EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No1901/2006, as amended

Synflorix

(Pneumococcal polysaccharide conjugate vaccine, adsorbed)

Procedure No: EMEA/H/C/000973

P46 056

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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I. Introduction

On August 8, 2014, the MAH submitted a completed paediatric study for Synflorix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

II. Scientific discussion

Information on the development program

The MAH stated that study Malaria-063 is a stand-alone study. The main objective of the study was to compare immune responses to the hepatitis B component of an experimental hepatitis B+ malaria (RTS,S/AS01$_E$) vaccine, and compare the antibody levels to that of Engerix-B.

It should be noted that Engerix-B, Rotarix, Infanrix/Hib and Polio Sabin are also administered in the study. Article 46 applications for these concerned vaccines have been sent in parallel to relevant authorities.

Information on the pharmaceutical formulation used in the study

The commercially available formulation of Synflorix was used in the study.

Clinical aspects

Introduction

The MAH submitted a final report for:

- MALARIA-063, Phase III randomized, open, controlled study to evaluate the immune response to the hepatitis B antigen of the RTS,S/AS01$_E$ candidate vaccine, when administered as primary vaccination integrated into an EPI regimen to infants living in sub-Saharan Africa

Clinical study

MALARIA-063, Phase III randomized, open, controlled study to evaluate the immune response to the hepatitis B antigen of the RTS,S/AS01$_E$ candidate vaccine, when administered as primary vaccination integrated into an EPI regimen to infants living in sub-Saharan Africa

Description

This was a phase III, multi-center, open, randomized, controlled trial with 11 study groups. Synflorix was one of the vaccines that were co-administered with the experimental vaccine RTS,S/AS01$_E$.

Methods

Objectives

Primary:

Immunogenicity

To demonstrate in terms of antibody response to the HBs antigen (HBsAg), the non-inferiority of RTS,S/AS01E to a primary vaccination regimen of a licensed hepatitis B vaccine (Engerix-B) integrated into an Expanded Program of Immunization (EPI) regimen.

Criteria for non-inferiority: one month post Dose 3, upper limit (UL) of the 2-sided 95% confidence interval (CI) on the difference in percent seroprotection below 5% between recipients of licensed hepatitis B vaccine (Engerix-B) and recipients of RTS,S/AS01E vaccine.

Secondary:

Immunogenicity

- To demonstrate the non-inferiority of antibody responses to the pneumococcal conjugate vaccine when co-administered with versus without RTS,S/AS01E as part of an EPI regimen.

  Criteria for non-inferiority: one month post Dose 3, UL of the 2-sided 95%CI on the geometric mean concentration (GMC) ratios of 10 pneumococcal serotypes concentrations (measured with an enzyme-linked immunosorbent assay [ELISA] test), is below a limit of 2 for the pneumococcal conjugate vaccine when co-administered with versus without RTS,S/AS01E.

- To describe the antibody responses to the 10 pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F), measured by ELISA and opsonophagocytic assay (OPA), when the pneumococcal conjugate vaccine is co-administered with and without RTS,S/AS01E as part of an EPI regimen.
- To describe the antibody response to the Protein D (PD) component of the pneumococcal conjugate vaccine when co-administered with versus without RTS,S/AS01E as part of an EPI regimen.

A number of other objectives were also included in the study, but as these were not related to Synflorix they will not be assessed within this procedure.

Safety

- Evaluation of the safety profile of the RTS,S/AS01E candidate malaria vaccine, when coadministered with a pneumococcal conjugate vaccine or a rotavirus vaccine integrated into an EPI regimen.

Study design

Subjects were randomized into 11 study groups in a 1:1:1 : 1:1:1 : 1:1:1 : 3 : 3 ratio (this means five treatment groups of which the three RTS,S/AS01E groups were randomized to receive three different lots).

Blood sampling:

- Groups RERo[P], RE[RoP] and HERo[P] will have a total of seven blood samples taken: at Visit 1 (screening) and Visit 8, 10, 13, 14, 15, 16 (post Dose 3 of RTS,S/AS01E or Engerix-B).
- Groups REP[Ro] and HEP[Ro] will have a total of 8 blood samples taken: at Visit 1 (screening) and Visit 8, 10, 12, 13, 14, 15, 16 (post Dose 3 of RTS,S/AS01E or Engerix-B).
- Blood for safety evaluation was collected at screening (Visit 1) to ensure healthy children were recruited.

