25 February 2016
EMA/190189/2016
Procedure Management and Committees Support Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Synflorix

pneumococcal polysaccharide conjugate vaccine (adsorbed)

Procedure no: EMEA/H/C/000973/P46/061

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Introduction

In December, 2015, the MAH submitted an on-going stand-alone paediatric study, in which Synflorix is a co-administered vaccine, in accordance with Article 46 of Regulation (EC) No1901/2006. The part of the study involving Synflorix is completed. The study vaccine was GlaxoSmithKline Biologicals' Plasmodium falciparum and hepatitis B vaccine (RTS,S/AS01$_E$ or Mosquirix). This vaccine is proposed for the active immunisation of children aged 6 weeks up to 17 months against malaria caused by Plasmodium falciparum and against hepatitis B.

The MAH stated that the data submitted do not influence the benefit-risk balance for *Synflorix*.

A short critical expert overview has also been provided.

1. Scientific discussion

1.1. Information on the development program

The applicant states that the study MALARIA-063, a 'Phase III randomized, open, controlled study to evaluate the immune response to the hepatitis B antigen of the RTS,S/AS01E candidate vaccine, when administered as primary vaccination integrated into an EPI regimen to infants living in sub-Saharan Africa' is a stand alone study in which Synflorix is a co-administered vaccine.

1.2. Clinical aspects

1.2.1. Introduction

The MAH submitted a final report to fulfil the requirements of the Article 46 of the Paediatric Regulation (EC) No 1901/2006 regulation towards the Synflorix license, for study:

- MALARIA-063, a 'Phase III randomized, open, controlled study to evaluate the immune response to the hepatitis B antigen of the RTS,S/AS01E candidate vaccine, when administered as primary vaccination integrated into an EPI regimen to infants living in sub-Saharan Africa'

1.2.2. Clinical study

Study MALARIA-063

A 'Phase III randomized, open, controlled study to evaluate the immune response to the hepatitis B antigen of the RTS,S/AS01E candidate vaccine, when administered as primary vaccination integrated into an EPI regimen to infants living in sub-Saharan Africa'

Description

Methods

Objectives

Only the objectives pertaining to the immunogenicity of a booster dose of Synflorix and to the safety follow-up from month 8 to month 26 are listed below:

Secondary:

Immunogenicity follow-up

- Evaluation of the antibody response to the 10 pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) induced by a booster dose of a licensed pneumococcal conjugate vaccine when co-administered with and without RTS,S/AS01E.

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.

CHMP comment:

In this report, only the response to a booster dose of Synflorix as well as immunogenicity and safety data collected from months 8-26 is presented and assessed. The objectives listed above only represent those related to the data included in this report. For a complete list of objectives (i.e. related to other vaccines), refer to the complete study protocol.

