14665	66.3
Not applicable	0	0.0	7118	100.0	7118	32.2

N = total number of subjects
n = number of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
% = n / Number of subjects with available results x 100
Data from completed trials

Table 3 Cumulative Subject Exposure to RTS,S/AS01 in Completed GSK-Sponsored Interventional Studies by Age, Sex and Racial Group for a Fourth Full/ Standard Dose for Completed Studies at the Time of the Fourth Dose (MALARIA-055) (Total Vaccinated Cohort, Fourth Dose)

	RTS S/AS01 N=5415		Total N=5415	
	Value or n	%	Value or n	%
Status				
Completed	5415	100.0	5415	100.0
Ongoing	0	0.0	0	0.0
Number of subjects				
MALARIA-055 PRI (110021)	4272	78.9	4272	78.9
MALARIA-073 (200596)	643	11.9	643	11.9
MALARIA-094 (204889)	500	9.2	500	9.2
Age [months] at 4th dose				
N with data	5415		5415	
Mean	26.6		26.6	
SD	5.2		5.2	
Median	26.0		26.0	
Minimum	17		17	
Maximum	44		44	
Missing	0		0	
Age category				
< 5 months	0	0.0	0	0.0
>= 5 months-17 months	4	0.1	4	0.1
> 17 months-18 years	5411	99.9	5411	99.9
>= 18 years	0	0.0	0	0.0
Missing	0	0.0	0	0.0
Gender				
MALE	2783	51.4	2783	51.4
FEMALE	2632	48.6	2632	48.6
MISSING	0	0.0	0	0.0
Geographic Ancestry				
AMERICAN INDIAN OR ALASKA NATIVE	0	0.0	0	0.0
ASIAN	0	0.0	0	0.0
BLACK OR AFRICAN AMERICAN	5415	100.0	5415	100.0
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0.0	0	0.0
WHITE	0	0.0	0	0.0
OTHER	0	0.0	0	0.0
UNKNOWN	0	0.0	0	0.0

N = total number of subjects
n = number of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
% = n / Number of subjects with available results x 100
Data from completed trials

Table 4 presents the exposure to Mosquirix in special populations: HIV-infected children, children with malnutrition and infants born prematurely.

Table 4 Summary of exposure of special populations exposed to Mosquirix (at least one dose of vaccine received)

Special population	Exposure to Mosquirix (at least one dose of vaccine received)
	Persons (n)
HIV-infected (Total)	**204**
HIV (Malaria-058)	99
HIV (Subset of Malaria-055 PRI)	105
Malnourished at the time of the first 3 doses (Subset of Malaria-055 PRI)	**1270**
Low weight-for-age (WAZ = [>-3; ≤ -2])	916
Very low weight-for-age (WAZ = [≤ -3])	354
Malnourished at the time of the fourth dose (Subset of Malaria-055 PRI)	**605**
Low weight-for-age (WAZ = [>-3; ≤ -2])	509
Very low weight-for-age (WAZ = [≤ -3])	96
Preterm infants (Subset of Malaria-055 PRI)	**244**

WAZ = weight-for-age z-score

It should be noted that in the Malaria-055 PRI study, weight-for-age Z-scores and the prematurity status were both recorded at screening. Although there were no protocol-defined objectives pertaining to preterm infants, safety and immunogenicity data were readily retrievable given the protocol-defined procedures required for recording gestational information in subjects who were part of the 6-12 weeks-of-age category. In the analysis, prematurity was defined as <37 weeks gestational age based on maternal history and review of medical records if available.

Also in this study, HIV-infection status was not tested for at screening, so the exposure data presented in Table 4 for HIV infection status in Malaria-055 represents the number of children known to be HIV-infected at study enrolment, or those subsequently diagnosed during the study based on clinical suspicion. In Malaria-058, the children all tested HIV-positive at study enrolment.

In Malaria-055, HIV-infected, malnourished and preterm children were included. It should be noted that one child could be part of one or more of the 3 sub-populations.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Criterion	Reason for exclusion	Is it considered to be included as missing information (Yes/No)	Rationale
A history of allergic reactions (particularly significant IgE-mediated events or anaphylaxis) to previous immunizations	As for other vaccines, a history of allergic reactions to any of the components of the vaccine constitutes a contraindication. Serious anaphylactic reactions that could lead to a life-threatening condition is a risk. Mosquirix should therefore not be administered to children with hypersensitivity to the active substance(s) or to any of the excipients or residue(s) contained in the vaccine or to a previous dose of Mosquirix or Hepatitis B vaccines	No	Hypersensitivity (including anaphylaxis) is included as an important potential risk (it is also a contraindication in the label)
Acute disease at the time of enrolment; defined as the presence of a moderate or severe illness with or without fever. Note: study vaccines could be administered to subjects with a minor illness, such as diarrhoea or a mild upper respiratory tract infection, with or without low-grade febrile illness (i.e. axillary temperature <37.5°C)	Children with an acute disease at the time of vaccine administration may be at higher risk for adverse events, including febrile convulsions, following vaccination. These children were therefore excluded to prevent bias in the evaluation of safety and efficacy of the vaccine. As with other vaccines, the administration of Mosquirix should be postponed in case of severe febrile illness. Minor infection should not result in the deferral of vaccination	No	In cases of active acute illness, it is common clinical practice in the medical community to delay vaccination until this is resolved; however, an assessment of benefit and risk of vaccination should be left to the medical judgment of the prescriber on a case-by-case basis
Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or	Standard safety exclusion criterion in subjects with significant underlying medical	No	In cases of active severe illness, it is common clinical

renal functional abnormality, as determined by physical examination or laboratory screening tests	conditions that would either affect the safety of the subjects participating in the study or would affect the efficacy or safety analyses if the underlying disease/ condition became exacerbated during the study		practice in the medical community to delay vaccination until this is resolved; however, an assessment of benefit and risk of vaccination should be left to the medical judgment of the prescriber on a case-by-case basis
Stage III or IV HIV disease, as defined by WHO. Subjects with a history of Stage III or IV HIV were NOT excluded	HIV infection is common in the target population and because immunodeficient subjects may not have an adequate immune response to vaccination, which could confound evaluation of vaccine efficacy and/or the safety of the subject, they were excluded	Yes	Not applicable
A past history of a neurological disorder or atypical febrile seizure (an atypical febrile seizure being defined per protocol as follows: one 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	Children with a history of a neurological disorder, including atypical febrile seizures, may be at higher risk for developing adverse events, including febrile convulsions, following vaccination	No	Febrile convulsion is included as an important identified risk (it is also included in the warning & precautions section of the label)
Malnutrition requiring hospital admission	Standard safety exclusion criterion in subjects with significant underlying medical conditions that would either affect the safety of the subjects participating in the study or would affect the efficacy or safety analyses if the underlying disease/ condition became exacerbated during the study	No	It is common clinical practice in the medical community to delay vaccination until an active severe illness is resolved; however, an assessment of benefit and risk of vaccination should

			be left to the medical judgment of the prescriber on a case-by-case basis
Severe anaemia (defined in the protocol as haemoglobin level <5.0 g/dL or a haemoglobin level of <8 g/dL associated with clinical signs of heart failure or severe respiratory distress)	Standard safety exclusion criterion in subjects with significant underlying medical conditions that would either affect the safety of the subjects participating in the study or would affect the efficacy or safety analyses if the underlying disease/ condition became exacerbated during the study	No	It is common clinical practice in the medical community to delay vaccination until an active severe illness is resolved; however, an assessment of benefit and risk of vaccination should be left to the medical judgment of the prescriber on a case-by-case basis
Major congenital defects	Standard safety exclusion criterion in subjects with significant underlying medical conditions that would either affect the safety of the subjects participating in the study or would affect the efficacy or safety analysis if the underlying disease/ condition became exacerbated during the study	No	In cases of active severe illness, it is common practice in the medical community to delay vaccination until this is resolved; however, an assessment of benefit and risk of vaccination should be left to the medical judgment of the prescriber on a case-by-case basis
Use of any investigational (or non-registered product; drug or vaccine) other than the study vaccine(s) within 30 days preceding the first dose of study vaccine, or planned use during the study period	To avoid any interaction that could confound the analyses	No	N/A
Previous participation in any other malaria vaccine trial	To avoid any interaction that could confound the analyses	No	N/A

SIV.2 Limitations to detect adverse reactions in clinical trial development program

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Which are rare	Because of the low frequency of some adverse events (e.g., occurring in <1/100,000 persons) clinical trials are not powered to detect rare events. In the last pooling (04 March 2024) including Phase 1-3 clinical development, 14,998 subjects have been exposed to at least one dose of Mosquirix	Adverse reactions with a frequency of >1/4,999 could be detected. Unexpected, rare adverse reactions might occur in the target population; however, these may also be coincidental events within the target population
Due to prolonged exposure	As Mosquirix is delivered in 3 doses over a 3-month period, with a 4th dose 18 months after third dose, there is no prolonged exposure	Not applicable
Due to cumulative effects	No cumulative exposure or specific organ toxicity has been observed with Mosquirix	Not applicable
Which have a long latency	Potential immune-mediated disorders may have a long latency from vaccine exposure to disease onset; therefore, collection of pIMDs in GSK clinical trials with vaccines containing novel adjuvants is set for at least one year after the last vaccine dose, which is a reasonable maximum theoretical risk interval for new onset of autoimmune diseases. Most of the phase II and III clinical trials assessing Mosquirix in children had safety follow-up of at least 12 months. Longer safety follow-up is available from Malaria-055 PRI, with a median follow-up of 48 months for the 5-17 months-of-age category and 38 months for the 6-12 weeks-of-age category.	None: one may assume that the development of autoimmunity (if a causal association between the event and vaccination exists) is similar to the classical time frame of several weeks suggested for the onset of post-infectious autoimmune phenomena. The risk becomes very low several months following the last vaccine dose received. [Tavares 2013].

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development program

Except for the CHMI study Malaria-027 and the immunogenicity study Malaria-048, all studies assessing RTS,S/AS01 were conducted in SSA countries where Malaria caused by *P. falciparum* is endemic and in a population (*i.e.* children 6 weeks to 4 years-of-age at time of the first dose) expected to benefit from the vaccine. In the pivotal phase 3 study Malaria-055 PRI, exclusion criteria were reduced to a minimum in an attempt to study the vaccine in the target population of children who usually attend EPI visits in SSA. This included HIV-infected, pre-term and low weight-for-age (*i.e.,* malnourished) children.

Children

Clinical trials evaluating Mosquirix were conducted in children from 6 weeks to 4 years-of-age at the time of the first dose. The pivotal Malaria-055 PRI trial included infants and children split into 2 separate age categories: 6 to 12 weeks-of-age at the time of the first dose, to allow the assessment of the co-administration with EPI vaccination, and 5 to 17 months-of-age at the time of the first dose. Although this study did not document the efficacy and safety profile of Mosquirix in children starting their 3-dose vaccination schedule between the age of 12 weeks and 5 months, the 2 evaluated age categories are considered representative in terms of potential differences of physiological stages.

Children with other relevant co-morbidities

- **Immunocompromised subjects, including HIV-infected subjects**

With the exception of the 2 studies described below (Malaria-055 PRI and Malaria-058), the subjects who presented with any confirmed, or suspected, immunosuppressive or immunodeficient condition, including HIV-infected subjects, were excluded from enrolment in clinical trials with Mosquirix.

The HIV disease burden in some parts of SSA is important and evidence suggests that the co-infections of HIV and Malaria act synergistically and result in worse outcomes [Skinner-Adams 2008].

In Malaria-055 PRI, children with known HIV/AIDS disease stage I and II (WHO AIDS staging) were eligible. A previous history of having Stage III or Stage IV HIV disease was not an exclusion criterion. The final sub-analysis of the safety of Mosquirix in HIV-infected children became available in 2014. It should be noted that HIV testing was not a study procedure; this analysis therefore includes only those children known to be HIV-infected at study enrolment and those subsequently diagnosed during the study on clinical suspicion.

In Malaria-055 PRI, at study end, 1.0% of the children and infants had a confirmed HIV-positive status (51 in R3R, 54 in R3C and 48 in C3C groups) and a few additional children and infants (9 in total) had an SAE coded as retroviral infection that was not confirmed by PCR or HIV antibody test (suspected HIV-positive status).

Six children were known to be HIV-infected at study enrolment; the others were identified as being HIV-infected during the conduct of the study; on the basis of clinical suspicion. Therefore, most of the children included in this analysis were not under treatment at the time of Mosquirix vaccination. Adherence to treatment during the study is unknown.

The proportion of subjects who tested HIV-positive, which was the condition to analyse the data, was balanced between the 2 study groups.

From Month 0 to SE, 153 children were diagnosed as HIV-infected; 51 in the R3R group, 54 in the R3C group and 48 in the C3C group. Similar percentages of these HIV-infected children reported at least one SAE in all 3 study groups: 92.2% (95% CI: 81.1 97.8) of children in the R3R group, 85.2% (95% CI: 72.9 93.4) of children in the R3C group and 87.5% (95% CI: 74.8-95.3) of children in the C3C group.

The percentage of subjects reporting a fatal SAE within 30 days was similar between treatment groups, taking into account the low number of subjects. Fatal SAEs were reported in 2.0%, 3.7% and 2.1% of subjects after dose 1 in R3R, R3C and C3C groups respectively, in 4.2%, 5.8% and 0% of subjects after dose 2, in 2.4%, 0% and 2.4% of subjects after dose 3 and in 0%, 2.9% and 0% of subjects after dose 4. Post-fourth dose, no particular imbalance in the incidence of SAEs over 30 days or up to SE was observed (refer to Malaria-055 Annex report 10).

The overall safety information from dose 1 to SE in the HIV-infected children showed they experienced similar incidences of SAEs and fatal SAEs in the 3 treatment groups (R3R, R3C and C3C) (Table 5).