Study population /Sample size

Male or female infants between 8 and 12 weeks of age at the time of first vaccination free of obvious health problems as established by medical history and clinical examination before entering into the study, who were born to a mother seronegative for HBsAg and human immunodeficiency virus (HIV) and for whom the investigator believed that the parents/Legally acceptable representatives (LARs) would comply with the requirements of the protocol. Results of laboratory screening tests for alanine aminotransferase (ALT), creatinine, hemoglobin, platelets count and total white cell count had to be within pre-defined limits. Subjects should not have received previous vaccination with diphtheria tetanus, B. pertussis (whole-cell or acellular), *Haemophilus influenzae* type B, *Streptococcus pneumoniae*, hepatitis B vaccine or rotavirus vaccine. Signed or thumb-printed informed consent was obtained from the parents/LARs of each subject.

A total of 705 subjects (141 per treatment group) were planned to be enrolled in order to have at least 600 evaluable subjects (approximately 120 subjects in each treatment group).

Treatments

Study vaccine: A candidate malaria vaccine RTS,S/AS01E. Vaccination schedule /site: 0, 1, 2-month schedule; children 8-12 weeks of age at first vaccination received intramuscular (IM) vaccinations into the left anterolateral thigh.

Reference vaccine/ Comparator, dose and mode of administration.

Hepatitis B vaccine: Engerix-B. 0, 1, 2-month schedule + booster at Month 50; infants 8-12 weeks of age at first vaccination received IM vaccinations into the left anterolateral thigh.

DTPaHib vaccine: Infanrix/Hib. 0, 1, 2-month schedule + booster at Month 16; infants 8-12 weeks of age at first vaccination received IM vaccinations into the right deltoid.

OPV: Polio Sabin. 0, 1, 2-month schedule; infants 8-12 weeks old at first vaccination received the OPV doses orally.

Pneumococcal conjugate vaccine: Synflorix. 0, 1, 2-month schedule + booster at Month 16; infants received IM vaccinations into the right anterolateral thigh.

Rotavirus vaccine: Rotarix. Two doses given one month apart; infants received the vaccinations orally.

Outcomes/endpoints

Only the endpoints related to the primary vaccination epoch (up to Month 3) and to the safety follow-up epoch (up to Month 8) are described here. Only primary endpoints and secondary endpoints relating to Synflorix are assessed within this procedure. Other endpoints will be assessed within other P46 procedures for the other products.

Immunogenicity:

- Non-inferiority of the immune response to the hepatitis B antigen induced by RTS,S/AS01E vaccine versus a licensed hepatitis B vaccine.
    - Anti-HBs antibody titers one month post Dose 3 of RTS,S/AS01E or Engerix-B.

Secondary Outcome/Efficacy Variables:

Immunogenicity:

- Non-inferiority of the immune response to the 10 pneumococcal serotype antigens when pneumococcal conjugate vaccine is given as part of an EPI regimen with and without RTS,S/AS01E co-administration.
    - Anti-pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) antibody concentrations one month post Dose 3 of pneumococcal conjugate vaccine.
- Immune response to the 10 pneumococcal serotype antigens of the pneumococcal conjugate vaccine, when given as part of an EPI regimen with and without RTS,S/AS01E co-administration.
    - Anti-pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) antibody concentrations one month post Dose 3 of pneumococcal conjugate vaccine.
    - Opsonophagocytic titers to each of the 10 pneumococcal serotypes one month post Dose 3 of pneumococcal conjugate vaccine.
- Immune response against the PD component of the pneumococcal antigen.
    - Anti-PD antibody concentrations* one month post Dose 3 of pneumococcal conjugate vaccine.

Safety:

For each of the 5 vaccination regimens corresponding to the 5 treatment groups (REP[Ro], RERo[P], RE[RoP], HEP[Ro] and HERo[P]), to describe the occurrence of solicited general and local adverse events (AEs) over a 7-day follow-up period (day of vaccination and 6 subsequent days) after the first, second and third doses of RTS,S/AS01E or a licensed hepatitis B vaccine.

For each of the 5 vaccination regimens corresponding to the 5 treatment groups (REP[Ro], RERo[P], RE[RoP], HEP[Ro] and HERo[P]), to describe the occurrence of unsolicited AEs over a 30-day follow-up period (day of vaccination and 29 subsequent days) after the first, second and third doses of RTS,S/AS01E or a licensed hepatitis B vaccine.