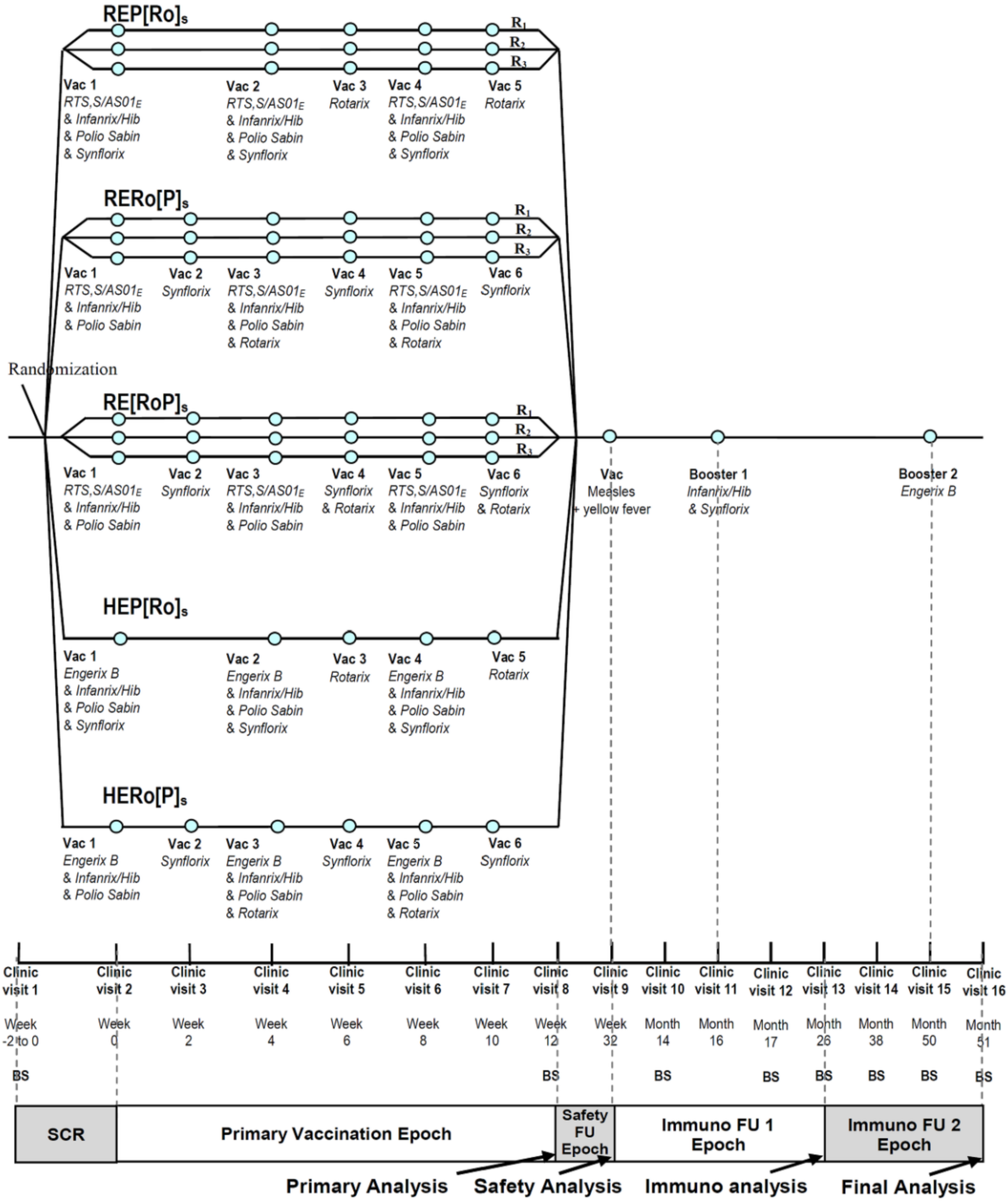
Study design

- Experimental design: Phase III, multi-center, open, randomized, controlled trial with 11 study groups.
- 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 (see Synopsis Table 1 for group labeling):
    - Groups RERo[P], RE[RoP] and HERo[P] will have a total of seven blood samples taken for immunogenicity assessment: at Visit 1 (screening) and post Dose 3 of RTS,S/AS01E or *Engerix-B:* Visit 8 (Month 3), 10 (Month 14), 13 (Month 26), 14 (Month 38), 15 (Month 50), and 16 (Month 51).
    - Groups REP[Ro] and HEP[Ro] will have a total of 8 blood samples taken for immunogenicity assessment: at Visit 1 (screening) and post Dose 3 of RTS,S/AS01E or

Engerix-B: Visit 8 (Month 3), 10 (Month 14), 12 (Month 17), 13 (Month 26), 14 (Month 38), 15 (Month 50), and 16 (Month 51).

- Blood for safety evaluation was collected at screening (Visit 1) to ensure healthy children were recruited.