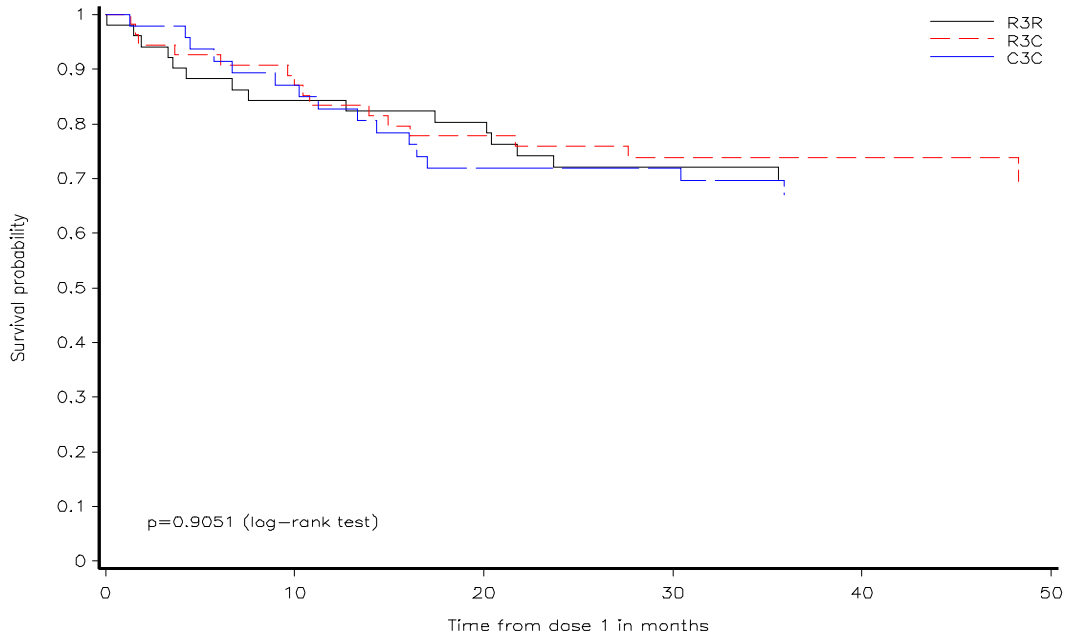
Table 5 Incidence of SAEs over the whole FU period in Malaria-055 PRI (TVC of HIV-infected infants and children)

	R3R N = 51				R3C N = 54				C3C N = 48			
			95% CI				95% CI				95% CI	
	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one SAE	47	92.2	81.1	97.8	46	85.2	72.9	93.4	42	87.5	74.8	95.3
At least one fatal SAE	15	29.4	17.5	43.8	15	27.8	16.5	41.6	15	31.3	18.7	46.3
At least one related SAE	1	2.0	0.0	10.4	0	0.0	0.0	6.6	0	0.0	0.0	7.4

R3R = subjects vaccinated according to a 3+1 vaccination schedule
R3C = subjects vaccinated with 3 doses only
C3C = Control
N = number of subjects receiving the fourth dose (Mosquirix) or Menjugate
n = number of subjects in a given category
% = n / Number of subjects with available results x 100

Survival curves do not show any significant differences between the 3 treatment groups (Figure 3)

Figure 3 Survival curves (Malaria-055 PRI, TVC of HIV+ children 6 weeks to 17 months)



Number at risk

R3R	51	45	43	41	39	34	23	10
R3C	54	50	47	43	41	37	26	9
C3C	48	44	40	36	32	31	22	10

R3R = subjects vaccinated according to a 3+1 vaccination schedule
R3C = subjects vaccinated with 3 doses only
C3C = Control
Survival curve stops when no more death occurs.

Although Mosquirix was immunogenic in HIV-infected children and infants, the anti-CS antibody response one-month post Dose 3 was lower in HIV-infected subjects (GMT=193.3 EU/mL) than in matched control subjects not diagnosed with HIV infection (GMT=491.5 EU/mL) (*p=0.0001*). Controls were matched based on study site, sex, age category, tribe and the number of hepatitis B doses received prior to the first dose of Mosquirix. The lower immunogenicity of Mosquirix in HIV-infected children is not unexpected and is mentioned in the RSI as a warning.

Data from Malaria-055 PRI have to be interpreted in the light of the results of Malaria-058, which was designed to evaluate safety, immunogenicity and disease progression parameters in 200 HIV-infected children from 6 weeks to 17 months-of-age (HIV stage I and II). At enrolment, 20% of the children were 6 weeks to 4 months-of-age and 80% of the children were 5 to 17 months-of-age.

Through the monitoring of markers of HIV disease progression (HIV viral load and CD4+ cell count of subjects), the potential impact of Mosquirix vaccination on HIV disease progression was evaluated as a secondary endpoint.

The study was conducted in the context of high anti-retroviral therapy use and co-trimoxazole prophylaxis: 73% of children were on ART at the first vaccine dose; the remaining children were rapidly put on treatment with 97% on anti-retroviral therapy at 1-month post dose 3. At first vaccine dose, 92% of study participants were on co-trimoxazole treatment.

The incidence of SAEs over 1-year post-vaccination (the primary objective of the study) was balanced between groups [41.4% (95%CI: 31.6 to 51.8) in Mosquirix groups compared to 36.6% (95%CI: 27.3 to 46.8) in control]. There were 9 fatal SAEs, 5 subjects (5.1%) in the Mosquirix groups and 4 subjects (4.0%) in the rabies vaccine group. The survival curves illustrate low mortality in both groups. None of the fatal SAEs were assessed as related to study vaccination by investigators.

No significant effect of Mosquirix was observed on CD4+ T-cell percentage, CD4 + T-cell absolute counts and WHO AIDS clinical classification. The progressive reduction in HIV viral load at 1 and 6 months post dose 3 was slightly more marked in the control vaccine group than in the Mosquirix group but there was no statistically significant indication that the 2 groups were different. No difference in HIV viral load reduction between the Mosquirix group and the rabies vaccine group was observed 12 months post dose 3.

Data from Malaria-058 showed some evidence of protection against malaria induced by Mosquirix in HIV-infected children on ART. Over 12 months post dose 3, vaccine efficacy against all episodes of clinical malaria was 37.2% (95% CI: -26.5% to 68.8%, ATP cohort for efficacy).

While a difference between Mosquirix and control groups in fatalities or HIV viral load in the immediate vaccination period may not be excluded, it has been conclusively shown that over a 1-year post-vaccination period, incidences of SAEs and deaths and viral load were similar in HIV-infected children vaccinated with Mosquirix or a control licensed vaccine.

Based on these results, combined with the immunogenicity and efficacy data, it can reasonably be concluded that the benefit/risk balance of Mosquirix in HIV-infected children (stage I and II) is positive. Considering the difficulties in recruiting HIV-infected subjects in Africa, due the fear of HIV-related stigma, the decrease of mother-to-child transmission and the ethical consideration to not encourage ART treatment, no further study is proposed to specifically assess Mosquirix in HIV-infected subjects considering that the existing data support a positive benefit/risk of the vaccine in HIV-infected subjects.

However, as the data in that population are limited, the Company is currently assessing the vaccine in the large observational post-approval safety/effectiveness study, EPI-MAL-003, which includes HIV-infected children. In this study, HIV infection is collected as part of the medical history; but no intervention regarding HIV testing or

treatment is performed. Therefore, the safety and effectiveness data from this study will reflect the vaccine profile in the general targeted population.

Although HIV-infected children might have defective immunity and a low immune response to some vaccines has been reported in the peer reviewed literature, the WHO recommends that children who are, or are suspected of being, infected with HIV but are not yet symptomatic, should be given all vaccines as recommended by the national EPI programme [William 2003].

Only BCG and, where applicable, yellow fever vaccine (both live attenuated vaccines) are contraindicated in children with symptomatic HIV-infection, due to the risk of disseminated invasive disease post-vaccination. In all other situations, the benefits of vaccination outweigh any associated risks. For non-live vaccines, HIV-infection has not been shown to be associated with an increased risk of adverse vaccine-related events. On the contrary, because of their increased susceptibility to infection, vaccination is advocated.

As HIV-infected children are more susceptible to malaria they may gain additional benefits from receiving the malaria candidate vaccine [Slutsker 2007]. Among HIV-infected children up to 5 years-of-age, rates of parasitaemia and parasite densities are higher than in those without HIV [Mermin 2004]. The risk of severe anaemia and hospitalisation for malaria is also increased in HIV-infected infants [Van Eijk 2002]. Furthermore, malaria episodes can transiently increase viral load, and thus could theoretically have an impact on HIV disease progression and HIV transmission [Kublin 2005].

Other congenital immunodeficiency conditions (such as B and T-cell defects, deficiencies of the early component of the classical complement pathway, congenital asplenia or ectodermal dysplasia with immunodeficiency) are much less frequent and are usually diagnosed based on clinical suspicion triggered by recurrent bacterial infections [Ryser 1988]. Therefore, undertaking clinical trials in children with these congenital immunodeficiencies to evaluate immunogenicity of the candidate vaccine within the first 2 years-of-life would be challenging since diagnosis is frequently made later.

Although information is limited on the use of malaria vaccines in these immunocompromised high-risk groups, other than in HIV infection, no additional studies are planned in immunocompromised subjects due to the low incidence of disease.

- **Malnourished subjects**

Malnutrition is a common and well-recognized public health problem in SSA countries. Based on the 2006 WHO Child Growth Standards, underweight is defined as a weight that is greater than two standard deviations (or “z scores”) below the median expected weight-for-age. This could be due to either stunting (low height-for-age) or wasting (low weight-for-height).

The subjects who present with moderate and severe malnutrition (weight-for-age Z-score less than -2) at screening were excluded from all studies, except the Malaria-055 PRI study where the exclusion criterion was malnutrition requiring hospital admission.

One of the safety objectives of the Malaria-055 PRI study was to evaluate the safety of Mosquirix when given according to a 3+1 vaccination schedule in low weight-for-age (*i.e.* a z-score less than -2) and very low weight-for-age (*i.e.* a z-score less than -3) infants.

Overall, the incidence of SAEs was similar in Mosquirix and control groups in children and infants who were low weight-for-age and very low weight-for-age and was slightly higher than the incidence in the general population of children and infants enrolled in Malaria-055 PRI.

In children 5-17 months-of-age, the incidence of AEs related to vaccination, or leading to withdrawal, was higher in the Mosquirix group as compared to the control group.

This trend was less pronounced in the infants, where the control group received MenC+DTPw-HepB/Hib+OPV vaccines. This difference is driven by a higher rate of pyrexia related to Mosquirix vaccination, which is in-line with the reactogenicity profile and the unsolicited AE data in the general population of children and infants.

The safety profile of *Mosquirix* in low weight-for-age and very low weight-for-age children and infants appears to be similar to the one in the general population.

Overall, after the fourth dose, the incidence of SAEs was similar in the 3 study groups (R3R, R3C and C3C) in children and infants with low weight-for-age at the time of the fourth dose and was also in line with the incidence observed in the general population of children and infants enrolled in Malaria-055 PRI.

Since no difference in immunogenicity was observed in low weigh-for-age children, the efficacy is not expected to be different in malnourished children as compared to the normal paediatric population.

No further evaluation is considered to be required in this sub-population.

- **Infants born prematurely**

The burden of preterm birth, as measured in absolute numbers, is concentrated in Africa and Asia, where about 85% of all preterm births occur [Beck 2010].

Infants born prematurely are at higher risk of infection than infants born at full term, for reasons that may include the relative immaturity of their immune system. Therefore, their response to vaccination is of particular interest.

Following recent recommendations, infants born prematurely should be vaccinated at the same chronological age, and according to the same schedule and using the same precautions, as full-term infants and children [CDC 2006]. However, the immune response to initial vaccine doses may be lower in preterm infants for certain antigens.

Protective antibody concentrations are often achieved with successful induction of immunological memory with most vaccines [Bonhoeffer 2006].

Infants born preterm (defined as <37 weeks of gestational age) were excluded from studies enrolling infants (*i.e.* 6-12 weeks at the time of first vaccination), with the exception of the Malaria-055 PRI study, where an evaluation of safety was performed in 362 infants 6-12 weeks-of-age at first dose (244 in the Mosquirix group and 118 in the control group) who had been born preterm.

This safety analysis was not conducted in children 5-17 months-of-age at first dose born preterm as it was considered that it should not be any more a factor influencing vaccine safety in this age category. As opposed to the analysis in HIV-infected and low weight-for-age children and infants, this analysis was not planned per-protocol but added in the statistical analysis plan for the analysis at study Month 20.

The majority of these infants had a gestational age between 33 and 36 weeks (90.6% and 89.0% of infants receiving Mosquirix and control vaccine, respectively).

From dose 1 up to dose 4, at least one SAE was reported in 19.7% (95% CI: 14.9 to 25.2) of infants receiving Mosquirix and by 11.0% (95% CI: 6.0 to 18.1) of infants receiving the control vaccine. The incidence of SAEs was higher in the Mosquirix group than in the control group, but the difference was not statistically significant.

Fatal SAEs were reported in 8 (3.3%, 95%CI: 1.4 to 6.4) infants who received Mosquirix and in 1 (0.8%, 95% CI: 0.0 to 4.6) infant who received control vaccine. Amongst the fatal SAE preferred terms, Fallot's tetralogy and HIV-infection (3 fatal SAEs in the Mosquirix group) were considered unrelated to Mosquirix due to the nature of the events. The other event preferred terms were associated with infectious complications in these premature infants (*i.e.,* bronchopneumonia, pneumonia, meningitis pneumococcal and pneumococcal sepsis).

Following the review of the individual cases, the apparent numerical imbalance of fatal SAEs is not considered to be a safety signal.

Based on the available safety information, the safety profile in pre-term infants does not appear to be different than the one of the global population of Malaria-055 PRI.

- **Patients of different racial and/or ethnic origin**

The Malaria-055 PRI study was conducted in 11 sites across 7 SSA countries, and enrolled children and infants from more than 60 different tribes. Despite the fact that the results from this study therefore represent a wide range of ethnic origins, all infants and young children enrolled were of black African heritage/African descent.

Although it is not always completely understood why differences exist in terms of immunological responses between populations, the main reason is believed to be related to differences in pathogen epidemiology, resulting in differences in maternal antibodies and/or natural exposure to the pathogen.

Differences in immunogenicity have been observed across the globe for other vaccines, but there is today no vaccine for which it is considered necessary to have differences in recommendations due to potential ethnic differences. If differences in recommendations do exist, they seem to always be related to epidemiological differences resulting in differences in potential public health benefits that can be provided.

Given the epidemiology of *P. falciparum* infections, it is not possible to generate meaningful data on infants and young children from non-black ethnic origins living in malaria-endemic regions in SSA and sufficiently exposed to *P. falciparum* infections to allow an assessment of the efficacy and safety of Mosquirix. However, the Company will monitor potential reports of subjects from regions other than SSA as part of its routine Pharmacovigilance activity.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

Mosquirix received a positive scientific opinion on 23 July 2015 from the EMA following an "Article 58" Application for active immunization of children aged 6 weeks up to 17 months against malaria caused by *P. falciparum* and against hepatitis B at a dose of 0.5 mL.

In October 2015, the WHO's Strategic Advisory Group of Experts on Immunisation and the Malaria Policy Advisory Committee recommended the pilot implementation of Mosquirix in 5 to 17-month-old children in 3 to 5 distinct settings in SSA with moderate-to-high malaria transmission intensity. This recommendation was adopted by WHO in January 2016.

Ghana, Kenya and Malawi were selected for the pilot implementation. Special Authorization for use of Mosquirix in the pilot were obtained from the respective National Regulatory Authorities of the 3 countries between April and May 2018. Vaccinations started on 24 April 2019.

The WHO updated its recommendation for broader use of Mosquirix in 5 to 17-months-old children in 2021.

On 15 July 2022, Mosquirix was prequalified by the WHO with the indication "for active immunization of children aged 5 to 17 months against malaria caused by *P. falciparum* and against hepatitis B".

Mosquirix was first approved on 10 March 2023 in Kenya for active immunization of children aged 5 to 17 months against malaria caused by *P. falciparum* and against hepatitis B.

SV.1 Post-authorization exposure

Changes with the post-marketing exposure do not alter considerations on the risk evaluation for Mosquirix.

SV.1.1 Method used to calculate exposure

Information on the actual number of subjects exposed to Mosquirix in the different countries is not available to the Company due to limited availability and the heterogeneity of data sources between and within countries (e.g., multiple national immunization schedules, specific mass vaccination campaigns, incidence of the disease, catch-up, outbreak containment). Therefore, the subject exposure is approximated by the number of doses distributed, which is the only worldwide data available with regard to subject exposure for a vaccine in a post-approval setting.