To describe the occurrence of serious adverse events (SAEs).

SAEs from the time of first vaccination until 3 month post Dose 1 (Visit 8) of RTS,S/AS01E or a licensed hepatitis B vaccine.

SAEs from the time of first vaccination until 8 month post Dose 1 (Visit 9) of RTS,S/AS01E or a licensed hepatitis B vaccine.

Fatal SAEs from study start until study end*.

Potential Immune-mediated disorders (pIMDs) from study start until study end*.

* The current report presents fatal SAEs and pIMDs reported between study start and Month 8. Longer follow-up will be reported in annex study reports.

Statistical Methods

Antibodies against pneumococcal conjugate vaccine antigens: non-inferiority of pneumococcal antigens responses

The 95% CI of the antibody GMC ratio (HEP[Ro] over REP[Ro]) was calculated for each of the 10 serotypes (ELISA) one month post Dose 3 of pneumococcal conjugate vaccine. If the UL of this CI was below 2, non-inferiority was concluded.

Results

Recruitment / Number analysed

The participant flow is described in Figure 2. The number of subjects in the different groups is shown in Table 28 (TVC).

Figure 2 Consort, according to vaccination with RTS,S/AS01E or Engerix-B (pooled lot groups and pooled groups for primary vaccination) (Month 3)