Figure 1 Study design



Vac = vaccination; **SCR** = Screening Epoch; **FU** = Follow-up; **BS** = blood sample
R = RTS,S/AS01$_E$; **E** = Infanrix/Hib + Polio Sabin EPI vaccines; **P** = pneumococcal conjugate vaccine (*Synflorix*);
Ro = Rotavirus vaccine (*Rotarix*); **H** = Hepatitis B vaccine (*Engerix B*);
R$_1$ = RTS,S/AS01$_E$ lot 1; **R$_2$** = RTS,S/AS01$_E$ lot 2; **R$_3$** = RTS,S/AS01$_E$ lot 3

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 and for whom the investigator believed that the parents/legally acceptable representatives would comply with the requirements of the protocol. The infants enrolled were living in Ghana and Burkina Faso. Results of laboratory screening tests for alanine aminotransferase, creatinine, hemoglobin, platelet 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/legally acceptable representatives of each subject.

Treatments

The duration of the study is approximately 52 months for each subject (including the screening period and 49 months of follow-up after the third vaccination of RTS,S/AS01E or *Engerix-B*).

Subjects were randomized in 5 treatment groups of which the three RTS,S/AS01$_E$ groups were randomized to receive three different RTS,S/AS01$_E$ lots. In treatment groups REP[Ro], RERo[P] and RE[RoP], three doses of RTS,S/AS01$_E$ were co-administered with DTPa/Hib (Infanrix/Hib) and OPV (Polio Sabin) at 8, 12 and 16 weeks of age with, according to the treatment group, two doses of a rotavirus vaccine (Rotarix) and/or three doses of a pneumococcal conjugate vaccine (Synflorix) co-administered or staggered. The control groups (HEP[Ro]s and HERo[P]s) received a licensed hepatitis B vaccine (Engerix-B) co-administered with Infanrix/Hib+Polio Sabin and either Rotarix or Synflorix.

All groups received Synflorix and Infanrix/Hib booster vaccinations at approximately 18 months of age. The report included in the present submission descibes the data from study month 8 (week 32) to study month 26 and presents the immunogenicity results for all subjects up to one month post-booster dose of Synflorix.

The study is still ongoing. An Engerix-B booster dose will be administered 48 months after the third dose of the primary vaccination schedule.

Outcomes/endpoints

Only secondary outcomes related to the data presented in this report are listed here, i.e. data related to the immunogenicity and safety of Synflorix. For the complete list of primary and secondary outcomes, please refer to the study protocol.

Secondary endpoints:

Immunogenicity follow-up

- Immune response to a booster dose of pneumococcal conjugate vaccine when primary vaccination 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 booster dose of pneumococcal conjugate vaccine.
    - Opsonophagocytic titers to each of the 10 pneumococcal serotypes one month post booster dose of pneumococcal conjugate vaccine.
    - Anti-protein D antibody titers one month post booster dose of pneumococcal conjugate vaccine.

Safety

- To describe the occurrence of serious adverse events (SAEs).
    - Fatal SAEs from study start until study end**.
    - Related SAEs**.
    - Potential immune-mediated disorders (pIMDs) from study start until study end**.

** This Annex Report presents fatal SAEs, related SAEs and pIMDs reported between Month 8 and Month 26 and from study start until Month 26. Longer follow-up will be reported in further Annex Reports.

Statistical Methods

Analyses were performed as per protocol and per Statistical Analysis Plan (SAP).

The present annex report includes all analyses performed on data collected from Month 8 (Visit 9) up to Month 26 (Visit 13) and included secondary immunogenicity and safety endpoints. Additionally, safety data from study start until Month 26 were reported.

Demography analyses were presented for the treatment groups, the pooled lot groups, and for the pooled group for primary endpoint. Study flow diagrams (Consort) were generated to present the number of subjects receiving doses and included in according-to-protocol (ATP) analyses. Summary of demographic characteristics (age at booster vaccination and gender) of each cohort was tabulated by group. The mean age at booster vaccination (in months) (plus range and standard deviation) of the vaccinated subjects, as a whole, and per group, was calculated.

The immunogenicity follow-up (FU) 1 analysis was based on the ATP cohort for immunogenicity analysis FU 1. Immunogenicity analysis was performed by treatment group, pooled lot group and/or pooled group for the primary endpoint. In some cases, depending on antigen, descriptive analyses were performed by treatment group for each site. Descriptive analysis by treatment group was also performed on the Total vaccinated cohort.