It is important to note that the distribution database from which data are retrieved is an in-house 'living' database and is subject to updates and corrections depending on information provided by GSK local country subsidiaries (e.g., vaccine doses may be returned by subsidiaries to the central warehouse). These constant updates may result in discrepancies between consecutive queries of the database. Distribution data are available per complete

month, but not for a specific date within a month. The time lag between an actual distribution to a country and recording in the database is 2 months on average. In order to minimize the risk of inaccuracy, and to better reflect the exposure data, the distribution data are retrieved with the DLP minus 2 months.

SV.1.2 Exposure

Considering the special authorization for use granted in Ghana, Kenya and Malawi in the context of the MVIP, the licenses recently approved until 11 June 2024 and other additional countries that have authorized the supply through UNICEF it is estimated that 13 037 336 doses have been distributed since launch. As vaccination with Mosquirix could vary between 1 and 4 doses per subject in accordance with local recommendations and compliance with the vaccination schedule the number of cumulative subjects exposed is estimated as being between 3 259 334 and 13 037 336.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

No potential for the illegal use of Mosquirix has been identified.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

SVII 1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

This section is not applicable.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

This section is not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Based on recent data from the IA of the EPI-MAL-003 study, a GSK-led PASS study, and the results of the WHO MVPE study, GSK proposes the removal of meningitis as an important potential risk from the safety concerns related to Mosquirix (RTS,S/AS01$_E$).

A signal of meningitis was observed in the pivotal Phase 3 study (MALARIA-055) with an imbalance in the number of meningitis cases with any etiology over the first year of follow-up post-dose 3 following the primary analysis. The analysis at study end showed that this imbalance in meningitis cases was more pronounced in the 5–17-month age group than in infants aged 6-12 weeks as follows:

- In the 5–17-month age group, the Relative Risk (RR) for meningitis 12 months and 18 months post Dose 3 was 5.5 [95% CI: 0.7-42.6] and 8.0 [95% CI: 1.1-60.3] respectively.
- In the 6–12-week age group, even though the RR is lower, the risk cannot be excluded for the infants (2.3 [95% CI: 0.5-10.4] at 12 months of follow-up and 1.5 [95% CI: 0.4-5.5] at 18 months' follow-up).
- Only 1 case of meningitis was reported after Mosquirix provided as a booster dose in the 5–17-month age group and no case in the 6–12-week age group.

However, the meningitis cases did not cluster around a specific time post-vaccination, highlighting the absence of temporal relationship between the vaccination and the occurrence of meningitis. This imbalance was also not consistent across the different age groups (higher risk in 5-17 months), doses (no imbalance after 4th dose), investigation sites, (38% of cases were reported in 1 of 11 trial sites) and a range of etiologies in the cases identified (due to local differences and no case definition).There was no identified biological mechanism that could explain how Mosquirix might cause meningitis and the pre-clinical data from animal studies on RTS,S and AS01 do not show any signs of meningitis, brain inflammation, or neurotoxicity in animals. Furthermore, meningitis is a complex disease with multiple potential causes, suggesting that the occurrence of meningitis in vaccinated individuals could be due to these other causes and not necessarily the vaccine itself [Guerra 2019].

The absence of a temporal relationship to vaccination and of a potential biological mechanism, and the variety of bacterial pathogens causing these meningitis cases did not argue in favor of a direct effect of Mosquirix vaccination. Thus, the most likely hypothesis to explain the meningitis signal seemed to be a chance finding, also pointed out by investigators, the independent data monitoring committee, consulted external experts, WHO, and EMA [WHO 2016; EMA 2015]

Because a causal relationship between Mosquirix and meningitis of any etiology could not be confirmed or excluded with the data available at the time of the initial dossier, meningitis has been evaluated in several PASS studies (EPI-MAL-002, EPI-MAL-003 and MVPE) to further characterize the risk.

EPI-MAL-003

EPI-MAL-003, monitors incidence of predefined AESI[1], other AE leading to hospitalization, meningitis, and severe malaria including cerebral malaria, after vaccine implementation. Using a cluster randomized design, this study compares the occurrence of adverse and malaria events between vaccinated and unvaccinated participants in two ways: temporal (before-after comparison with EPI-MAL-002) and concurrent (cluster design comparison of exposed and unexposed clusters).

EPI-MAL-002 is a disease surveillance study with prospective cohort event monitoring among infants and young children living in a demographic census in sub-Saharan Africa countries. The diseases under surveillance for safety prior to implementation of RTS,S/AS01$_E$ are the same as listed AESIs in EPI-MAL-003.

The design of both studies, EPI-MAL-002 and EPI-MAL-003, included AS with home visits and continuous monitoring of outpatient visits and hospitalizations at all health care facilities and EHS with continuous monitoring of hospitalizations in both exposed and unexposed clusters. The EPI-MAL-003 Interim Analysis was done only on AS data.

The EPI-MAL-003 study has included 45 000 children in AS to assess vaccine safety, effectiveness, and impact. There are 22 564 children in the exposed clusters (20 639 of them vaccinated and 1 869 not vaccinated) and 22 436 children in the unexposed clusters (267 of them vaccinated and 22 137 not vaccinated). The Before-After analysis included 16 733 non-vaccinated participants from the EPI-MAL-002 study.

On the one hand, one of the co-primary safety objective of the EPI-MAL-003 study estimated the incidence of etiology-confirmed meningitis in children vaccinated with RTS,S/AS01$_E$. On the other hand, one of the secondary safety endpoints estimated the incidence of etiology-confirmed, bacterial confirmed, probable or clinically suspected meningitis in children vaccinated with RTS,S/AS01$_E$ and also assessed the potential association between vaccination and the occurrence of meningitis.

[1] AESI monitored in EPI-MAL-002 and EPI-MAL-003: ADEM, Encephalitis, Guillain-Barré Syndrome, Generalised convulsive seizures, Hypotonic Hypo-responsive syndrome, Intussusception, Hepatic insufficiency, renal insufficiency, Juvenile chronic arthritis, SJS and TEN, Henoch Schoenlein purpura, Kawasaki diseases, Diabetes mellitus type 1, Thrombo-cytopenia, Anaphylaxis.

The EPI-MAL-003 interim analysis has been performed based on accumulated and cleaned data (by the Medical Data Review team and the External Expert Panel) of all the children enrolled in the AS cohort and followed-up up to one year post-dose 3. This interim analysis has evaluated the safety and effectiveness endpoints. The effectiveness endpoints were evaluated 1 year after the third dose of RTS,S/AS01$_E$ vaccine, and for children who have received the 3 doses before 12 months of age. The safety results related to final diagnosis of meningitis within at-risk period of 12 months post dose 3 are presented in the table below.

Table 7 - Cumulative numbers, IR and IRR of meningitis cases according to protocol definition (Final diagnosis) after Mosquirix primary schedule – Active Surveillance - Analysis set

Endpoints	Group	N	n*	n	IR per 100 000 PYs (95% CI)	Crude IRR (95% CI), p value	IRR adjusted on country (95% CI), p value
Cluster design comparison (Analysis Set)							
Primary endpoint Etiology-confirmed meningitis	Vaccinated	20 618	1	1	4.1 (0.1-23.0)	1.02 (0.06-16.29) p=0.990	0.96 (0.06-15.34) p=0.977
	Unvaccinated	21 747	1	1	4.0 (0.1-22.6)		
Secondary safety endpoint Meningitis - protocol defined*	Vaccinated	20 618	6	6	24.7 (9.1-53.9)	0.61 (0.22-1.68) p=0.340	0.59 (0.21-1.62) p=0.306
	Unvaccinated	21 747	10	10	40.5 (19.4-74.4)		

N = number of evaluable participants with follow-up during the at-risk period; n* = number of first events post each dose during the follow-up period at risk; n = number of participants with at least one event reported during the follow-up period at risk
95% confidence interval (CI) = Lower Limit (LL), Upper Limit (UL)
Person-Years = sum of the follow-up periods at risk of the participants (in years)
Endpoint = final classification of meningitis case i.e., suspected meningitis case identified at hospitalization, confirmed at 1st line laboratory results and reviewed on 2nd line laboratory results by EEP
Incidence rate per 100 000 person-years = number of first events post each dose per 100 000 person-years estimated as n* / Person-years
Adjusted incidence rate ratio = estimation of risk ratio using Poisson or Negative binomial regression model with Country as a fixed effect and unvaccinated as reference status
*Meningitis - protocol defined = Etiology confirmed, bacterial confirmed, probable or clinically suspected meningitis

These results indicated that both primary (etiology confirmed) and secondary (confirmed and suspected cases) meningitis-related endpoints were rare, with no difference in meningitis incidence rates observed between the two groups. The safety signal observed in the Phase 3 clinical trial for meningitis is not observed in the EPI-MAL-003 IA, 12 months post primary vaccination. In conclusion, there is no evidence of an increased risk of meningitis with Mosquirix vaccination.

MVPE

The MVPE is a phased implementation and evaluation of the RTS,S/AS01$_E$ malaria vaccine in Ghana, Kenya, and Malawi, focusing on feasibility, safety, and impact. The

WHO's MVPE study involved both vaccinated and unvaccinated children aged 5 to 48 months in Ghana, Kenya, and Malawi. Over 360,000 children per year were eligible for the Mosquirix vaccine. By the end of the study, 1.29 million children received their first dose, 1.07 million their third dose, and 0.44 million their fourth dose [WHO 2024b].

The MVPE results from the primary analysis (24 months post-implementation, meaning one year post dose 3) did not show evidence of an increased incidence of hospital admissions with meningitis comparing age-eligible children living in implementation areas with those in the comparison areas (IRR 0.81 [95% CI: 0.43, 1.55]). The WHO DSMB and the RTS,S SAGE/ MPAC Working Groups concluded that the meningitis safety signal seen in the Phase 3 clinical trial was not seen in the pilot implementation [WHO 2021]

Following SAGE/ MPAC conclusions, the WHO recommendation was revised to include the routine use of Mosquirix for the prevention of *P. falciparum* malaria in children of 5-17 months of age living in regions with moderate to high malaria transmission.

The MVPE results from the final analysis (46 months post-implementation, meaning one year post dose 4) showed that the IRR of meningitis among children eligible for at least 1 dose of Mosquirix was 1.025 (95% CI: 0.899-1.169), and among children eligible to have received 3 doses, 1.042 (95% CI: 0.903-1.201). In conclusion, the MVIP data were clearly not consistent with the meningitis signal in the Phase 3 trial [WHO 2024b].

The EPI-MAL-003 and MVPE studies provided robust evidence that there is no increased risk of meningitis following the administration of Mosquirix. Besides, these data are not consistent with the meningitis signal in the Phase 3 trial, supporting the previous conclusion from the IDMC, consulted external experts, WHO, and EMA that the imbalance observed in the phase 3 trial was a chance finding [WHO 2016; EMA 2015]).

Even though the EPI-MAL-003 study is still ongoing, the EPI-MAL-003 IA includes accumulated and cleaned data (by the Medical Data Review team and the External Expert Panel) of all the children enrolled in the Active Surveillance cohort and followed-up up to one-year post-dose 3. One-year post-dose 3 is the same risk window within which the original signal was observed. The final analysis will provide information on children enrolled in Active Surveillance cohort with a follow-up up to 2 years post-dose 4. Therefore, the EPI-MAL-003 final analysis will not provide additional information on the current observed risk, which is meningitis imbalance occurring within one year period following dose 3.

In summary, the accumulated scientific and epidemiological data from EPI-MAL-003 and MVPE studies do not provide evidence of an increased risk of meningitis following Mosquirix vaccination and the risk can be considered well characterised. Whilst still ongoing, the EPI-MAL-003 final analysis will not provide additional information on the current observed risk. Based on this, the risk is no longer considered to meet the criteria of a safety concern for inclusion in the RMP.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

<table>
<tr><th colspan="2">IDENTIFIED Risk No. 1 [febrile convulsion]</th></tr>
<tr><td>Potential mechanisms</td><td>Febrile convulsions form a particular subgroup of generalized convulsive seizures. Although an interaction of genetics, brain maturity, and fever is hypothesized, the pathophysiology of febrile seizures is largely unknown. Seizures occurring soon after immunization are mostly triggered by fever, which may or may not be related to the vaccine [Bonhoeffer 2004].</td></tr>
<tr><td>Evidence source(s) and strength of evidence</td><td>The risk of febrile convulsion was identified during Phase II clinical trials and confirmed in the first analysis of the pivotal Malaria-055 PRI trial [Guerra, 2019].

First 3 doses: Based on the safety pooling, an increased risk of febrile convulsion (per Brighton Collaboration diagnostic certainty level 1-3) within 7 days post the first 3 doses of Mosquirix, was identified in subjects aged 5 to 17 months (at the time of first dose), with a similar frequency to that observed in the pivotal Malaria-055 PRI study of 1.1/1,000 doses (95%CI: 0.6-1.6). No increased risk of febrile seizure, when compared to the control group, was identified in the 6 to 12 weeks-of-age category. The overall incidence of seizures within 7 days (0-6) days post the first 3 doses of study vaccine (per 1,000 doses) from the Safety Pooling (ITT population) were as follows:

<table>
<tr><th></th><th colspan="5">R3R+R3C</th><th colspan="5">C3C</th><th colspan="4">RR</th></tr>
<tr><th></th><th colspan="3"></th><th colspan="2">95% CI</th><th colspan="3"></th><th colspan="2">95% CI</th><th></th><th colspan="2">95% CI</th><th>p-value</th></tr>
<tr><th>Age category</th><td>N</td><td>n</td><td>n/1000</td><td>LL</td><td>UL</td><td>N</td><td>n</td><td>n/1000</td><td>LL</td><td>UL</td><td></td><td>LL</td><td>UL</td><td></td></tr>
<tr><td>5-17 months</td><td>18896</td><td>20</td><td>1.1</td><td>0.6</td><td>1.6</td><td>10179</td><td>7</td><td>0.7</td><td>0.3</td><td>1.4</td><td>1.54</td><td>0.65</td><td>3.64</td><td>0.4205</td></tr>
<tr><td>6-12 weeks</td><td>14507</td><td>2</td><td>0.1</td><td>0.0</td><td>0.5</td><td>7720</td><td>3</td><td>0.4</td><td>0.1</td><td>1.1</td><td>0.35</td><td>0.06</td><td>2.12</td><td>0.3494</td></tr>
</table>
R3R – 4-dose group
R3C – 3-dose group
C3C – Control group
RR – Relative Risk
N - Number of doses
n - Number of cases

Fourth dose: In Malaria-055 PRI, an increased risk of febrile convulsion (per Brighton Collaboration diagnostic certainty level 1-3) within 7 days posts the fourth dose was identified in subjects in both age categories (i.e. 6 to 12 weeks and 5 to 17 months at the time of the first dose), at frequencies of 2.5/1,000 doses (95%CI: 0.9-5.3) and 2.2/1,000 doses (95%CI: 0.6-5.6) respectively. The overall incidence of febrile seizures within seven days (0-6) days post the fourth dose (per 1,000 doses) in Malaria-055 (ITT population) was as follows:</td></tr>
</table>

	R3R					R3C					C3C				
				95% CI					95% CI					95% CI	
Age category	N	n	n/1000	LL	UL	N	n	n/1000	LL	UL	N	n	n/1000	LL	UL
5-17 months	2447	6	**2.5**	0.9	5.3	2472	3	**1.2**	0.3	3.5	2473	1	**0.4**	0.0	2.3

RR R3R versus R3C				RR R3R versus C3C			
	95% CI				95% CI		
	LL	UL	p-value		LL	UL	p-value
2.00	0.51	8.07	0.3409	**6.06**	0.73	50.33	0.0687

	R3R					R3C					C3C				
				95% CI					95% CI					95% CI	
Age category	N	n	n/1000	LL	UL	N	n	n/1000	LL	UL	N	n	n/1000	LL	UL
6-12 weeks	1825	4	**2.2**	0.6	5.6	1837	0	0.0	0	2	1827	1	**0.5**	0.0	3.0

RR R3R versus R3C				RR R3R versus C3C			
	95% CI				95% CI		
	LL	UL	p-value		LL	UL	p-value
-	-	-	-	**4.00**	0.45	35.79	0.2182

R3R – 4-dose group
R3C – 3-dose group
C3C – Control group
RR – Relative Risk
N - Number of doses
n - Number of cases

Cases of febrile convulsion were further monitored in the frame of the MVIP though the GSK-sponsored studies (EPI-MAL-002 and EPI-MAL-003) and the WHO-sponsored study MVPE. The IA results of EPI-MAL-003 study (1 year post D3), showed that among the hospitalised children, 10 (0.05%) RTS,S/AS01$_E$ vaccinated participants (12 events) reported febrile convulsion vs 8 (0.04%) unvaccinated participants (8 events). No febrile convulsion was reported within 3 days of the primary vaccination schedule and 1 case (0.005%) of febrile convulsion was reported within 7 days of the primary RTS,S/AS01$_E$ vaccination schedule.