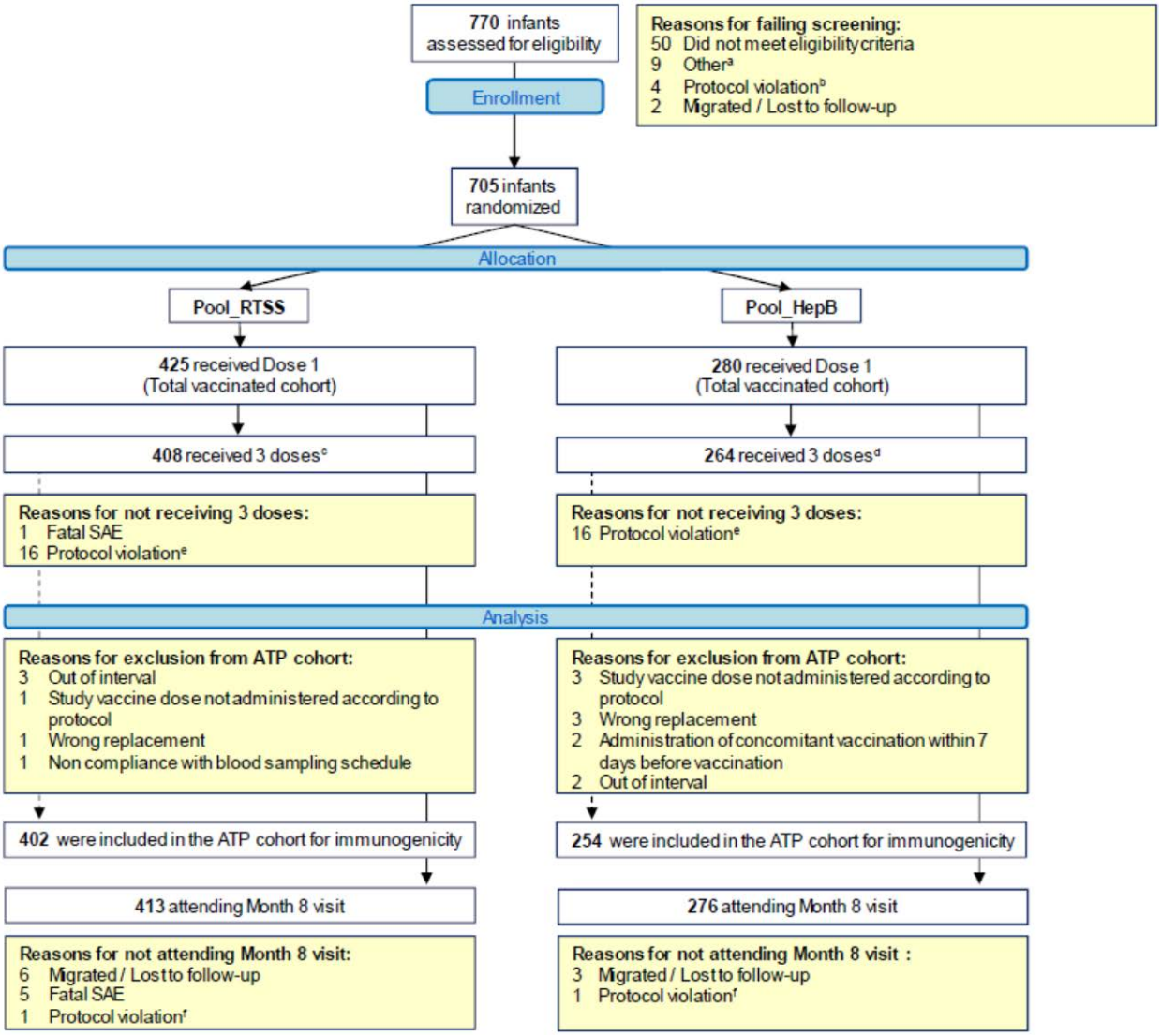

Table 28 Number and percentage of subjects who received study vaccine doses by vaccine (Total vaccinated cohort)

	pool_RTSS *INFANRIX*/HIB VACCINE N = 425		pool_RTSS *POLIO SABIN* N = 425		pool_RTSS *ROTARIX* VACCINE N = 425		pool_RTSS RTS,S AS01E N = 425		pool_RTSS *SYNFLORIX* VACCINE N = 425		Pool_HepB *ENGERIX* N = 280		Pool_HepB *INFANRIX*/HIB VACCINE N = 280		Pool_HepB *POLIO SABIN* N = 280		Pool_HepB *ROTARIX* VACCINE N = 280		Pool_HepB RTS,S AS01E N = 280	
Total number of doses received	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
0	0	0.0	0	0.0	17	4.0	0	0.0	0	0.0	2	0.7	0	0.0	0	0.0	16	5.7	278	99.3
1	17	4.0	17	4.0	1	0.2	17	4.0	17	4.0	16	5.7	16	5.7	16	5.7	1	0.4	0	0.0
2	0	0.0	0	0.0	407	95.8	0	0.0	1	0.2	0	0.0	0	0.0	0	0.0	263	93.9	0	0.0
3	408	96.0	408	96.0	0	0.0	408	96.0	407	95.8	262	93.6	264	94.3	264	94.3	0	0.0	2	0.7
Any	425	100	425	100	408	96.0	425	100	425	100	278	99.3	280	100	280	100	264	94.3	2	0.7

	Pool_HepB *SYNFLORIX* VACCINE N = 280	
Total number of doses received	n	%
0	1	0.4
1	15	5.4
2	0	0.0
3	264	94.3
Any	279	99.6

pool_RTSS = All study groups with RTS,S/AS01E vaccine (REP[Ro]_1 + REP[Ro]_2 + REP[Ro]_3 + RERo[P]_1 + RERo[P]_2 + RERo[P]_3 + RE[RoP]_1 + RE[RoP]_2 + RE[RoP]_3)
Pool_HepB = All study groups with Engerix-B vaccine (HEP[Ro]+ HERo[P])
N = number of subjects in each group included in the considered cohort
n/% = number/percentage of subjects receiving the specified total number of doses
Any = number and percentage of subjects receiving at least one dose

Efficacy results

Only results relating to Synflorix will be summarised and assessed in this assessment report.

Immune response to pneumococcal conjugate vaccine antigens (ELISA) according to co-administration vaccine regimen

ATP cohort for immunogenicity

Anti-pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) antibody seropositivity rates and GMCs assessed by ELISA, per co-administration vaccine regimen, are presented in table 83.

Table 83 Anti-pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F antibody seropositivity rates and GMCs (ELISA) following Synflorix vaccination in co-administration with RTS,S/AS01E or Engerix-B, Month 3 (ATP cohort for immunogenicity)