Immune response to pneumococcal conjugate vaccine antigens; descriptive analysis. For each vaccine serotype (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F), the percentage of seropositive subjects, i.e. with serotype-specific anti-pneumococcal antibody concentration ≥ 0.05 µg/ml, with 95% CI were determined at each blood sampling timepoint for the groups REP[Ro] and HEP[Ro]. For each vaccine serotype, the proportion of subjects with serotype-specific anti-pneumococcal antibody concentration ≥ 0.2 µg/ml was also tabulated. The distribution of antibody concentrations was summarized with 95% CI at all timepoints at which serological samples were taken. Antibody concentrations after the booster dose were also investigated using RCCs. The same analysis was repeated on data resulting from opsonophagocytic assay and anti-pneumococcal protein D.

Analysis of safety. This Annex Report presents fatal SAEs, related SAEs and pIMDs reported between Month 8 and Month 26 and from study start until Month 26. Longer follow-up will be reported in further Annex Reports.

Results

Recruitment / Number analysed

Number of subjects vaccinated in each group:

Table 1 Malaria-063: Study treatment groups

Treatment Group	Study Group	Primary vaccination schedule	Number of subjects vaccinated
REP[Ro]$_S$	REP[Ro]$_S$ lot 1 REP[Ro]$_S$ lot 2 REP[Ro]$_S$ lot 3	RTS,S/AS01$_E$ co-administered with DTPa/Hib (*Infanrix*/Hib), OPV(Polio *Sabin)* and PCV (*Synflorix)* Rotavirus (*Rotarix)* staggered administration	142
RERo[P]$_S$	RERo[P]$_S$ lot 1 RERo[P]$_S$ lot 2 RERo[P]$_S$ lot 3	RTS,S/AS01$_E$ co-administered with DTPa/Hib (*Infanrix*/Hib), OPV(Polio *Sabin)* and rotavirus (*Rotarix)* PCV (*Synflorix)* staggered administration	142
RE[RoP]$_S$	RE[RoP]$_S$ lot 1 RE[RoP]$_S$ lot 2 RE[RoP]$_S$ lot 3	RTS,S/AS01$_E$ co-administered with DTPa/Hib (*Infanrix*/Hib) and OPV(Polio *Sabin)* PCV (*Synflorix)* and rotavirus (*Rotarix*) staggered administration	141
HEP[Ro]$_S$	HEP[Ro]$_S$	*Engerix-B* co-administered with DTPa/Hib (*Infanrix*/Hib), OPV(Polio *Sabin)* and PCV (*Synflorix)* Rotavirus (*Rotarix)* staggered administration	141
HERo[P]$_S$	HERo[P]$_S$	*Engerix-B* co-administered with DTPa/Hib (*Infanrix*/Hib), OPV(Polio *Sabin)* and rotavirus (*Rotarix)* PCV (*Synflorix)* staggered administration	139

Baseline data

Infants included in the study were 8 to 12 weeks of age at the time of the first vaccination. A total of 705 subjects of 8.3 weeks of age (SD ±0.7 weeks) were enrolled and vaccinated in this study.

Immune response to Synflorix

Immune response to the 10 vaccine pneumococcal serotypes and protein D (PD) of Synflorix was measured 1 month after the booster dose of Synflorix in the REP[Ro] and HEP[Ro] groups.

For each vaccine pneumococcal serotype, at least 98.5% of subjects who previously received Synflorix with RTS,S/AS01$_E$ (REP[Ro]) presented antibody concentration ≥0.2 µg/ml (ATP cohort for immunogenicity – FU 1, Table 2). Among subjects who initially received Synflorix with a licensed hepatitis B vaccine (HEP[Ro]), these percentages were at least 98.4%. Compared to one month post-dose 3, robust increase in antibody GMCs were observed for a majority of vaccine pneumococcal serotypes in both groups. Following the primary vaccination course, the non-inferiority of the antibody response to pneumococcal serotypes when Synflorix was co-administered with RTS,S/AS01$_E$ was demonstrated for all the vaccine pneumococcal serotypes, except the serotype 18C (refer to procedure EMA/H/C/973/P46 056). The descriptive immunogenicity data presented in this report showed a similar booster response in both REP[Ro] and HEP[Ro] groups for this 18C serotypes (Table 2).