Characterization of the risk

Overall, simple febrile seizures are the most common seizure disorder in young children, with an overall incidence of approximately 2-5% [Stehr-Green 2008]. Seizures occurring soon after immunization are mostly triggered by fever induced by the vaccine.

Although frightening for parents, the vast majority of febrile seizures are harmless. The prognosis for febrile seizures following immunization is identical to that of other febrile seizures, which are benign and of which only 2–3% of children who experience them will go on to develop epilepsy [Bonhoeffer 2004].

	Over the entire Phase 3 study follow-up, the only important identified risk identified in children aged 5 to 17 months at the time of the first dose was febrile convulsion, which occurred within 7 days post vaccination with Mosquirix In a further analysis the risk period was limited to the first 2–3 days that corresponded to the peak of fever post vaccination [Guerra, 2019]. No evidence of an increased risk in the long-term has been demonstrated.
Risk factors and risk groups	Febrile convulsions usually occur in individuals aged between 3 months and 6 years [Bonhoeffer 2004], with a peak incidence at 18 months [Waruiru 2004]. Approximately 6-15% of febrile seizures cases occur after 4 years-of-age, with occurrence after age 6 years being unusual [Waruiru 2004]. A personal and/or family history of febrile seizures in siblings and parents is a risk factor.
Preventability	No preventative measures are available. The updated American Academy of Pediatrics (AAP) clinical guidelines for the management of children with simple febrile seizures states that antipyretics have been shown to be ineffective in preventing recurrent febrile seizures, and, although some anticonvulsants do prevent recurrences, the risk of adverse events outweighs the benefit [American Academy of Pediatrics 2011].
Impact on the benefit-risk balance of the product	Malaria caused by P. falciparum is an important cause of acute symptomatic seizures in children admitted to hospitals in SSA, and these seizures are associated with neurological disabilities and epilepsy. In Kenya, over 90% of all acute symptomatic seizures have been attributed to malaria and a reduction in malaria lead to a significant decrease in the incidence of seizure [Kariuku 2011]. The short-lived increased risk of convulsions observed immediately post-vaccination has therefore to be put into the perspective of the expected decreased risk of malaria-related convulsions on a longer period of time following vaccination with Mosquirix.
Potential public health impact of safety concern	The potential public health impact is thought to be limited.
POTENTIAL Risk: Hypersensitivity (including anaphylaxis)	
Potential mechanisms	Anaphylaxis is triggered by the binding of the triggering allergen to specific IgE. It implies previous exposure and sensitization to the triggering substance or to a cross-reactive allergen. When an allergen binds to the IgE receptors on the surface of mast cells and basophils this results in cellular activation and degranulation. These cells release pre-formed inflammatory mediators, such as histamine and tryptase, which elicit the signs and symptoms of anaphylaxis. This mechanism is also known as the Type I immediate hypersensitivity reaction in the Gel and Coombs classification [Ruggeberg 2007].
Evidence source(s) and strength of evidence	Mosquirix contains recombinant yeast-derived hepatitis B antigen and the Institute of Medicine concluded that the available evidence convincingly supports a causal relationship between hepatitis B vaccine and anaphylaxis in yeast-sensitive individuals [Stratton 2011].

	No cases of anaphylaxis after vaccination with RTS,S/AS01$_E$ have been reported in Clinical Trials. Cases of anaphylaxis are actively collected in the EPI-MAL-003 study to further characterize the risk. No cases of anaphylaxis related to vaccination with Mosquirix have been reported so far in EPI-MAL-003.
Characterization of the risk	Estimating the epidemiology of anaphylaxis remains problematic as many cases are not diagnosed or reported. Incidence is estimated to be 4-50 cases per 100,000 persons per year with a prevalence of 0.05%-2%. Evidence suggests that the incidence may have been increasing since the beginning of the 21st century, with younger age groups mainly affected [De Bisschop 2012]. Anaphylaxis following immunization is a serious, but rare, occurrence (estimates are in the range of 1-10 per 1 million doses distributed depending on the vaccine studied) [Ruggeberg 2007]. In an observational follow-up study encompassing approximately 8 million person-years based on the UK general practice research database (GPRD) for the period January 1, 1994, to December 31, 1999, the incidence of anaphylaxis was estimated to be 8.4 per 100,000 person-years [Peng 2004]. This study included a total of 675 cases of anaphylaxis. Approximately 10% of cases experienced hypotension and shock that required urgent treatment. The most common causes were insect stings and oral medicines. Only 24 cases (3.6%) during the 6-year period of the study were shown to have occurred after vaccination. A prospective study (February 1995 – July 2000) of 432 patients referred to a community-based practice in the Australian Capital Territory estimated the minimum occurrence and incidence of new cases of anaphylaxis at 12.6 and 9.9 episodes/100,000 patient-years respectively. Ages ranged between 1-82 years, though patients were generally young with a mean age of 27.4 years [Mullins 2003]. In the pooled Mosquirix safety data set, 3 cases of severe hypersensitivity have been reported within 30 days following vaccination with Mosquirix, which were one case of erythema multiforme and two cases of bronchospasm. There were no cases of anaphylaxis.
Risk factors and risk groups	Hypersensitivity to any component of the vaccine and signs and symptoms of hypersensitivity after previous administration of Mosquirix. A family history of hypersensitivity.
Preventability	Thorough screening for contraindications and precautions taken prior to vaccination can often prevent reactions. Staff must have in-place, and be familiar with, the procedures for managing a reaction. Staff should be familiar with the signs and symptoms of anaphylaxis because they usually begin within minutes of exposure to the offending agent.
Impact on the benefit-risk balance of the product	Anaphylaxis is an acute hypersensitivity reaction with multi-organ-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction [Ruggeberg 2007]. Rapid management and adequate treatment of anaphylaxis could prevent a fatal outcome.
Potential public health impact of safety concern	As anaphylaxis is usually very rare, no significant potential public health impact after Mosquirix administration is expected.

Potential Risk: Potential immune-mediated disorders (pIMDs)	
Potential mechanisms	pIMDs are a subset of adverse events that include autoimmune diseases and other inflammatory and/or neurological disorders of interest which may or may not have an autoimmune etiology. Proposed mechanisms by which vaccines might induce autoimmune disorders are frequently extrapolated from the known capacity of the infectious agents that the vaccine targets [Tavares 2013]. Paediatric inflammatory and autoimmune diseases include a wide array of systemic or organ-specific conditions characterized by an exaggerated immune reactivity, which generally occurs in immunogenetically predisposed children. Several pathologies belong to this classification. [Stocco 2012]. The theoretical risk of acquiring an autoimmune disorder following vaccination is raised by the immunological mechanism of action of vaccines and the potentially further enhanced response by the immunostimulatory effects of the adjuvant system.
Evidence source(s) and strength of evidence	Case reports of autoimmune diseases temporally associated with the administration of all vaccines (both adjuvanted and non-adjuvanted) have been described in the scientific literature. Most of these reports refer to vaccines targeting viral illnesses. The rationale for the monitoring of these events for all vaccines containing adjuvant systems (i.e., adjuvant combinations), relates to their possible effects on the regulation of the immune system and the potential, yet theoretical, risk that they may induce unwanted immune inflammatory processes in susceptible individuals. A list of selected pIMDs of interest for the paediatric population were actively collected in the EPI-MAL-002 study and keep on being collected in EPI-MAL-003 to further monitor this potential risk. No cases of pIMDs related to vaccination with Mosquirix have been reported after primary vaccination in EPI-MAL-003.
Characterisation of the risk	Incidence rates vary among the autoimmune disorders [Cooper 2003]. According to the National Institutes of Health, 5–8% of the US population suffers from this group of disorders. GSK uses a pre-defined list of pIMDs, which contains specific disorders that could represent an autoimmune or immune-mediated inflammatory process, and this list is included in all study protocols of GSK-sponsored studies evaluating products using adjuvant systems, with the aim of focusing Investigator attention on those events of interest (regardless of seriousness), and to facilitate their thorough documentation. In the pooled analysis of Mosquirix safety data, no pIMD was reported by Investigators; however, a search of the safety database using MedDRA of the SAEs included in the pooled safety analysis allowed the identification of 9 pIMDs (4 in the Mosquirix groups and 5 in the control group). The details, including the outcome, of all 9 cases is presented in the table below:

pIMD	Study	Study vaccine	No. of doses	Outcome
Encephalitis	Mal-055	Mosquirix	1	Death
		Mosquirix	3	Death
		Mosquirix	3	Death
		Control	3	Death
		Control	3	Death
		Control	3	Permanent neurological disability
Stevens-Johnson syndrome	MAL-047	Control	3	Recovered without sequelae
Erythema multiforme	MAL-055	Mosquirix	1	Recovered without sequelae
Psoriasis	MAL-055	Control	2	Recovered without sequelae

There were 5 pIMDs (3 in the Mosquirix groups and 2 in the control group) identified following a fourth dose (i.e. only from Malaria-055 PRI data). The details, including the outcome, of all 5 cases is presented in the table below:

pIMD	Study	Study vaccine	No. of doses	Outcome
Encephalitis	MAL-055	Mosquirix	4	Recovered without sequelae
		Mosquirix	4	Permanent neurological disability
		Mosquirix	4	Ataxia and hemiparesis
		Control	4	Recovered without sequelae
Vitiligo		Control	4	Recovered without sequelae

Risk factors and risk groups

As autoimmune disorders are a potential risk for Mosquirix, but have not been observed in clinical trials, it is difficult to identify specific groups at risk or predictive risk factors. Naturally-occurring autoimmune diseases are multi-aetiological conditions with multiple risk factors, including genetic predisposition. All ages are affected with onset from childhood to late adulthood, as well as all racial, ethnic and socioeconomic groups. Most autoimmune diseases disproportionally affect women.

Preventability	No preventative measures have been identified.
Impact on the benefit-risk balance of the product	Immune-mediated disorders represent a heterogeneous group of disorders with different clinical manifestations and courses. Many are chronic, disabling disorders with a substantial impact on quality of life for individual patients. Apart from the chronic nature and decreased quality of life, an additional burden imposed by these disorders is depression and anxiety.
Potential public health impact of safety concern	The public health impact cannot be assessed as autoimmune disorders are a theoretical risk for Mosquirix.
Potential Risk: Rebound effect	
Potential mechanisms	Rebound is a term used to describe higher susceptibility to malaria in recipients of any malaria intervention when that intervention is withdrawn. Children who receive an intervention may not develop natural immunity through exposure to infection, then, as a consequence, when that intervention is withdrawn its recipients may have less natural immunity than children of the same age in the population that did not receive the intervention. The delay in acquisition of natural immunity may also induce a clinical risk, which may be age-specific; in younger children severe malaria anaemia is predominant, whereas in older children, it is cerebral malaria [Aponte 2007]. Rebound has been conclusively demonstrated in studies of highly efficacious antimalarial prophylactic drug regimens in young children from endemic countries and occurred immediately upon stopping the prophylaxis [Aponte 2007]. In the context of less efficacious interventions, such as insecticide-treated bed nets, rebound has not been observed consistently or to such a degree that would affect the overall benefit of the intervention.
Evidence source(s) and strength of evidence	Vaccine efficacy data from a small investigator-supported study (Malaria-059), which was an open-label extension of a phase IIb study (Malaria-049) and VE from both the large phase III (pivotal) trial Malaria-055 PRI and its extension study Malaria-076.
Characterisation of the risk	In the small investigator-supported study Malaria-059, where subjects (223 in the group who received 3 doses of Mosquirix and 224 in the control group) were followed-up over a period of 7 years, the incidence of clinical malaria was lower in the Mosquirix group during the first 3 years of follow-up and was similar in both treatment groups for the 4th year. In the 5th and 6th years of follow-up, the incidence of clinical malaria was higher in the Mosquirix group than in the control group, while for the 7th year, the incidence of clinical malaria was slightly higher in the control group than in the Mosquirix group. VE against all episodes of clinical malaria over the entire 7 years, as assessed by negative binomial regression, was 4.4% (95% confidence interval [CI], −17.0 to 21.9; P = 0.66) in the intention-to-treat (ITT) analysis. VE was lower in the cohort with higher-than-average exposure to malaria parasites (1.9% [95% CI, -20.6 to 20.3]) than in the cohort with lower exposure (25.9% [95% CI, -9.5 to 49.8]). Efficacy waned over time (P = 0.006 for the interaction between vaccination and time), including negative efficacy during the 5th year among children with higher-than-average exposure to malaria parasites (ITT: −43.5%; 95% CI, −100.3 to −2.8 [P = 0.03]). Overall, the study showed that a 3-dose schedule with Mosquirix was initially protective

	against clinical malaria but that this was offset by rebound in later years in areas with higher exposure to malaria parasites [Olotu 2016].The results of Malaria-059 should however be interpreted with caution as there are limitations to the study; the extension was unblinded at 8 months post dose 3 and the sample size was small. In the large phase III (pivotal) Malaria-055 PRI trial, the efficacy of Mosquirix against clinical malaria decreased over time but remained positive over the entire study period in children aged 5-17 months at the time of the first dose, regardless of whether they received a 4th dose or not. No increased incidence of clinical disease was observed; hence, there was no evidence of a rebound effect for clinical malaria within the 4-year follow-up period in this trial; however, VE against severe malaria was negative during the period between study Month 21 and Study End (SE); during this period, 73 out of 2,057 children in the according-to-protocol (ATP) cohort (3.5%) from the 3-dose (R3C) group experienced at least one episode of severe malaria compared to 48 out of 2,051 (2.3%) in the control group (C3C), which corresponds with a statistically significant negative VE of -51.6% (95% CI -123 to -3.9, p = 0.0264). From study Month 0 until SE, children in the 4-dose (R3R) group had a positive VE of 28.5% (95% CI 6.3 to 45.7, p=0.0664) and children in the 3-dose (R3C) group had a slightly negative VE of –5.8% (95% CI –35.0 to 17.0, p=0.0100). The results of the long-term follow-up study of Malaria-055 (i.e. Malaria-076) showed that, for both severe and clinical malaria, VE over the entire follow-up period (i.e. from the start of Malaria-055 to the end of Malaria-076) where a 4th dose was given remained positive for both age categories. A small increase in the incidence of clinical malaria in Mosquirix-vaccinated subjects at older ages was observed in one site (Nanoro), which resulted in erosion of the overall impact in terms of malaria cases averted over the entire follow-up period; however, this did not outweigh the earlier benefit in terms of clinical malaria cases averted in this high and seasonal transmission setting. Importantly, no increased risk for severe malaria was observed in any of the 3 sites. However, the study had several limitations precluding any strong conclusions regarding this safety concern. These limitations included limited sample size, delay in study initiation and collection of retrospective data and a lower incidence of severe disease observed in older children.
Risk factors and risk groups	Rebound is theoretically more likely to occur when 1) the intervention is given early in life, before naturally-acquired immunity has been induced; 2) the intervention is highly efficacious, preventing natural exposure and 3) the intervention is removed (or efficacy wanes) abruptly [Aponte 2007].
Preventability	In the Malaria-055 PRI trial, no rebound effect was observed in those subjects who received a 4th dose of Mosquirix.
Impact on the benefit-risk balance of the product	Despite periods of rebound having been observed in some transmission settings the benefit, in terms of malaria cases averted, means that the overall benefit-risk balance of the product remains favourable.
Potential public health impact of safety concern	Despite periods of rebound having been observed in some transmission settings, the potential public health impact is thought to be limited.