				≥ 0.05 µg/ml				≥ 0.2 µg/ml				GMC				
						95% CI				95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL	Min	Max
anti-1 antibody	REP[Ro]	PIII(M3)	141	141	100	97.4	100	141	100	97.4	100	3.1	2.8	3.6	0.5	19.6
	HEP[Ro]	PIII(M3)	135	135	100	97.3	100	135	100	97.3	100	3.6	3.1	4.2	0.4	25.0
anti-4 antibody	REP[Ro]	PIII(M3)	141	141	100	97.4	100	140	99.3	96.1	100	3.5	3.0	4.0	0.2	17.7
	HEP[Ro]	PIII(M3)	134	134	100	97.3	100	134	100	97.3	100	4.2	3.5	4.9	0.2	28.8
anti-5 antibody	REP[Ro]	PIII(M3)	141	141	100	97.4	100	141	100	97.4	100	5.1	4.5	5.8	0.8	28.7
	HEP[Ro]	PIII(M3)	135	135	100	97.3	100	135	100	97.3	100	6.5	5.6	7.4	0.5	36.5
anti-6B antibody	REP[Ro]	PIII(M3)	141	136	96.5	91.9	98.8	123	87.2	80.6	92.3	1.1	0.8	1.3	<0.1	16.6
	HEP[Ro]	PIII(M3)	135	129	95.6	90.6	98.4	118	87.4	80.6	92.5	1.2	1.0	1.6	<0.1	15.4
anti-7F antibody	REP[Ro]	PIII(M3)	141	141	100	97.4	100	141	100	97.4	100	4.4	3.9	4.9	0.9	25.1
	HEP[Ro]	PIII(M3)	135	135	100	97.3	100	135	100	97.3	100	4.9	4.3	5.7	0.5	39.4
anti-9V antibody	REP[Ro]	PIII(M3)	141	140	99.3	96.1	100	137	97.2	92.9	99.2	2.8	2.4	3.3	<0.1	21.1
	HEP[Ro]	PIII(M3)	135	135	100	97.3	100	134	99.3	95.9	100	3.7	3.3	4.2	0.1	23.7
anti-14 antibody	REP[Ro]	PIII(M3)	141	141	100	97.4	100	141	100	97.4	100	5.8	5.0	6.7	0.2	45.3
	HEP[Ro]	PIII(M3)	134	134	100	97.3	100	132	98.5	94.7	99.8	5.7	4.7	7.0	0.1	78.6
anti-18C antibody	REP[Ro]	PIII(M3)	141	141	100	97.4	100	139	98.6	95.0	99.8	3.4	2.8	4.1	0.1	41.3
	HEP[Ro]	PIII(M3)	134	134	100	97.3	100	134	100	97.3	100	6.2	5.1	7.5	0.3	135.6
anti-19F antibody	REP[Ro]	PIII(M3)	141	141	100	97.4	100	139	98.6	95.0	99.8	4.2	3.4	5.2	0.1	55.5
	HEP[Ro]	PIII(M3)	134	134	100	97.3	100	129	96.3	91.5	98.8	5.1	4.1	6.4	0.1	66.6
anti-23F antibody	REP[Ro]	PIII(M3)	140	134	95.7	90.9	98.4	129	92.1	86.4	96.0	1.3	1.1	1.6	<0.1	16.8
	HEP[Ro]	PIII(M3)	134	128	95.5	90.5	98.3	120	89.6	83.1	94.2	1.5	1.1	1.9	<0.1	16.7

REP[Ro] = RTS,S/AS01E + EPICoAd (Infanrix/Hib + Polio Sabin + Synflorix) + Rotarix staggered
HEP[Ro] = Engerix-B + EPICoAd (Infanrix/Hib + Polio Sabin + Synflorix) + Rotarix staggered
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PIII(M3) = Post Dose 3, Month 3

Non-inferiority of the immune response to the 10 pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) assessed by ELISA, per co-administration vaccine regimen, is presented in table 84.

Table 84 Non-inferiority assessment of pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F antibody ELISA responses to Synflorix when coadministered with RTS,S/AS01E vs Engerix-B, GMC ratios, Month 3 (ATP cohort for immunogenicity)

					GMC ratio (HEP[Ro] / REP[Ro])		
	HEP[Ro]		REP[Ro]			95% CI	
Antibody	N	GMC	N	GMC	Value	LL	UL
anti-1 antibody (µg/ml)	135	3.6	141	3.1	1.15	0.95	1.39
anti-4 antibody (µg/ml)	134	4.2	141	3.5	1.20	0.97	1.48
anti-5 antibody (µg/ml)	135	6.5	141	5.1	1.27	1.06	1.52
anti-6B antibody (µg/ml)	135	1.2	141	1.1	1.17	0.83	1.65
anti-7F antibody (µg/ml)	135	4.9	141	4.4	1.12	0.94	1.33
anti-9V antibody (µg/ml)	135	3.7	141	2.8	1.32	1.08	1.63
anti-14 antibody (µg/ml)	134	5.7	141	5.8	0.99	0.77	1.27
anti-18C antibody (µg/ml)	134	6.2	141	3.4	1.81	1.38	2.38
anti-19F antibody (µg/ml)	134	5.1	141	4.2	1.21	0.89	1.65
anti-23F antibody (µg/ml)	134	1.5	140	1.3	1.12	0.81	1.55

REP[Ro] = RTS,S/AS01E + EPICoAd (Infanrix/Hib + Polio Sabin + Synflorix) + Rotarix staggered
HEP[Ro] = Engerix-B + EPICoAd (Infanrix/Hib + Polio Sabin + Synflorix) + Rotarix staggered
GMC = geometric mean antibody concentration
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit

Immune response to pneumococcal conjugate vaccine antigens (OPA) according to co-administration vaccine regimen

ATP cohort for immunogenicity

Anti-pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) antibody seropositivity rates and GMTs assessed by OPA, per co-administration vaccine regimen, are presented in table 86.

Table 86 Anti-pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F antibody seropositivity rates and GMTs (OPA) following Synflorix vaccination in co-administration with RTS,S/AS01E or Engerix-B, Month 3 (ATP cohort for immunogenicity)

				≥ 8 1/DIL				GMT				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
OPA-1	REP[Ro]	PIII(M3)	132	89	67.4	58.7	75.3	48.9	34.6	68.9	<8.0	3015.0
	HEP[Ro]	PIII(M3)	124	88	71.0	62.1	78.8	65.0	45.0	93.7	<8.0	3366.0
OPA-4	REP[Ro]	PIII(M3)	130	127	97.7	93.4	99.5	768.3	617.6	955.8	<8.0	10157.0
	HEP[Ro]	PIII(M3)	123	123	100	97.0	100	810.9	676.5	972.0	50.0	11686.0
OPA-5	REP[Ro]	PIII(M3)	133	126	94.7	89.5	97.9	77.6	61.9	97.3	<8.0	4898.0
	HEP[Ro]	PIII(M3)	124	116	93.5	87.7	97.2	93.8	73.6	119.6	<8.0	1131.0
OPA-6B	REP[Ro]	PIII(M3)	128	107	83.6	76.0	89.5	444.4	295.0	669.5	<8.0	13106.0
	HEP[Ro]	PIII(M3)	121	98	81.0	72.9	87.6	389.3	250.1	606.1	<8.0	8943.0
OPA-7F	REP[Ro]	PIII(M3)	132	132	100	97.2	100	3774.0	3232.7	4405.8	162.0	27999.0
	HEP[Ro]	PIII(M3)	124	124	100	97.1	100	3947.4	3338.3	4667.7	59.0	98164.0
OPA-9V	REP[Ro]	PIII(M3)	132	128	97.0	92.4	99.2	1257.7	977.3	1618.7	<8.0	11574.0
	HEP[Ro]	PIII(M3)	122	121	99.2	95.5	100	1469.3	1180.4	1828.8	<8.0	42178.0
OPA-14	REP[Ro]	PIII(M3)	132	131	99.2	95.9	100	1426.3	1136.0	1790.9	<8.0	26900.0
	HEP[Ro]	PIII(M3)	123	118	95.9	90.8	98.7	1269.0	965.1	1668.6	<8.0	10167.0
OPA-18C	REP[Ro]	PIII(M3)	124	110	88.7	81.8	93.7	192.6	139.2	266.4	<8.0	4325.0
	HEP[Ro]	PIII(M3)	118	109	92.4	86.0	96.5	249.7	185.0	337.0	<8.0	5289.0
OPA-19F	REP[Ro]	PIII(M3)	129	105	81.4	73.6	87.7	159.3	109.9	231.0	<8.0	3768.0
	HEP[Ro]	PIII(M3)	123	106	86.2	78.8	91.7	228.8	160.4	326.3	<8.0	8494.0
OPA-23F	REP[Ro]	PIII(M3)	132	109	82.6	75.0	88.6	760.9	476.3	1215.5	<8.0	27030.0
	HEP[Ro]	PIII(M3)	121	99	81.8	73.8	88.2	735.6	456.3	1185.9	<8.0	17182.0

REP[Ro] = RTS,S/AS01E + EPICoAd (Infanrix/Hib + Polio Sabin + Synflorix) + Rotarix staggered
HEP[Ro] = Engerix-B + EPICoAd (Infanrix /Hib + Polio Sabin + Synflorix) + Rotarix staggered
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PIII(M3) = Post Dose 3, Month 3

Assessor's comment: The immunogenicity results relating to the 10 pneumococcal antigens are well in agreement with previously reported results. Statistical non-inferiority was demonstrated for all serotypes except 18C, although there is no regulatory consequence of these results.