For each vaccine pneumococcal serotype, at least 86.2% of subjects who previously received the Synflorix with RTS,S/AS01$_E$ (REP[Ro]) presented opsonophagocytic titers ≥8, while among subjects who initially received the Synflorix with a licensed hepatitis B vaccine (HEP[Ro]), these percentages were at least 90.9% (Table 3). Compared to one month post-dose 3, robust increases in OPA GMTs were observed for a majority of vaccine pneumococcal serotypes in both groups.

With respect to the immune response to the protein D, 99.2% of subjects who initially received the Synflorix with RTS,S/AS01$_E$ (REP[Ro]) or with a licensed hepatitis B vaccine (HEP[Ro]) were

seropositive for anti-PD antibodies (≥100 EU/ml). The anti-PD antibody GMTs were 2648.3 EU/ml (95% CI: 2194.2 to 3196.4) and 2819.1 EU/ml (95% CI: 2391.1 to 3323.7) in the REP[Ro] and HEP[Ro] groups, respectively.

CHMP comment:

The immune response of Synflorix to the pneumococcal serotypes and protein D did not markedly differ between the two groups previously receiving the study vaccine RTS,S/AS01$_E$ and Engerix-B, respectively. The booster dose resulted in robust increases in antibody GMCs and OPA GMTs, as compared to one month post-dose 3, for most of the pneumococcal serotypes included.

Table 2 **Percentage of subjects with anti-pneumococcal serotypes antibody concentration ≥ 0.2 µg/ml and GMCs (by ELISA) following *Synflorix* vaccination, at one month post dose 3 and one month post booster dose (ATP cohort for immunogenicity - FU 1)**

				≥ 0.2 µg/ml				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
anti-1 antibody	REP[Ro]	PIII(M3)	141	141	**100**	97.4	100	**3.1**	2.8	3.6
		Post-BS1	133	132	**99.2**	95.9	100	**4.5**	3.8	5.4
	HEP[Ro]	PIII(M3)	135	135	**100**	97.3	100	**3.6**	3.1	4.2
		Post-BS1	126	126	**100**	97.1	100	**5.4**	4.5	6.4
anti-4 antibody	REP[Ro]	PIII(M3)	141	140	**99.3**	96.1	100	**3.5**	3.0	4.0
		Post-BS1	132	132	**100**	97.2	100	**6.1**	5.1	7.2
	HEP[Ro]	PIII(M3)	134	134	**100**	97.3	100	**4.2**	3.5	4.9
		Post-BS1	125	125	**100**	97.1	100	**6.8**	5.7	8.0
anti-5 antibody	REP[Ro]	PIII(M3)	141	141	**100**	97.4	100	**5.1**	4.5	5.8
		Post-BS1	133	132	**99.2**	95.9	100	**6.5**	5.5	7.8
	HEP[Ro]	PIII(M3)	135	135	**100**	97.3	100	**6.5**	5.6	7.4
		Post-BS1	126	126	**100**	97.1	100	**7.6**	6.4	9.1
anti-6B antibody	REP[Ro]	PIII(M3)	141	123	**87.2**	80.6	92.3	**1.1**	0.8	1.3
		Post-BS1	133	132	**99.2**	95.9	100	**4.7**	4.0	5.5
	HEP[Ro]	PIII(M3)	135	118	**87.4**	80.6	92.5	**1.2**	1.0	1.6
		Post-BS1	126	125	**99.2**	95.7	100	**4.1**	3.5	4.9
anti-7F antibody	REP[Ro]	PIII(M3)	141	141	**100**	97.4	100	**4.4**	3.9	4.9
		Post-BS1	133	133	**100**	97.3	100	**7.1**	6.2	8.2
	HEP[Ro]	PIII(M3)	135	135	**100**	97.3	100	**4.9**	4.3	5.7
		Post-BS1	126	126	**100**	97.1	100	**7.2**	6.3	8.2
anti-9V antibody	REP[Ro]	PIII(M3)	141	137	**97.2**	92.9	99.2	**2.8**	2.4	3.3
		Post-BS1	133	133	**100**	97.3	100	**6.0**	5.1	7.1
	HEP[Ro]	PIII(M3)	135	134	**99.3**	95.9	100	**3.7**	3.3	4.2
		Post-BS1	126	126	**100**	97.1	100	**5.7**	4.9	6.6
anti-14 antibody	REP[Ro]	PIII(M3)	141	141	**100**	97.4	100	**5.8**	5.0	6.7
		Post-BS1	133	132	**99.2**	95.9	100	**9.0**	7.6	10.7
	HEP[Ro]	PIII(M3)	134	132	**98.5**	94.7	99.8	**5.7**	4.7	7.0
		Post-BS1	126	126	**100**	97.1	100	**9.0**	7.4	10.8
anti-18C antibody	REP[Ro]	PIII(M3)	141	139	**98.6**	95.0	99.8	**3.4**	2.8	4.1
		Post-BS1	133	133	**100**	97.3	100	**13.7**	11.5	16.3
	HEP[Ro]	PIII(M3)	134	134	**100**	97.3	100	**6.2**	5.1	7.5
		Post-BS1	126	126	**100**	97.1	100	**14.5**	12.3	17.2
anti-19F antibody	REP[Ro]	PIII(M3)	141	139	**98.6**	95.0	99.8	**4.2**	3.4	5.2
		Post-BS1	133	132	**99.2**	95.9	100	**6.0**	4.9	7.4
	HEP[Ro]	PIII(M3)	134	129	**96.3**	91.5	98.8	**5.1**	4.1	6.4
		Post-BS1	126	126	**100**	97.1	100	**7.2**	5.8	8.8
anti-23F antibody	REP[Ro]	PIII(M3)	140	129	**92.1**	86.4	96.0	**1.3**	1.1	1.6
		Post-BS1	133	131	**98.5**	94.7	99.8	**4.1**	3.4	5.1
	HEP[Ro]	PIII(M3)	134	120	**89.6**	83.1	94.2	**1.5**	1.1	1.9
		Post-BS1	126	124	**98.4**	94.4	99.8	**3.9**	3.2	4.8

REP[Ro] = RTS,S/AS01$_E$ + *Infanrix*/Hib + *Polio Sabin* + *Synflorix*; *Rotarix* staggered
HEP[Ro] = *Engerix*-B +*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
PIII(M3) = Blood sampling 1 month after the third dose; Post-BS1 = Blood sampling 1 month after booster dose 1

Table 3 **Anti-pneumococcal serotypes antibody seropositivity rates and GMTs (by OPA) following *Synflorix* vaccination, at one month post dose 3 and one month post booster dose 1 (ATP cohort for immunogenicity - FU 1)**

				≥ 8 1/DIL				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
OPA-1	REP[Ro]	PIII(M3)	132	89	**67.4**	58.7	75.3	**48.9**	34.6	68.9
		Post-BS1	130	122	**93.8**	88.2	97.3	**649.9**	464.7	908.9
	HEP[Ro]	PIII(M3)	124	88	**71.0**	62.1	78.8	**65.0**	45.0	93.7
		Post-BS1	121	116	**95.9**	90.6	98.6	**840.1**	603.4	1169.7
OPA-4	REP[Ro]	PIII(M3)	130	127	**97.7**	93.4	99.5	**768.3**	617.6	955.8
		Post-BS1	126	123	**97.6**	93.2	99.5	**2347.1**	1847.4	2982.0
	HEP[Ro]	PIII(M3)	123	123	**100**	97.0	100	**810.9**	676.5	972.0
		Post-BS1	116	115	**99.1**	95.3	100	**2527.8**	2064.1	3095.7
OPA-5	REP[Ro]	PIII(M3)	133	126	**94.7**	89.5	97.9	**77.6**	61.9	97.3
		Post-BS1	129	124	**96.1**	91.2	98.7	**324.2**	244.1	430.5
	HEP[Ro]	PIII(M3)	124	116	**93.5**	87.7	97.2	**93.8**	73.6	119.6
		Post-BS1	121	117	**96.7**	91.8	99.1	**392.8**	291.3	529.6
OPA-6B	REP[Ro]	PIII(M3)	128	107	**83.6**	76.0	89.5	**444.4**	295.0	669.5
		Post-BS1	130	127	**97.7**	93.4	99.5	**955.3**	761.4	1198.6
	HEP[Ro]	PIII(M3)	121	98	**81.0**	72.9	87.6	**389.3**	250.1	606.1
		Post-BS1	116	114	**98.3**	93.9	99.8	**828.2**	652.7	1050.9
OPA-7F	REP[Ro]	PIII(M3)	132	132	**100**	97.2	100	**3774.0**	3232.7	4405.8
		Post-BS1	130	130	**100**	97.2	100	**9167.3**	7979.2	10532.3
	HEP[Ro]	PIII(M3)	124	124	**100**	97.1	100	**3947.4**	3338.3	4667.7
		Post-BS1	118	118	**100**	96.9	100	**7794.6**	6577.6	9236.8
OPA-9V	REP[Ro]	PIII(M3)	132	128	**97.0**	92.4	99.2	**1257.7**	977.3	1618.7
		Post-BS1	130	129	**99.2**	95.8	100	**3035.3**	2523.3	3651.3
	HEP[Ro]	PIII(M3)	122	121	**99.2**	95.5	100	**1469.3**	1180.4	1828.8
		Post-BS1	118	118	**100**	96.9	100	**3164.6**	2669.8	3751.1
OPA-14	REP[Ro]	PIII(M3)	132	131	**99.2**	95.9	100	**1426.3**	1136.0	1790.9
		Post-BS1	127	126	**99.2**	95.7	100	**1975.7**	1565.8	2493.0
	HEP[Ro]	PIII(M3)	123	118	**95.9**	90.8	98.7	**1269.0**	965.1	1668.6
		Post-BS1	119	117	**98.3**	94.1	99.8	**1865.0**	1463.9	2375.9
OPA-18C	REP[Ro]	PIII(M3)	124	110	**88.7**	81.8	93.7	**192.6**	139.2	266.4
		Post-BS1	127	123	**96.9**	92.1	99.1	**1694.1**	1188.6	2414.7
	HEP[Ro]	PIII(M3)	118	109	**92.4**	86.0	96.5	**249.7**	185.0	337.0
		Post-BS1	115	112	**97.4**	92.6	99.5	**1548.7**	1096.3	2188.0
OPA-19F	REP[Ro]	PIII(M3)	129	105	**81.4**	73.6	87.7	**159.3**	109.9	231.0
		Post-BS1	130	112	**86.2**	79.0	91.6	**344.5**	223.0	532.3
	HEP[Ro]	PIII(M3)	123	106	**86.2**	78.8	91.7	**228.8**	160.4	326.3
		Post-BS1	121	110	**90.9**	84.3	95.4	**469.7**	320.0	689.4
OPA-23F	REP[Ro]	PIII(M3)	132	109	**82.6**	75.0	88.6	**760.9**	476.3	1215.5
		Post-BS1	127	125	**98.4**	94.4	99.8	**3199.8**	2543.7	4025.1
	HEP[Ro]	PIII(M3)	121	99	**81.8**	73.8	88.2	**735.6**	456.3	1185.9
		Post-BS1	118	117	**99.2**	95.4	100	**3198.1**	2526.5	4048.4

REP[Ro] = RTS,S/AS01$_E$ + *Infanrix*/Hib + *Polio Sabin* + *Synflorix*; *Rotarix* staggered
HEP[Ro] = *Engerix*-B + *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
PIII(M3) = