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 MINIMISE OR FURTHER CHARACTERISE 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.

IIA. List of important risks and missing information

Important risks of *Mosquirix* are risks that need special risk management activities to further investigate or minimise 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	• Meningitis (any aetiology) • Hypersensitivity (including anaphylaxis) • Potential immune-mediated disorders (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

IIB. Summary of important risks

IDENTIFIED Risk No. 1 [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 three doses: Based on the safety pooling, an increased risk of febrile convulsion (per Brighton Collaboration diagnostic certainty level 1-3) within seven days post the first three 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 seven days (0-6) days post the first three 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

Fourth dose: In Malaria-055 PRI, an increased risk of febrile convulsion (per Brighton Collaboration diagnostic certainty level 1-3) within seven 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 seven 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**	

<table>
<tr><td></td><td>
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<tr><td></td><td>LL</td><td>UL</td><td>p-value</td><td></td><td>LL</td><td>UL</td><td>p-value</td></tr>
<tr><td>-</td><td>-</td><td>-</td><td>-</td><td>4.00</td><td>0.45</td><td>35.79</td><td>0.2182</td></tr>
</table>
</td></tr>
<tr><td>Risk factors and risk groups</td><td>Febrile convulsions usually occur in individuals aged between three months and six 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 six years being unusual. A personal and/or family history of febrile seizures in siblings and parents is a risk factor.</td></tr>
<tr><td>Risk minimisation measures</td><td><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.</td></tr>
<tr><td>Additional pharmacovigilance activities</td><td>– EPI-MAL-002/ -003 and WHO’s Malaria Vaccine Pilot Evaluation (MVPE), if reported as an adverse event following immunization (AEFI).
See section VI.4 of this summary for an overview of the post-authorisation development plan.</td></tr>
<tr><td colspan="2">POTENTIAL Risk No. 1 [meningitis (any aetiology)]</td></tr>
<tr><td>Evidence for linking the risk to the medicine</td><td>Meningitis was a safety signal identified during the first analysis of the Malaria-055 PRI study data whereby the relative risk for developing meningitis (of any aetiology) in the 12 and 18 months post dose three was relatively high in the 5-17 months-of-age category (i.e. 5.5 (95%CI: 0.7-42.6) and 8.0 (95%CI: 1.1-60.3), respectively). In the 6-12 weeks-of-age category, the relative risk was lower (2.3 (95%CI: 0.5-10.4) at 12 months and 1.5 (95%CI: 0.4-5.5) at 18 months of follow-up, respectively.</td></tr>
<tr><td>Risk factors and risk groups</td><td>Risks factors or risk period have not been identified in the clinical trials. However, HIV-infection and sickle cell disease, frequent conditions in Sub Saharan Africa, are risks factors for meningitis.</td></tr>
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Risk minimisation measures	***<routine risk minimization measures>*** – Section 4.4 of the SmPC. – Section 2 of the package insert/leaflet. ***<additional risk minimisation measures>*** – None.
Additional pharmacovigilance activities	– EPI-MAL-002/ -003 and WHO's Malaria Vaccine Pilot Evaluation (MVPE). *See section VI.4 of this summary for an overview of the post-authorisation development plan.*
POTENTIAL Risk No. 2 [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.
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-002 / -003 (**note:** anaphylaxis is included in the list of Adverse Events of Special Interest (AESIs)) and WHO's Malaria Vaccine Pilot Evaluation (MVPE), if reported as an adverse event following (AEFI). *See section VI.4 of this summary for an overview of the post-authorisation development plan.*
POTENTIAL Risk No. 3 [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.
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-002 / -003 (**note:** pIMDs are a sub-set of the Adverse Events of Special Interest (AESIs)) and WHO's Malaria Vaccine Pilot Evaluation (MVPE), if reported as an adverse event following immunization (AEFI). *See section VI.4 of this summary for an overview of the post-authorisation development plan.*
POTENTIAL Risk No. 4 [rebound effect]	
Evidence for linking the risk to the medicine	Vaccine efficacy (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 and WHO's Malaria Vaccine Pilot Evaluation (MVPE) *See section VI.4 of this summary for an overview of the post-authorisation development plan.*
POTENTIAL Risk No. 5 [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 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 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.
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-002/ -003 and WHO's Malaria Vaccine Pilot Evaluation (MVPE). *See section VI.4 of this summary for an overview of the post-authorisation development plan.*
POTENTIAL Risk No. 6 [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.
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 and WHO's Malaria Vaccine Pilot Evaluation (MVPE). *See section VI.4 of this summary for an overview of the post-authorisation development plan.*
MISSING INFORMATION No. 1 [impact/effectiveness]	
Risk minimisation measures	***<routine risk minimization measures>*** – None. ***<additional risk minimisation measures>*** – None.
Additional pharmacovigilance activities	– EPI-MAL-002/ -003 and WHO's Malaria Vaccine Pilot Evaluation (MVPE) (for impact on mortality). *See section VI.4 of this summary for an overview of the post-authorisation development plan.*
MISSING INFORMATION No. 2 [*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 No. 3 [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 development plan.*
MISSING INFORMATION No. 4 [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-002 / -003. *See section VI.4 of this summary for an overview of the post-authorisation development plan.*
MISSING INFORMATION No. 5 [gender-specific mortality]	

Risk minimisation measures	***<routine risk minimization measures>*** – None. ***<additional risk minimisation measures>*** – None.
Additional pharmacovigilance activities	– EPI-MAL-002/ -003 and WHO's Malaria Vaccine Pilot Evaluation (MVPE). *See section VI.4 of this summary for an overview of the post-authorisation development plan.*

IIC. Post-authorisation development plan

IIC.1. Studies which are conditions of the marketing authorisation

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

IIC.2. Other studies in post-authorisation development plan

Study short name: EPI-MAL-002.

Purpose of the study: As the background incidence for many diseases in sub-Saharan Africa is lacking, this epidemiological study will collect baseline (*i.e.* before *Mosquirix* implementation) incidence data of certain pre-defined diseases of special interest, including, but not limited to, the important identified and potential risks outlined in the safety specification, as well as any other conditions that require hospitalisation. This study will not address any safety concerns per se, it is a pre-implementation (*i.e.* baseline) study to generate data for comparison with that generated in the post-implementation study (EPI-MAL-003; see immediately below).

Study short name: EPI-MAL-003.

Purpose of the study: This study will monitor 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, will allow for an estimation of both vaccine impact and effectiveness as well as the feasibility of implementing a 4th dose. This study will address 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 planned to 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 will address 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 will monitor the genetic diversity in circumsporozoite sequences in the circulating *P. falciparum* parasite population both before and after *Mosquirix* implementation.

Study short name: WHO's Malaria Vaccine Pilot Evaluation (MVPE).

Purpose of the study: This study is designed to monitor the pilot implementation (by the Ministries of Health in the three countries in sub-Saharan Africa (*i.e.* Ghana, Kenya and Malawi) selected to conduct the pilot)) of *Mosquirix* into routine healthcare systems. The study will address the following safety concerns listed in the safety specification: febrile convulsions, meningitis, rebound effect, cerebral malaria, gender-specific mortality and vaccine effectiveness/impact. It will also evaluate the feasibility of implementing a fourth dose.