Safety results

Summary

Safety

Summary of safety according to co-administration vaccine regimen

- Over a 7-day follow-up period (day of vaccination and 6 subsequent days) after each vaccine dose, the incidence of local symptoms (solicited and unsolicited) with a co-administration of pneumococcal conjugate vaccine was 16.3% in the REP[Ro] group, and 13.9% in the HEP[Ro]

group. The incidence of local solicited and unsolicited symptoms with a DTPa/Hib vaccine was 17.2% in the REP[Ro] group, 11.9% in the RERo[P] group, 12.3% in the RE[RoP] group, 13.7% in the HEP[Ro] group and 9.1% in the HERo[P] group. The incidence of local solicited and unsolicited symptoms after vaccination with RTS,S/AS01E was 14.4% in the REP[Ro] group, 10.2% in the RERo[P] group and 12.1% in the RE[RoP] group. The incidence of local solicited and unsolicited symptoms after vaccination with hepatitis B vaccine was 12.6% in the HEP[Ro] group and 6.3% in the HERo[P] group. The incidence of Grade 3 local solicited and unsolicited symptoms after any vaccine was ≤0.2%.

- Over a 7-day follow-up period (day of vaccination and 6 subsequent days) after each vaccine dose the incidence overall doses of solicited local symptoms was as follows:
    - The incidence of pain at the site of any co-administered vaccine was 11.6% when RTS,S/AS01E was administered with EPI vaccines alone (RE[RoP]), 13.2% when coadministered with a pneumococcal conjugate vaccine and EPI vaccines (REP[Ro]) and 9.4% when co-administered with a rotavirus vaccine and EPI vaccines (RERo[P]). When a licensed hepatitis B vaccine was co-administered with a pneumococcal conjugate vaccine and EPI vaccines (HEP[Ro]), the incidence of pain was 10.5% and when co-administered with a rotavirus vaccine and EPI vaccines (HERo[P]), the incidence of pain was 6.0%. No Grade 3 pain was reported in all other groups.
    - The incidence of redness at the site of any co-administered vaccine was 0.7% when RTS,S/AS01E was administered with EPI vaccines alone (RE[RoP]) and 0.7% when coadministered with a pneumococcal conjugate vaccine and EPI vaccines (REP[Ro]). No redness was reported when RTS,S/AS01E was co-administered with a rotavirus vaccine and EPI vaccines (RERo[P]). When a licensed hepatitis B vaccine was co-administered with a pneumococcal conjugate vaccine and EPI vaccines (HEP[Ro]), the incidence of redness was 1.0% and when co-administered with a rotavirus vaccine and EPI vaccines (HERo[P]), the incidence of redness was 0.3%. No Grade 3 redness was reported in all groups.
    - The incidence of swelling at the site of any co-administered vaccine was 2.1% when RTS,S/AS01E was administered with EPI vaccines alone (RE[RoP]), 2.1% when coadministered with a pneumococcal conjugate vaccine and EPI vaccines (REP[Ro]) and 1.0% when co-administered with a rotavirus vaccine and EPI vaccines (RERo[P]). When a licensed hepatitis B vaccine was co-administered with a pneumococcal conjugate vaccine and EPI vaccines (HEP[Ro]), the incidence of swelling was 3.6% and when co-administered with a rotavirus vaccine and EPI vaccines (HERo[P]), the incidence of swelling was 0.8%. No Grade 3 swelling was reported in all groups.
- Over a 7-day follow-up period (day of vaccination and 6 subsequent days) after each vaccine dose the solicited general symptoms with highest incidence overall doses were:
    - temperature (26.4%) and irritability/fussiness (7.8%) in REP[Ro] group.
    - temperature (13.7%) and irritability/fussiness (5.3%) in RERo[P] group.
    - temperature (14.2%) and irritability/fussiness (7.8%) in RE[RoP] group.
    - temperature (13.9%) and irritability/fussiness (5.9%) in HEP[Ro] group.
    - temperature (7.8%) and irritability/fussiness (1.6%) in HERo[P] group.

All other solicited general symptoms (drowsiness and loss of appetite) were reported after ≤2.4% of vaccine dose.

- Grade 3 temperature (axillary temperature > 39.0°C) was reported after 1.2% of doses in the REP[Ro] group, 0.7% of doses in the RE[RoP] group, 0.2% of doses in the HEP[Ro] group and 1.0% of doses in the HERo[P] group. No other Grade 3 solicited general symptoms were reported.
- Over a 7-day follow-up period (day of vaccination and 6 subsequent days) after each vaccine dose, the solicited general symptoms related to vaccination with highest incidence overall doses were:
    - temperature (20.0%) and irritability/fussiness (3.3%) in REP[Ro] group.
    - temperature (10.7%) and irritability/fussiness (2.8%) in RERo[P] group.
    - temperature (9.7%) and irritability/fussiness (2.6%) in RE[RoP] group.
    - temperature (9.7%) and irritability/fussiness (1.7%) in HEP[Ro] group.
    - temperature (5.5%) and irritability/fussiness (0.5%) in HERo[P] group.

  All other solicited general symptoms related to vaccination were reported after ≤0.5% of vaccine dose.
- Over a 30-day follow-up period (day of vaccination and 29 subsequent days), at least one unsolicited AE was reported by 85.2%, 81.0% and 85.1% in REP[Ro], RERo[P] and RE[RoP] groups and 85.1% and 75.5% in HEP[Ro] and HERo[P] groups. Malaria, gastroenteritis, bronchitis, rhinitis, and pharyngitis were the most frequently reported unsolicited AE in each groups.
- The percentage of subjects reporting at least one Grade 3 unsolicited AE within 30 days post vaccination was 0.7%, 1.4% and 1.4% in REP[Ro], RERo[P] and RE[RoP] groups and 0.7% and 1.4% in HEP[Ro] and HERo[P] groups. Bronchopneumonia and gastroenteritis and were the most frequently reported Grade 3 unsolicited AEs (3 and 2 subjects respectively).
- The percentage of subjects reporting at least one unsolicited AE related to vaccination within 30 days post vaccination was 0.7%, 0.7% and 3.5% in REP[Ro], RERo[P] and RE[RoP] groups and 2.1% and 4.3% in HEP[Ro] and HERo[P] groups. Pyrexia was the most frequently reported unsolicited AEs related to vaccination in each groups (1 subject in REP[Ro] and RERo[P] groups, 5 subjects in RE[RoP] group, 3 subjects in HEP[Ro] group and 6 subjects in HERo[P] group).
- From Dose 1 until 8 months post Dose 1 (Visit 9), the percentage of subjects reporting at least one SAE was 0.7%, 4.9% and 5.0% in REP[Ro], RERo[P] and RE[RoP] groups and 2.1% and 3.6% in HEP[Ro] and HERo[P] groups. Bronchopneumonia and gastroenteritis were the most frequently reported SAEs (6 and 5 subjects respectively). None of the SAEs were judged to be related to vaccination.
- Over a 30-day follow-up period (day of vaccination and 29 subsequent days), 4 fatal SAEs were reported in 2 subjects vaccinated with RTS,S/AS01E vaccine (1 subject in REP[Ro] and 1 subject in RE[RoP]). None of these fatal SAEs were judged to be related to vaccination.

- From the start of the study until Month 8 (Visit 9), there were 8 fatal SAEs reported in 5 subjects vaccinated with RTS,S/AS01E vaccine (1 subject in REP[Ro], 2 subjects in RERo[P] and 2 subjects in RE[RoP]). None of these fatal SAEs were judged to be related to vaccination.
- No potential immune mediated disorders were reported from the start of the study until Month 8 (Visit 9).

Assessor's comment: There were no new safety issues for Synflorix based on the results of this study.

Discussion on clinical aspects

The current study was a study of an experimental malaria vaccine, and Synflorix was one of several vaccines included to study concomitant vaccination. A total of 425 subjects received at least one dose of Synflorix co-administered with the RTS,S vaccine and other vaccines and 279 subjects received at least one dose of Synflorix co-administered with Engerix-B and other vaccines. Thus, the addition of these results to the already presented extensive amount of data does not impact the benefit risk of Synflorix. The immune responses did not cause concern of lack of efficacy, and the safety dada did not give rise to new safety concerns. No further regulatory action is considered necessary.

III. Rapporteur's overall conclusion and recommendation

Overall conclusion

The article 46 paediatric submission is considered fulfilled, and no further regulatory action is needed. The provided data do not cause concern regarding efficacy or safety for Synflorix.

Recommendation

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

Additional clarifications requested

Not applicable.