Potential Risk: Cerebral malaria	
Potential mechanisms	There is a theoretical concern that when vaccine efficacy wanes over time, vaccinated children once again become vulnerable to malaria infection, potentially making them temporarily more susceptible to clinical and severe malaria compared to children of the same age that were not vaccinated. This is frequently referred as "rebound effect". This phenomenon is expected to be observed with any intervention (or combination of interventions) which decreases the exposure of children to *P. falciparum.* The delay in acquisition of natural immunity to *P. falciparum* and the increase in the mean age of susceptibility to severe malaria that results from the use of malaria control measures could potentially temporarily increase rates of more severe forms of the disease. Amongst the severe presentations of the malaria disease, severe malaria anaemia is predominant in younger children, whereas cerebral malaria is observed in older children.
Evidence source(s) and strength of evidence	Based on an ad-hoc analysis of the Malaria-055 data in the 5-17 months-of-age category, there was an imbalance in the number of cerebral malaria cases (with or without severe malaria anaemia) in the Mosquirix-vaccinated groups (i.e. R3C+R3R) (43/5948; 0.72%) when compared to the control group (10/2974; 0.34%). For this ad-hoc analysis, a computer algorithm was used to identify cases with parasitaemia >5,000/µL and a Blantyre coma score (BCS) ≤2 as a proxy for cerebral malaria (CM), regardless of whether the CM clinical diagnosis was confirmed by the investigators and without excluding children with comorbidities. Over the first 20 months of the trial, 22 cases occurred in the Mosquirix groups (R3R + R3C; N=5,948) (0.34%) compared to six cases in the control group (N=2,974) (0.20%). From Month 21 to Study End, there were 12 cases in the R3R group (N=2,681) (0.45%), nine in the R3C group (N=2,719) (0.33%), and four in the C3C group (N=2,702) (0.15%). During the entire study there were 12 deaths among the cerebral malaria cases (10 in the Mosquirix groups and two in the control group). A similar imbalance was not observed in the 6-12 weeks-of-age category, where there was 13/4358 (0.30%) versus 7/2179 (0.32%) cases of cerebral malaria over the entire study period in the Mosquirix and control groups, respectively. Such imbalance was not observed in the long-term follow-up study (i.e. Malaria-076) during which there was only one case of cerebral malaria in the 6-12 weeks age category (in a subject who received four doses of Mosquirix) and only 2 cases in the 5-17 months age category (both in subjects who received three doses of Mosquirix); however, as described for the risk of rebound effect, the results of Malaria-076 should be interpreted with caution given the limitations of the study.Cerebral malaria has been further monitored in the frame of the MVIP though the EPI-MAL002, EPI-MAL-003 and MVPE studies: • The MVPE results from the primary analysis after 2 years of pilot implementation showed no evidence of an increase in hospital admissions with cerebral malaria, comparing age-eligible children living in implementation areas with those in the comparison areas (IRR excluding probable meningitis 0.77 [95%CI 0.44, 1.35]); including probable meningitis 0.96 [95% CI: 0.61, 1.52]).[WHO 2021].. The MVPE results from the final analysis after 4 years of pilot implementation showed an IRR for cerebral malaria of 0.935 [95%CI 0.630-1.388], which did not show evidence of an increased incidence associated with Mosquirix introduction [WHO 2024b].

<table>
<tr><td></td><td>
The results of EPI-MAL-003, within at-risk period of 12 months post D3, are presented in the table below.
<table>
<tr><th>Protocol definition</th><th>Group</th><th>N</th><th>n*</th><th>n</th><th>IR per 100 000 PYs (95% CI)</th><th>Crude IRR (95% CI), p value</th><th>IRR adjusted on Country 95% CI</th></tr>
<tr><td colspan="8">Cluster design comparison (Analysis Set)</td></tr>
<tr><td rowspan="2">Cerebral malaria</td><td>Vacc</td><td>20 618</td><td>3</td><td>3</td><td>12.4 (2.6-36.2)</td><td rowspan="2">1.53 (0.26-9.15) p=0.642</td><td rowspan="2">1.43 (0.24-8.58) p=0.694</td></tr>
<tr><td>Unvacc</td><td>21 747</td><td>2</td><td>2</td><td>8.1 (1.0-29.2)</td></tr>
</table>
N = number of evaluable participants with follow-up during the at-risk period; n* = number of first events post each dose during the follow-up period at risk; n = number of participants with at least one event reported during the follow-up period at risk
Endpoint = hospitalised case confirmed as cerebral malaria and with final diagnosis assessed by External expert panel
Adjusted incidence rate ratio = estimation of risk ratio using Poisson or Negative binomial regression model with Country as a fixed effect and unvaccinated as reference status;

These results showed that the cerebral malaria cases were rare: 3 in vaccinated vs 2 in unvaccinated subjects. The safety signal observed in the Phase 3 clinical trial for cerebral malaria is not observed in the EPI-MAL-003 IA, 12 months post primary vaccination.
</td></tr>
<tr><td>Characterisation of the risk</td><td>Cerebral malaria is the most severe neurological complication of infection with P. falciparum and children in SSA are the most affected. Without treatment, it's invariably fatal. In children, parenteral antimalarials (quinine or artemisinin derivatives) are indicated, but even with this, 15-20% die. In adults, mortality is lower if treated with i.v. artesunate. Those who do survive are at increased risk of neurological and cognitive deficits, behavioural difficulties, and epilepsy, which makes cerebral malaria a leading cause of childhood neuro-disability in SSA [Idro 2010].
The reported hospital case-fatality rate of cerebral malaria in children ranges from 10% to 40%; however, some studies indicate the average case-fatality rate at about 16% (Dumas 1986; White 1987; Molyneux 1989; Waller 1995).
In the Malaria-055 study, among the 43 cases classified as cerebral malaria in the Mosquirix treatment groups (i.e. R3R+R3C), 10 (23%) had a fatal outcome and among the 10 cases classified as cerebral malaria in the control group, two (20%) had a fatal outcome. The Company took the definition of a case of cerebral malaria as any hospitalization with parasitemia >5000/µL and a Blantyre coma score ≤2.</td></tr>
<tr><td>Risk factors and risk groups</td><td>Amongst the severe presentations of the malaria disease, severe malaria anaemia is predominant in younger children, whereas cerebral malaria is observed in older children.</td></tr>
<tr><td>Preventability</td><td>Not applicable.</td></tr>
<tr><td>Impact on the benefit-risk balance of the product</td><td>The impact on the individual is high as cerebral malaria can have a serious outcome (severe sequelae or even death).</td></tr>
<tr><td>Potential public health impact of safety concern</td><td>In the Malaria-055 study, severe malaria with a Blantyre Coma Score of ≤2 (i.e., that compatible with cerebral malaria) represented only a small proportion of all severe malaria cases. While the number of cases of severe malaria was higher in sites with moderate or high malaria transmission intensity, the overall public health impact, in</td></tr>
</table>

	terms of cases averted, tended to remain positive and there was no indication of a rebound effect in subjects that received a 4th dose. In addition, the long-term follow-up study (i.e. Malaria-076) showed no increase in the incidence of severe malaria; however, as described for the risk of rebound effect, the results of Malaria-076 should be interpreted with caution given the limitations of the study. Cerebral malaria has been further monitored in the frame of the MVIP though the EPI-MAL002, EPI-MAL-003 and MVPE studies. The available results from the MVIP do not show evidence of an increase in incidence of cerebral malaria in implementation areas and no evidence that impact differed from that for other forms of severe malaria, but the wide confidence intervals reflect the relatively small number of cases on which these estimates are based [WHO 2024b].
Potential Risk: Behavioural changes regarding usage of other malaria preventive measures	
Potential mechanisms	Changing behaviour regarding the usage of other protective measures and treatment-seeking in the population due to vaccination.
Evidence source(s) and strength of evidence	It is a general risk that has been raised with other new vaccine introductions. The surveillance study EPI-MAL-005 and the MVPE study are in place to address the behavioural changes regarding the usage of other malaria preventive measures. During the first 2 years of pilot implementation of the vaccine, when the malaria vaccine introduction was accompanied by a comprehensive communication program, no decreased use of other malaria interventions was observed.
Characterisation of the risk	Mosquirix is intended as an additional preventive measure against P. falciparum malaria, on top of existing interventions.
Risk factors and risk groups	Not applicable.
Preventability	The correct use of the other malaria preventive measure, as recommended locally.
Impact on the benefit-risk balance of the product	The partial efficacy/effectiveness of the vaccine alone might not be sufficient to decrease the number of malaria episodes in a given individual when the use of other malaria control interventions is stopped.
Potential public health impact of safety concern	Reduced usage of other preventive measures following the introduction of Mosquirix may decrease the overall impact of malaria control programs.

SVII.3.2 Presentation of the missing information

Missing Information: Iimpact / Effectiveness	
Evidence source(s) and strength of evidence	According to EMA good pharmacovigilance practices (GVP): Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases, section P.I.B.1.3.2, additional Pharmacovigilance activities were needed to assess the effectiveness of the vaccine, especially where pre-authorisation data are limited.The effectiveness (direct effect) and impact (indirect, total and overall effects) of Mosquirix when administered as part of routine medical practice has been monitored in the frame of the EPI-MAL-003 and MVPE studies, conducted in the framework of MVIP. • For the EPI-MAL-003 IA the analyses of the Total Effect (crude IRR), comparing vaccinated participants in exposed clusters with unvaccinated participants in unexposed clusters, showed a significant vaccine effectiveness against malaria of 26% (95% CI: 23-28; p<0.001), against severe malaria of 57% (95% CI: 39-70; p<0.001), against all-cause hospitalization of 18% (95% CI: 12-23; p<0.001) and against malaria-attributed hospitalization of 33% (95% CI: 25-41; p<0.001). Similar results were shown when adjusting the estimates for country. IRs of all-cause mortality were 560.0 (95% CI: 452.0-686.0) per 100 000 PY in vaccinated vs 675.8 (95% CI: 567.0-799.4) per 100 000 PY in unvaccinated children, resulting in a non-significant vaccine effectiveness of 17% (95% CI: -8-36; p=0.162). A significant vaccine effectiveness against the prevalence of anaemia was also shown (16% [95% CI: 0.07-0.24; p<0.001]). • In addition, the MVPE results from the interim analysis after 2 years of pilot implementation showed that among children eligible for 3 vaccine doses, RTS,S introduction was associated with a 32% reduction (95% CI: 5–51%) in hospital admission with severe malaria, and a 9% reduction (95% CI: 0–18%) in all-cause mortality (all-cause mortality except injuries). (Asante, 2024). The MVPE results from the final analysis (46 months after pilot implementation) showed that among children eligible for 3 vaccine doses, there was a 13% (95% CI: 2.7-22) reduction in total deaths (all-cause mortality except injuries), and a 22% (95% CI: 3.4-36) reduction in hospitalization for severe malaria. The final analysis showed effectiveness of RTS,S/AS01 vaccine against severe malaria of 19.8% in children eligible to receive at least 1 dose, and 21.6% in children who received at least 3 doses [WHO 2024b].
Anticipated risk/consequence of the missing information or population in need of further characterisation	There are no anticipated risks or consequences on the safety profile in the target population.
Missing Information: *P. falciparum* Strain Replacement	
Evidence source(s) and	The data from study Malaria-066 were considered too limited to document strain replacement and EMA requested to keep *P falciparum* strain replacement as missing information during the Art.58 procedure.

strength of evidence	Results from a genotyping study showed that VE estimates tended to be higher for the matched P. falciparum genotypes vs mismatched genotypes in children 5-17 months of age at first dose [Neafsey, 2015]. However, overall only 10% of the parasite strains from children that participated in Malaria-055 had a genotype that matched the genotype of the strain used in the vaccine. The VE as demonstrated in Malaria-055 is therefore representative of the VE that can be expected from RTS,S/AS01$_E$ in an environment where only a small proportion of the parasites match the vaccine strain. Considering the low frequency of the vaccine genotype in P. falciparum strains circulating amongst infants and children in SSA, the relatively small magnitude of the strain-specific effect observed in the study, and the small size of the population protected, the risk of strain replacement is considered to be very low. Additional data on potential strain replacement are being collected after vaccine implementation in the study EPI-MAL-010. The objective of the study is to monitor the genetic diversity in CS sequences of parasite populations in vaccinated infants and children.
Anticipated risk/consequence of the missing information or population in need of further characterisation	Considering the low frequency of the vaccine genotype in *P. falciparum* strains circulating amongst infants and children in sub-Saharan Africa, the results of the Malaria-055 efficacy study can be considered representative for the vaccine when used in an environment where the circulating parasites with matching genotype are rare. In addition, the relatively small magnitude of the strain-specific effect observed in study Malaria-066, and the small size of the population protected, the risk of strain replacement is considered to be very low. There are no anticipated risks or consequences on the safety profile in the target population.
Missing Information: Plasmodium Species Replacement	
Evidence source(s) and strength of evidence	As is the case for *P falciparum* strain replacement, Plasmodium species replacement was considered as missing information in the initial RMP. The surveillance study EPI-MAL-005 is in place to obtain longitudinal estimates of the prevalence of Plasmodium species other than *Plasmodium falciparum*; overall and by age group.
Anticipated risk/consequence of the missing information or population in need of further characterisation	There are no anticipated risks or consequences on the safety profile in the target population.

<table>
<tr><th colspan="2">Missing Information: Safety In HIV-Infected Children</th></tr>
<tr><td>Evidence source(s) and strength of evidence</td><td>GSK study Malaria-058, which was a study specifically designed to evaluate the safety and immunogenicity of Mosquirix in 200 HIV-infected children from 6 weeks to 17 months of age (WHO HIV stage I and II). The study MAL-055 also included HIV-infected children and infants, although no systematic screening for HIV infection was performed. The proportion of participants identified and confirmed as HIV-infected between screening and SE was balanced across treatment groups: 0.9% (48 participants) in the control group and 1.0% in the RTS,S/AS01 groups (51 participants in the R3R and 54 participants in the R3R group) for the combined age categories, as shown in the table below .Among HIV-infected children and infants, the safety profile appeared to be similar between Mosquirix and the control vaccine recipients.

<table>
<tr><th></th><th colspan="2">R3R
N=5156</th><th colspan="2">R3C
N=5150</th><th colspan="2">C3C
N=5153</th></tr>
<tr><th></th><th>n</th><th>%</th><th>n</th><th>%</th><th>n</th><th>%</th></tr>
<tr><td>HIV confirmed</td><td>51</td><td>1.0</td><td>54</td><td>1.0</td><td>48</td><td>0.9</td></tr>
</table>
R3R – 4-dose group
R3C – 3-dose group
C3C – Control group
N - Number of subjects
n - Number of HIV-confirmed subjects (subjects tested positive by PCR or HIV antibody test.)
% = n / Number of subjects with available results x 100

Refer to Section SIV.3 for further information and in-depth analysis of the HIV-infected population.</td></tr>
<tr><td>Anticipated risk/consequence of the missing information or population in need of further characterisation</td><td>Currently available data suggest that HIV-infected children are more likely to experience local and systemic reactogenicity (injection site pain and injection site erythema, fever, somnolence, irritability, decreased appetite) compared to children of unknown HIV infection status.</td></tr>
<tr><th colspan="2">Missing Information: Gender-Specific Mortality</th></tr>
<tr><td>Evidence source(s) and strength of evidence</td><td>Post hoc analysis on the data from the pivotal Malaria-055 trial indicated that all-cause mortality in the girls who received Mosquirix was 2-fold higher than in the girls who received the control vaccine (123/5091 [2.4%] vs 33/2603 [1.3%]; for both age categories pooled); while in boys, all-cause mortality was slightly lower in the group that received Mosquirix compared to the boys in the control group (95/5215 vs 55/2550).

Gender-specific mortality has been further monitored in the frame of MVIP though the EPI-MAL-002, EPI-MAL-003 and MVPE studies.

• The results from the MVPE interim analysis after 2 years of pilot implementation showed a rate ratio of female to male mortality of 1.08 (95% CI: 0.93 - 1.25), p=0.321,</td></tr>
</table>

and this was similar by age group. These results did not show evidence that the effect of RTS,S/AS01 introduction on all-cause mortality differed between girls and boys. [WHO 2021). The MVPE results from the final analysis after 4 years of pilot implementation showed that the IRR comparing mortality in implementation areas with that in comparison areas was 0.888 (95%CI 0.809-0.975), p=0.0133. The separate estimates for girls and boys were similar: 0.895 (0.804-0.995) (girls) and 0.879 (0.777-0.971) (boys). [WHO 2024b].

- The results of EPI-MAL-003, within at-risk period of 12 months post D3, are presented in the table below.

Protocol definition	Group	N	n	IR per 100 000 PYs (95% CI)	Crude IRR (95% CI), p value	IRR adjusted on Country (95% CI) p value
Cluster design comparison						
Death – all causes *Females*	Vacc	10 181	80	669.7 (531.0-833.5)	0.94* (0.70-1.28) p=0.710	0.95 (0.70-1.28) p=0.723
	Unvacc	10 939	88	709.4 (568.9-873.9)		
Death – all causes *Males*	Vacc	10 437	80	650.1 (515.5-809.1)	0.88* (0.65-1.19) p=0.399	0.89 (0.66-1.2) p=0.437
	Unvacc	10 808	91	739.8 (595.7-908.4)		

at-risk period ; n = number of deaths during the follow-up period at risk
Person-Years = sum of the follow-up periods at risk of the participants (in years)
Incidence rate per 100 000 person-years = number of deaths per 100 000 person-years estimated as n /Person-years
Adjusted incidence rate ratio = estimation of risk ratio using Poisson or Negative binomial regression model with Country as a fixed effect and unvaccinated as reference status; 95%

These results showed that deaths occurred at similar rates in males and females. The safety signal observed in the Phase 3 clinical trial for gender mortality imbalance is not observed in the EPI-MAL-003 IA, 12 months post primary vaccination.

Anticipated risk/consequence of the missing information or population in need of further characterisation

There is no evidence of the incidence of all-cause mortality in girls vaccinated with Mosquirix might being higher than in non-vaccinated girls.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 8 Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Febrile convulsion
Important potential risks	• Hypersensitivity (including anaphylaxis) • pIMDs • Rebound effect • Cerebral malaria • Behavioural changes regarding usage of other malaria preventive measures
Missing information	• Impact/effectiveness • *P. falciparum* strain replacement • Plasmodium species replacement • Safety in HIV-infected children • Gender-specific mortality

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are required:

- **Specific adverse reaction follow-up questionnaires for** seizure, lack of efficacy/vaccination failure and anaphylaxis:

These follow-up questionnaires are designed to solicit event-specific information on these adverse events of special interest/safety concerns to facilitate better evaluation of any cases received. Refer to **Annex 4** for the full questionnaire forms.

- **Other forms of routine pharmacovigilance activities:** None

III.2 Additional pharmacovigilance activities

The EPI-MAL-003 study monitors the onset of the pre-defined diseases, as well as any other conditions that require hospitalization, after vaccine implementation. The list of pre-defined diseases of special interest[2] to be assessed has been developed in collaboration with paediatric experts, as recommended during Scientific Advice (EMA/CHMP/SAWP/95043/2011). This study started in Q1 2019 and is still ongoing.

The study EPI-MAL-005, is conducted in the same settings to obtain longitudinal estimates of the prevalence of *P. falciparum* during the peak malaria transmission season and to collect information on the use of other interventional measures to control malaria. This study started in Q4 2014, in the same sites as the EPI-MAL-002 study is still ongoing. The first 9 surveys have been completed in all sites and the 10 survey is ongoing.

An ancillary study to EPI-MAL-005 (EPI-MAL-010), is evaluating the potential for strain replacement by monitoring the genetic diversity in CS in the *P. falciparum* parasite population before and after vaccine implementation in infants and children below 5 years-of-age. This study started in Q4 2021, and it is still ongoing.

[2] AESI monitored in EPI-MAL-003: ADEM, Encephalitis, Guillain-Barré Syndrome, Generalised convulsive seizures, Hypotonic Hypo-responsive syndrome, Intussusception, Hepatic insufficiency, renal insufficiency, Juvenile chronic arthritis, SJS and TEN, Henoch Schoenlein purpura, Kawasaki diseases, Diabetes mellitus type 1, Thrombo-cytopenia, Anaphylaxis.

Study short name and title: EPI-MAL-003 (GSK eTrack No.: 115056) – *A prospective surveillance study to evaluate the safety, effectiveness and impact of* Mosquirix *in infants and young children in sub-Saharan Africa.*

Rationale and study objectives: This study monitors the occurrence of the same AEs/diseases as the baseline study (i.e., EPI-MAL-002) but post Mosquirix implementation. Both studies are intended to be conducted in the same settings using the same methodology for the identification and characterisation of cases and will include a strong capacity development component. The approach of generating baseline data from the EPI-MAL-002 study and data from unvaccinated children in EPI-MAL-003, allows for an estimation of both vaccine impact and effectiveness as well as the feasibility of implementing a 4th dose. This study addresses the following safety concerns listed in the safety specification: febrile convulsion, meningitis, pIMDs, rebound effect, anaphylaxis, cerebral malaria, gender-specific mortality, vaccine effectiveness and impact and safety in HIV-infected children.

Study design: A disease surveillance study with prospective cohort event monitoring including both a temporal (i.e., a before/after comparison with EPI-MAL-002) and concurrent (i.e., cluster design comparison of exposed and unexposed clusters) comparisons of the occurrence of adverse and malaria events between Mosquirix-vaccinated and Mosquirix-unvaccinated subjects. The study includes both active (i.e., home visits and continuous monitoring of outpatient visits and hospitalisations at all healthcare facilities) and enhanced hospitalisation surveillance (i.e., continuous monitoring of hospitalisations) in both exposed and unexposed clusters.

Study population: Children <5 years-of-age living in a geographically limited area with a demographic surveillance system in-place and a well-developed infrastructure to monitor population health and vaccination programs. The study has enrolled 45 000 children in active surveillance, including 22 564 children in the exposed clusters (with 20 639 vaccinated and 1 869 unvaccinated children) and 22 436 children in the unexposed clusters (with 267 vaccinated and 22 137 unvaccinated children) for evaluation of vaccine safety, effectiveness, and impact.

The total study duration is approximately 62 months, including an estimated recruitment period of approximately 18 months in active surveillance and active follow-up through home visits up to 44 months (children reporting an SAE will have a follow-up of 12 months even if this exceeds the longitudinal follow-up of 44 months).

Milestones: The study started in Q1 2019. Study completion is expected in Q3 2024 and the final study report is expected to become available in Q2 2026 (these latter 2 milestones are tentative as they are dependent on recruitment rates).

Study short name and title: EPI-MAL-005 (GSK eTrack No.: 116682) - *An epidemiology study to assess Plasmodium falciparum parasite prevalence and malaria control measures in catchment areas of two interventional studies pre- and post Mosquirix introduction (EPI-MAL-002 and EPI-MAL-003) to assess, under field conditions, vaccine benefit/risk in children in SSA.*

Rationale and study objectives: This epidemiology study runs in parallel with the EPI-MAL-002 and EPI-MAL-003 studies, enrolling from the same population. The primary objectives of this study are to produce longitudinal estimates of parasite prevalence in humans and to record malaria control measure usage in those areas where the EPI-MAL-002 and EPI-MAL-003 studies take place. As requested by WHO/JTEG, parasite prevalence as an indicator of malaria transmission intensity (MTI) may also contribute to the evidence base for a Mosquirix recommendation in different MTI settings. It is expected that following vaccine introduction through national immunisation systems there will be a reduction in the incidence of malaria in those subjects vaccinated with Mosquirix in EPI-MAL-003 when compared to baseline rates recorded in EPI-MAL-002. Annual fluctuations in malaria incidence occur as a result of changes in transmission intensity, which may be caused by changes in environmental factors, such as rainfall, or changes in the usage of other malaria control interventions. Therefore, by taking into account these variations in MTI and malaria control intervention coverage, it is possible to estimate more accurately the vaccine's impact on clinical disease during the EPI-MAL-003 study. These data also allow for an assessment of any association between vaccination and gametocyte carriage in the 0-2 years-of-age group, as an indicator of the potential effect of the vaccine on malaria transmission. This study addresses the following safety concerns listed in the safety specification: behavioral changes regarding the usage of other malaria preventive measures and *Plasmodium* species replacement.

Study design: A multi-center longitudinal cross-sectional study at centers in SSA participating in the EPI MAL 002 and EPI-MAL-003 studies.

Study population: Children aged 6 months to <10 years participating in the EPI-MAL-002 and EPI-MAL-003 studies. Up to 7 sites and 9 cross-sectional surveys are anticipated and the total expected sample size per site and per survey is a maximum of 400 subjects aged 6 months to <5 years and a maximum of 200 subjects aged 5 to <10 years. The total duration of the study will be up to 9 years.

Milestones: This study started in Q4 2014. Study completion is expected in Q3 2024 and the final study report is expected to become available in Q4 2025.

Study short name and title: EPI-MAL-010 (GSK eTrack No.: 205071) - *A longitudinal, cross-sectional, retrospective, ancillary epidemiology study of the EPI-MAL-005 study to evaluate the genetic diversity in the Plasmodium falciparum parasite circumsporozoite sequences before and after the implementation of Mosquirix in malaria-positive subjects ranging from 6 months to less than 5 years-of-age.*

Rationale and study objectives: *P. falciparum* is a pathogen with high genetic variability and a high number of different circulating strains. The parasite has evolved mechanisms to vary cell surface antigens and elude the host's immune response. For this reason, there is a safety concern that Mosquirix selects specific parasite variants, or alters the number of parasite haplotypes, by exerting selective pressure over time. This study will monitor the genetic diversity in circumsporozoite sequences in the circulating *P. falciparum* parasite population both before and after Mosquirix implementation.

Study design: A longitudinal, retrospective, epidemiological, cross-sectional ancillary study of EPI-MAL-005. In order to characterise *P. falciparum* haplotypes, genotyping will be conducted on samples from subjects aged 6 months to <5 years with *P. falciparum* infection, collected in the framework of the EPI-MAL-005 study at 2 sites before and after Mosquirix implementation; one site in East Africa and one site in West Africa. Those sites will be the same during the entire duration of the study.

Study population: Children aged 6 months to <5 years enrolled in the EPI-MAL-005 study at the 2 sites before and after the start of Mosquirix implementation. The study will re-use DNA samples collected and processed during the EPI-MAL-005 study. Only positive samples (for *P. falciparum* infection) will be sent for sequencing. Assuming a prevalence of *P. falciparum* infection of 25% (this prevalence figure has been evaluated by malaria slide reading after the EPI-MAL-005 study first cross-sectional survey), a total of 100 positive samples per cross-sectional survey and per site are expected to be sent for sequencing. The total duration of the study will be up to 9 years.

Milestones: This study started (*i.e.* first shipment of samples to in Q4 2021 . Study completion (*i.e.* last results received from the testing facility) is expected in Q3 2024 and the final study report is expected to become available in Q4 2025.

III.3 Summary Table of additional Pharmacovigilance activities

Table 8 On-going and planned additional pharmacovigilance activities

Study (Status)	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
N/A	N/A	N/A	N/A	N/A
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization under exceptional circumstances				
N/A	N/A	N/A	N/A	N/A
Category 3 - Required additional pharmacovigilance activities				
EPI-MAL-003 A prospective surveillance study to evaluate the safety, effectiveness and impact of Mosquirix in infants and young children in SSA. **Ongoing**	This study will monitor the occurrence of the same AEs/diseases as the baseline study (i.e. EPI-MAL-002) but post Mosquirix implementation. Generating baseline data in EPI-MAL-002 and data from unvaccinated children in this study will allow for an estimation of both vaccine impact and effectiveness, as well as the feasibility of implementing a 4th dose.	- Febrile convulsions - Meningitis - pIMDs -Anaphylaxis - Cerebral malaria - Gender-specific mortality - Rebound effect - Vaccine effectiveness and impact -Safety in HIV-infected children	Final study report	Q2 2026
EPI-MAL-005 An epidemiology study to assess Plasmodium falciparum parasite prevalence and malaria control	An epidemiology study to generate longitudinal estimates of Plasmodium falciparum parasite prevalence and to record malaria control measures in the catchment areas of 2 studies pre- and post Mosquirix introduction (i.e. EPI-MAL-002 and EPI-	- Behavioral changes regarding the usage of other malaria preventive measures	Final study report	Q4 2025

Study (Status)	Summary of objectives	Safety concerns addressed	Milestones	Due dates
measures in catchment areas of 2 interventional studies pre- and post Mosquirix introduction (EPI-MAL-002 and EPI-MAL-003) to assess, under field conditions, vaccine benefit/risk in children in SSA **Ongoing**	MAL-003) and to assess, under field conditions, vaccine benefit/risk in children in SSA.	- Plasmodium species replacement		
EPI-MAL-010 A longitudinal, cross-sectional, retrospective, ancillary epidemiology study of the EPI-MAL-005 study to evaluate the genetic diversity in the Plasmodium falciparum parasite circumsporozoite sequences before and after the implementation of Mosquirix in malaria-positive subjects ranging from 6 months to less than 5 years-of-age **Ongoing**	A longitudinal, cross-sectional ancillary study of the EPI-MAL-005 study to evaluate genetic diversity in circumsporozoite sequences before and after the implementation of Mosquirix in malaria-positive subjects ranging from 6 months to <5 years-of-age	- Plasmodium falciparum strain replacement	Final study report	Q4 2025

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There is no post-authorization efficacy study required for this product

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table 9 Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimisation activities
Febrile convulsion	**Routine risk communication** Sections 4.4 and 4.8 of the SmPC. Sections 2 and 4 of the package insert/leaflet. **Routine risk minimisation activities recommending specific clinical measures to address the risk** The following text is included in section 4.4 of the SmPC: 'vaccinees, especially those with a history of febrile convulsions, should be closely followed up as vaccine related fever may occur after vaccination (see section 4.8). In case of fever, antipyretic measures should be initiated according to local guidelines. The following text is included in section 2 of the package insert/leaflet: 'talk to your doctor or pharmacist before your child is given Mosquirix if your child has a tendency to seizures/fits due to a fever, or if there is a history in the family of this. In this case, it is important that you ask your doctor or nurse what to do if your child has fever after being vaccinated with Mosquirix'.
Hypersensitivity (including anaphylaxis)	**Routine risk communication** Sections 4.3, 4.4 and 4.8 of the SmPC. Sections 2 and 4 of the package insert/leaflet. **Routine risk minimisation activities recommending specific clinical measures to address the risk** The following text is included in section 4.4 of the SmPC: 'appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine'.
Potential immune-mediated disorders (pIMDs)	**Routine risk communication** None. **Routine risk minimisation activities recommending specific clinical measures to address the risk** None.

Rebound effect	**Routine risk communication** Sections 4.4 and 5.1 of the SmPC. **Routine risk minimisation activities recommending specific clinical measures to address the risk** The following text is included in section 4.4 of the SmPC: 'Protection against P. falciparum malaria wanes over time and vaccination may delay the acquisition of natural immunity (see section 5.1)'. If symptoms compatible with malaria develop, appropriate diagnosis and treatment should be sought.
Cerebral malaria	**Routine risk communication** None. **Routine risk minimisation activities recommending specific clinical measures to address the risk** None.
Behavioral changes regarding usage of other malaria preventative measures	**Routine risk communication** Section 4.4 of the SmPC. Section 1 of the package insert/leaflet. **Routine risk minimisation activities recommending specific clinical measures to address the risk** The following text is included in section 4.4 of the SmPC: 'the use of other malaria control measures recommended locally should not be interrupted'. The following text is included in section 1 of the package insert/leaflet: 'it is very important that you continue to take precautions to prevent your child from being bitten by mosquitoes: make sure your child sleeps under a bed net treated with insecticide and follow all other precautions as recommended by your doctor or nurse'.
Impact / effectiveness	**Routine risk communication** Refer to Section of the 5.1 of the SmPC. **Routine risk minimisation activities recommending specific clinical measures to address the risk** None.
***P. falciparum* strain replacement**	**Routine risk communication** None.

	Routine risk minimisation activities recommending specific clinical measures to address the risk None.
Plasmodium species replacement	**Routine risk communication** None. **Routine risk minimisation activities recommending specific clinical measures to address the risk** None.
Safety in HIV-infected children	**Routine risk communication** Sections 4.4 and 4.8 of the SmPC. Section 2 of the package insert/leaflet. **Routine risk minimisation activities recommending specific clinical measures to address the risk>** None.
Gender-specific mortality	**Routine risk communication** None. **Routine risk minimisation activities recommending specific clinical measures to address the risk** None.

V.2. Additional Risk Minimization Measures

Routine risk minimization activities as described in Part V.1. are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimization Measures

Table 10 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Febrile convulsion	**Routine risk minimization measures** Sections 4.4 and 4.8 of the SmPC	**Routine pharmacovigilance activities beyond adverse**

	Sections 2 and 4 of the package insert/leaflet **Additional risk minimisation measures** None	**reactions reporting and signal detection** Targeted follow-up questionnaire **Additional pharmacovigilance activities** EPI-MAL-003
Hypersensitivity (including anaphylaxis)	**Routine risk minimization measures** Sections 4.3, 4.4 and 4.8 of the SmPC Sections 2 and 4 of the insert/leaflet **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** Targeted follow-up questionnaire **Additional pharmacovigilance activities** EPI-MAL 003 (note: anaphylaxis is included in the list of AESIs)
Potential immune-mediated disorders (pIMDs)	**Routine risk minimization measures** None **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** EPI-MAL 003 (note: pIMDs are a sub-set of the AESIs),
Cerebral malaria	**Routine risk minimization measures** None **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** EPI-MAL-003

Rebound effect	**Routine risk minimization measures** Sections 4.4 and 5.1 of the SmPC **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** EPI-MAL-003
Behavioural changes regarding usage of other malaria preventive measures	**Routine risk minimization measures** Section 4.4 of the SmPC. Section 1 of the package insert/leaflet **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** EPI-MAL-005
Impact/effectiveness	**Routine risk minimization measures** Section 5.1 of the SmPC. **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** EPI-MAL--003
***P. falciparum* strain replacement**	**Routine risk minimization measures** None **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** EPI-MAL-010

Plasmodium species replacement	**Routine risk minimization measures** None **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** EPI-MAL-005
Safety in HIV-infected children	**Routine risk minimization measures** Sections 4.4 and 4.8 of the SmPC. **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** EPI- MAL-003
Gender-specific mortality	**Routine risk minimization measures** None **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities** EPI- MAL-003

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Mosquirix (*Plasmodium falciparum* and hepatitis B vaccine (recombinant, adjuvanted))

This is a summary of the risk management plan (RMP) for Mosquirix. The RMP details the important risks of Mosquirix, how these risks can be minimised, and how more information will be obtained about Mosquirix's risks and uncertainties (missing information).

Mosquirix's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Mosquirix should be used.

I. The medicine and what it is used for

Mosquirix is indicated for active immunisation of children aged 6 weeks up to 17 months against malaria caused by *Plasmodium falciparum* and against hepatitis B (see SmPC for the full indication). It contains a portion of the *Plasmodium falciparum* circumsporozoite protein fused with hepatitis B surface antigen (RTS), combined with hepatitis B surface antigen (S) and adjuvanted with $AS01_E$ as the active substance and is given by intramuscular injection.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Mosquirix, together with measures to minimise such risks and the proposed studies for learning more about Mosquirix'*s* risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (*e.g.,* with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessments, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Mosquirix is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Mosquirix are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Mosquirix. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Febrile convulsion
Important potential risks	• Hypersensitivity (including anaphylaxis) • pIMDs • Rebound effect • Cerebral malaria • Behavioral changes regarding usage of other malaria preventive measures
Missing information	• Impact/effectiveness • *P. falciparum* strain replacement • Plasmodium species replacement • Safety in HIV-infected children • Gender-specific mortality

II.B Summary of important risks

Identified Risk: Febrile convulsion	
Evidence for linking the risk to the medicine	The risk of febrile convulsion was identified during Phase II clinical trials and confirmed in the first analysis of the pivotal Malaria-055 PRI trial. **First 3 doses**: Based on the safety pooling, an increased risk of febrile convulsion (per Brighton Collaboration diagnostic certainty level 1-3) within 7 days post the first 3 doses of Mosquirix, was identified in subjects aged 5 to 17 months (at the time of first dose), with a similar frequency to that observed in the pivotal Malaria-055 PRI study of 1.1/1,000 doses (95%CI: 0.6-1.6). No increased risk of febrile seizure, when compared to the control group, was identified in the 6 to 12 weeks-of-age category. The overall incidence of seizures within 7 days (0-6) days post the first 3 doses of study vaccine (per 1,000 doses) from the Safety Pooling (ITT population) were as follows:

	R3R+R3C					C3C					RR			
				95% CI					95% CI			95% CI		p-value
Age category	**N**	**n**	**n/1000**	**LL**	**UL**	**N**	**n**	**n/1000**	**LL**	**UL**		**LL**	**UL**	
5-17 months	18896	20	1.1	0.6	1.6	10179	7	0.7	0.3	1.4	1.54	0.65	3.64	0.4205
6-12 weeks	14507	2	0.1	0.0	0.5	7720	3	0.4	0.1	1.1	0.35	0.06	2.12	0.3494

R3R – 4-dose group
R3C – 3-dose group
C3C – Control group
RR – Relative Risk
N - Number of doses
n - Number of cases

Fourth dose: In Malaria-055 PRI, an increased risk of febrile convulsion (per Brighton Collaboration diagnostic certainty level 1-3) within 7 days post the fourth dose was identified in subjects in both age categories (i.e. 6 to 12 weeks and 5 to 17 months at the time of the first dose), at frequencies of 2.5/1,000 doses (95%CI: 0.9-5.3) and 2.2/1,000 doses (95%CI: 0.6-5.6) respectively. The overall incidence of seizures within 7 days (0-6) days post fourth dose (per 1,000 doses) in Malaria-055 (ITT population) were as follows:

	R3R					R3C					C3C				
				95% CI					95% CI					95% CI	
Age category	N	n	n/1000	LL	UL	N	N	n/1000	LL	UL	N	n	n/1000	LL	UL
5-17 months	2447	6	**2.5**	0.9	5.3	2472	3	**1.2**	0.3	3.5	2473	1	**0.4**	0.0	2.3

RR R3R versus R3C				RR R3R versus C3C			
	95% CI				95% CI		
	LL	UL	p-value		LL	UL	p-value
2.00	0.51	8.07	0.3409	**6.06**	0.73	50.33	0.0687

	R3R					R3C					C3C				
				95% CI					95% CI					95% CI	
Age category	N	n	n/1000	LL	UL	N	N	n/1000	LL	UL	N	n	n/1000	LL	UL
6-12 weeks	1825	4	**2.2**	0.6	5.6	1837	0	0.0	0	2	1827	1	**0.5**	0.0	3.0

RR R3R versus R3C				RR R3R versus C3C			
	95% CI				95% CI		
	LL	UL	p-value		LL	UL	p-value
-	-	-	-	**4.00**	0.45	35.79	0.2182

R3R – 4-dose group
R3C – 3-dose group
C3C – Control group
RR – Relative Risk
N – Number of doses
n – Number of cases

Cases of febrile convulsion are further monitored in the frame of the MVIP though the GSK-sponsored studies (EPI-MAL-002 and EPI-MAL-003) and the WHO-sponsored study MVPE.
The IA results of EPI-MAL-003 study (1 year post D3), showed that among the hospitalised children, 10 (0.05%) RTS,S/AS01$_E$ vaccinated participants (12 events) reported febrile convulsion vs 8 (0.04%) unvaccinated participants (8 events). No febrile convulsion was reported within 3 days of the primary

	vaccination schedule and 1 case (0.005%) of febrile convulsion was reported within 7 days of the primary RTS,S/AS01$_E$ vaccination schedule.
Risk factors and risk groups	Febrile convulsions usually occur in individuals aged between 3 months and 6 years, with a peak incidence at 18 months. Approximately 6-15% of febrile seizures cases occur after four years-of-age, with occurrence after age 6 years being unusual. A personal and/or family history of febrile seizures in siblings and parents is a risk factor.
Risk minimisation measures	**Routine risk minimization measures** Sections 4.4 and 4.8 of the SmPC Sections 2 and 4 of the package insert/leaflet **Additional risk minimisation measures** None
Additional pharmacovigilance activities	EPI-MAL-003 if reported as an AEFI. See section VI.4 of this summary for an overview of the post-authorisation development plan.
Potential Risk: Hypersensitivity (including anaphylaxis)	
Evidence for linking the risk to the medicine	Mosquirix contains recombinant yeast-derived hepatitis B antigen and the Institute of Medicine concluded that the available evidence convincingly supports a causal relationship between hepatitis B vaccine and anaphylaxis in yeast-sensitive individuals. No cases of anaphylaxis after vaccination with RTS,S/AS01E have been reported in Clinical Trials.Cases of anaphylaxis are actively collected in the EPI-MAL-003 study to further characterize the risk. No cases of anaphylaxis related to vaccination with Mosquirix have been reported so far in EPI-MAL-003.
Risk factors and risk groups	Hypersensitivity to any component of the vaccine and signs and symptoms of hypersensitivity after previous administration of Mosquirix. A family history of hypersensitivity.
Risk minimisation measures	**Routine risk minimization measures** Sections 4.3, 4.4 and 4.8 of the SmPC Sections 2 and 4 of the insert/leaflet

	Additional risk minimisation measures None
Additional pharmacovigilance activities	EPI-MAL-003 (note: anaphylaxis is included in the list of AESIs, if reported as an AEFI. See section VI.4 of this summary for an overview of the post-authorisation development plan
Potential Risk: Potential immune-mediated disorders (pIMDs)	
Evidence for linking the risk to the medicine	Case reports of autoimmune diseases temporally associated with the administration of all vaccines (both adjuvanted and non-adjuvanted) have been described in the scientific literature. Most of these reports refer to vaccines targeting viral illnesses. The rationale for the monitoring of these events for all vaccines containing adjuvant systems (i.e., adjuvant combinations), relates to their possible effects on the regulation of the immune system and the potential, yet theoretical, risk that they may induce unwanted immune inflammatory processes in susceptible individuals. A list of selected pIMDs of interest for the paediatric population were actively collected in the EPI-MAL-002 study and keep on being collected in EPI-MAL-003 to further monitor this potential risk. No cases of pIMDs related to vaccination with Mosquirix have been reported after primary vaccination in EPI-MAL-003.
Risk factors and risk groups	As autoimmune disorders are a potential risk for Mosquirix, but have not been observed in clinical trials, it is difficult to identify specific groups at risk or predictive risk factors. Naturally-occurring autoimmune diseases are multi-aetiological conditions with multiple risk factors, including genetic predisposition. All ages are affected with onset from childhood to late adulthood, as well as all racial, ethnic and socioeconomic groups. Most autoimmune diseases disproportionally affect women.
Risk minimisation measures	**Routine risk minimization measures** None **Additional risk minimisation measures** None
Additional pharmacovigilance activities	EPI-MAL-003 (**note:** pIMDs are a sub-set of the AESIs), See section VI.4 of this summary for an overview of the post-authorisation development plan.
Potential Risk: Rebound effect	

Evidence for linking the risk to the medicine	VE data from a small investigator-supported study (Malaria-059), which was an open-label extension of a phase IIb study (Malaria-049) and VE from both the large phase III (pivotal) trial Malaria-055 PRI and its extension study Malaria-076.
Risk factors and risk groups	Rebound is theoretically more likely to occur when 1) the intervention is given early in life, before naturally-acquired immunity has been induced; 2) the intervention is highly efficacious, preventing natural exposure and 3) the intervention is removed (or efficacy wanes) abruptly.
Risk minimisation measures	**Routine risk minimization measures** Sections 4.4 and 5.1 of the SmPC **Additional risk minimisation measures** None
Additional pharmacovigilance activities	**EPI-MAL-003** section VI.4 of this summary for an overview of the post-authorisation elopment plan.
Potential Risk: Cerebral malaria	
Evidence for linking the risk to the medicine	Based on an ad-hoc analysis of the Malaria-055 data in the 5-17 months-of-age category, there was an imbalance in the number of cerebral malaria cases (with or without severe malaria anaemia) in the Mosquirix-vaccinated groups (i.e. R3C+R3R) (43/5948; 0.72%) when compared to the control group (10/2974; 0.34%). Over the first 20 months of the trial, 22 cases occurred in the Mosquirix groups (R3R + R3C; N=5,948) (0.34%) compared to 6 cases in the control group (N=2,974) (0.20%). For this ad-hoc analysis, a computer algorithm was used to identify cases with parasitaemia >5,000/µL and a Blantyre coma score (BCS) ≤2 as a proxy for cerebral malaria (CM), regardless of whether the CM clinical diagnosis was confirmed by the investigators and without excluding children with comorbidities. From Month 21 to Study End, there were 12 cases in the R3R group (N=2,681) (0.45%), 9 in the R3C group (N=2,719) (0.33%), and 4 in the C3C group (N=2,702) (0.15%).

Evidence for linking the risk to the medicine

During the entire study there were 12 deaths among the cerebral malaria cases (10 in the Mosquirix groups and two in the control group). A similar imbalance was not observed in the 6-12 weeks-of-age category, where there was 13/4358 (0.30%) versus 7/2179 (0.32%) cases of cerebral malaria over the entire study period in the Mosquirix and control group, respectively. No such imbalance was observed in the long-term follow-up study (i.e. Malaria-076) during which there was only one case of cerebral malaria in the 6-12 weeks age category (in a subject who received four doses of Mosquirix) and only two cases in the 5-17 months age category (both in subjects who received three doses of Mosquirix); however, as described for the risk of rebound effect, the results of Malaria-076 should be interpreted with caution given the limitations of the study.

Cerebral malaria has been further monitored in the frame of the MVIP though the EPI-MAL002, EPI-MAL-003 and MPVE studies.

The MVPE results from the primary analysis after 2 years of pilot implementation showed no evidence of an increase in hospital admissions with cerebral malaria, comparing age-eligible children living in implementation areas with those in the comparison areas (IRR excluding probable meningitis 0.77 [95%CI 0.44, 1.35]); including probable meningitis 0.96 [95% CI: 0.61, 1.52]).[WHO, 2021). The MVPE results from the final analysis after 4 years of pilot implementation showed an IRR for cerebral malaria of 0.935 [95%CI 0.630-1.388], which did not show evidence of an increased incidence associated with Mosquirix introduction [WHO 2024b].

The results of EPI-MAL-003, within at-risk period of 12 months post D3, are presented in the table below.

Protocol definition	Group	N	n*	n	IR per 100 000 PYs (95% CI)	Crude IRR (95% CI), p value	IRR adjusted on Country 95% CI
Cluster design comparison (Analysis Set)							
Cerebral malaria	Vacc	20 618	3	3	12.4 (2.6-36.2)	1.53 (0.26-9.15) p=0.642	1.43 (0.24-8.58) p=0.694
	Unvacc	21 747	2	2	8.1 (1.0-29.2)		

N = number of evaluable participants with follow-up during the at-risk period; n* = number of first events post each dose during the follow-up period at risk; n = number of participants with at least one event reported during the follow-up period at risk.
Endpoint = hospitalised case confirmed as cerebral malaria and with final diagnosis assessed by EEP
Adjusted incidence rate ratio = estimation of risk ratio using Poisson or Negative binomial regression model with Country as a fixed effect and unvaccinated as reference status;

These results showed that the cerebral malaria cases were rare: 3 in vaccinated vs 2 in unvaccinated subjects. The safety signal observed in the Phase 3 clinical trial for cerebral malaria is not observed in the EPI-MAL-003 IA, 12 months post primary vaccination.

Risk factors and risk groups	Amongst the severe presentations of the malaria disease, severe malaria anaemia is predominant in younger children, whereas cerebral malaria is observed in older children.
Risk minimisation measures	**Routine risk minimization measures** None **Additional risk minimisation measures** None
Additional pharmacovigilance activities	EPI-MAL-003 See section VI.4 of this summary for an overview of the post-authorisation development plan.
Potential Risk: Behavioural changes regarding usage of other malaria preventive measures	
Evidence for linking the risk to the medicine	It is a general risk that has been raised with other new vaccine introductions. The surveillance study EPI-MAL-005 and the MVPE study are in place to address the behavioural changes regarding the usage of other malaria preventive measures. During the first 2 years of pilot implementation of the vaccine, when the malaria vaccine introduction was accompanied by a comprehensive communication program, no decreased use of other malaria interventions was observed.
Risk factors and risk groups	Not applicable
Risk minimisation measures	**Routine risk minimization measures** Section 4.4 of the SmPC Section 1 of the package insert/leaflet **Additional risk minimisation measures** None
Additional pharmacovigilance activities	EPI-MAL-005 See section VI.4 of this summary for an overview of the post-authorisation development plan.

Missing information: Impact / Effectiveness	
Risk minimisation measures	**Routine risk minimization measures** Section 5.1 of the SmPC. **Additional risk minimisation measures** None.
Additional pharmacovigilance activities	EPI-MAL--003 for impact on mortality. See section VI.4 of this summary for an overview of the post-authorisation development plan.
Missing information: *p. Falciparum* strain replacement	
Risk minimisation measures	**Routine risk minimization measures** None. **Additional risk minimisation measures** None
Additional pharmacovigilance activities	EPI-MAL-010. See section VI.4 of this summary for an overview of the post-authorisation development plan.
Missing Information: Plasmodium species replacement	
Risk minimisation measures	**Routine risk minimization measures** None. **Additional risk minimisation measures** None.
Additional pharmacovigilance activities	EPI-MAL-005. See section VI.4 of this summary for an overview of the post-authorisation developm plan.

Missing Information: Safety in HIV-infected children	
Risk minimisation measures	**Routine risk minimization measures** Sections 4.4 and 4.8 of the SmPC. Section 2 of the package insert/leaflet. **Additional risk minimisation measures** None.
Additional pharmacovigilance activities	EPI-MAL-003. See section VI.4 of this summary for an overview of the post-authorisation development plan.
MISSING INFORMATION: Gender-Specific Mortality	
Risk minimisation measures	**Routine risk minimization measures** None. **Additional risk minimisation measures** None.
Additional pharmacovigilance activities	EPI-MAL-003 See section VI.4 of this summary for an overview of the post-authorisation development plan.

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Mosquirix.

II.C.2 Other studies in post-authorization development plan

Study short name: EPI-MAL-003.

Purpose of the study: This study monitors the occurrence of the same AEs/diseases as the baseline study (*i.e.,* EPI-MAL-002) but post Mosquirix implementation. Both studies

are intended to be conducted in the same settings using the same methodology for the identification and characterisation of cases and will include a strong capacity development component. The approach of generating baseline data from the EPI-MAL-002 study and data from unvaccinated children in EPI-MAL-003, allows the estimation of both vaccine impact and effectiveness as well as the feasibility of implementing a 4th dose. This study addresses the following safety concerns listed in the safety specification: febrile convulsion, meningitis, pIMDs, rebound effect, anaphylaxis, cerebral malaria, gender-specific mortality, vaccine effectiveness and impact and safety in HIV-infected children.

Study short name: EPI-MAL-005.

Purpose of the study: This epidemiology study is run in parallel with the EPI-MAL-002 and EPI-MAL-003 studies, enrolling from the same population. The primary objectives of this study are to produce longitudinal estimates of parasite prevalence in humans and to record malaria control measure usage in those areas where the EPI-MAL-002 and EPI-MAL-003 studies will take place. As requested by WHO/JTEG, parasite prevalence as an indicator of malaria transmission intensity (MTI) may also contribute to the evidence base for a Mosquirix recommendation in different MTI settings. It is expected that following vaccine introduction through national immunisation systems there will be a reduction in the incidence of malaria in those subjects vaccinated with Mosquirix in EPI-MAL-003 when compared to baseline rates recorded in EPI-MAL-002. Annual fluctuations in malaria incidence occur as a result of changes in transmission intensity, which may be caused by changes in environmental factors, such as rainfall, or changes in the usage of other malaria control interventions. Therefore, by taking into account these variations in MTI and malaria control intervention coverage, it will be possible to estimate more accurately the vaccine's impact on clinical disease during the EPI-MAL-003 study. These data will also allow for an assessment of any association between vaccination and gametocyte carriage in the 0-2 years-of-age group, as an indicator of the potential effect of the vaccine on malaria transmission. This study addresess the following safety concerns listed in the safety specification: behavioral changes regarding the usage of other malaria preventive measures and *Plasmodium* species replacement.

Study short name: EPI-MAL-010.

Purpose of the study: *P. falciparum* is a pathogen with high genetic variability and a high number of different circulating strains. The parasite has evolved mechanisms to vary cell surface antigens and elude the host's immune response. For this reason, there is a safety concern that Mosquirix selects specific parasite variants, or alters the number of parasite haplotypes, by exerting selective pressure over time. This study monitors the genetic diversity in circumsporozoite sequences in the circulating *P. falciparum* parasite population both before and after Mosquirix implementation.

PART VII: ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

The following Targeted Follow-up Questionnaires are provided:

- Febrile convulsion
- Vaccination failure/lack of efficacy
- Hypersensitivity (including anaphylaxis)

GSK

Targeted Follow Up Questionnaire
Mosquirix & Seizures

Patient age, gender, initials:	**Sex/weight (is patient obese if weight unknown):**	**GSK CASE No:**

Description of the Event:

	Yes	**No**
Was the event witnessed?	☐	☐
Was the event preceded by an aura? • If *yes*, please specify:	☐	☐
Were the symptoms generalized or limited to a portion of the body? • If *limited,* please describe location:	☐	☐
Did the patient lose consciousness? • If *yes,* was he/she disoriented or drowsy upon regaining consciousness?	☐	☐
Did the patient experience urine/fecal incontinence?	☐	☐
Did the patient experience fever?	☐	☐

Please describe the course of the illness and outcome

Diagnostic Tests

	Yes	**No**

Was any neurological investigation performed to confirm the diagnosis or identify a possible underlying cause (e.g., EEG, CT scan, MRI scan, etc.)? ☐ ☐

- If *yes*, please indicate date and results:

Was there any evidence of a neurological lesion or infection (encephalitis, meningitis, malaria) which might have been the cause of the seizure? ☐ ☐

- If *yes*, please describe:

Were serum electrolytes abnormal? ☐ ☐

- If *yes*, indicate results:

Were any other relevant laboratory investigations performed? ☐ ☐

History

Past personal and familial medical history (specifically related to convulsions, febrile convulsions, epilepsy, head injury and other CNS disorders)

Relevant Vaccination History

Trade name	Batch n°	Primary / Booster	Date	Route	Site of injection

Concomitant medication (including over-the counter medications)				
Trade Name	Dose	Freq/Route	Start date	Reason for medication

Personal and medical information may be made available to GlaxoSmithKline to provide and support the services that GlaxoSmithKline uses to process such information in order to meet its legal and regulatory obligations. GlaxoSmithKline takes steps to ensure that these service providers protect the confidentiality and security of this personal and medical information, and to ensure that such information is processed only for the provision of the relevant services to GlaxoSmithKline and in compliance with applicable law.

GSK

Targeted Follow Up Questionnaire
Mosquirix & Vaccination Failure/Lack of Efficacy

Patient age, gender, initials: **Sex/weight (is patient obese if weight unknown):** **GSK CASE No:**

Description of the Event:

Were there any of the following symptoms present?

	Yes	No
Fever ➢ if yes temperature: ……..°C (oral/axillary/rectal)	☐	☐
Seizures ➢ if yes, ≥2 occurrences in 24 hours	☐	☐
Prostration	☐	☐
Respiratory distress	☐	☐
Impaired consciousness	☐	☐
Jaundice	☐	☐
Pulmonary oedema	☐	☐
Abnormal bleeding	☐	☐
Circulatory collapse	☐	☐
Renal impairment	☐	☐
Coma • Blantyre score	☐	☐

Please describe the course of the illness, treatment provided and outcome

Diagnostic Tests:

Please provide a summary of main results of abnormal laboratory values / investigations (or provide copies of relevant results):

	Yes	No
Were RDT, slide reading tests or any other relevant laboratory investigations that strongly suggest *P. falciparum* infection performed?	☐	☐

- If *yes*, please indicate date and results

Blood examination:

Haemoglobin: ……. Haematocrit: ……. Mean Corpuscular Volume: ……..…

Mean Corpuscular Haemoglobin Concentration: ……. Glucose: …….

Lactate: ……

Arterial blood gas:

pH:…… PaO_2:…….. $PaCO_2$:……..

Bicarbonates concentration:…… Base excess: ……..

Any other diagnostic test:

Complete Blood count:

History:

Past personal and familial medical history (specifically, history of a condition or medication that may result in immunodeficiency):

Relevant Vaccination History

Trade name	Batch n°	Primary / Booster	Date	Route	Site of injection

Concomitant medication (including over-the counter medications)

Trade Name	Dose	Freq/Route	Start date	Reason for medication

Personal and medical information may be made available to GlaxoSmithKline to provide and support the services that GlaxoSmithKline uses to process such information in order to meet its legal and regulatory obligations. GlaxoSmithKline takes steps to ensure that these service providers protect the confidentiality and security of this personal and medical information, and to ensure that such information is processed only for the provision of the relevant services to GlaxoSmithKline and in compliance with applicable law.

Version 1.0; Effective date October 2023

GSK

Targeted Follow Up Questionnaire
Hypersensitivity/ anaphylaxis

Patient age, gender, initials: **Sex/weight (is patient obese if weight unknown):** **GSK CASE No:**

Description of the Event:

Did the patient present with any of the following? Tick all that apply.

	Yes	No
Bronchospasm or respiratory distress	☐	☐
Facial and /or laryngeal edema	☐	☐
Hypotension causing dizziness / collapse	☐	☐
Nausea, vomiting, diarrhea	☐	☐
Coombs' positive hemolytic anemia	☐	☐
Evidence of bone marrow suppression – agranulocytosis/ thrombocytopenia / anemia	☐	☐
Fever	☐	☐
Urticaria or rash	☐	☐
Arthropathy	☐	☐
Lymphadenopathy	☐	☐
Proteinuria	☐	☐
Eosinophilia	☐	☐
Other – please specify	☐	☐

How many doses of the suspect drug had the patient taken before the hypersensitivity reaction occurred?

How was the patient managed?

What was the duration of the event(s)? *[e.g., hours/days]*

Did the patient make a full recovery? • If *no*, please describe outcome	**Yes** ☐	**No** ☐

Diagnostic Tests

Please provide a summary of main results of abnormal laboratory values / investigations (or provide copies of relevant results):

Were the following tests performed? If *yes*, please indicate date and attach results	**Yes**	**No**
Laboratory tests including full blood count/ Coombs' Test	☐	☐
ECGs- baseline and after onset of adverse event	☐	☐
Bone marrow aspiration	☐	☐
De-challenge/ Re-challenge results	☐	☐
Skin biopsy	☐	☐
Were any other relevant laboratory investigations performed? Please list	☐	☐

History:

Please provide a full drug history

Has the patient had any allergic reactions to other drugs? **Yes** ☐ **No** ☐

- If *yes*, please specify

Please provide any other information of relevance

Personal and medical information may be made available to GlaxoSmithKline to provide and support the services that GlaxoSmithKline uses to process such information in order to meet its legal and regulatory obligations. GlaxoSmithKline takes steps to ensure that these service providers protect the confidentiality and security of this personal and medical information, and to ensure that such information is processed only for the provision of the relevant services to GlaxoSmithKline and in compliance with applicable law.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.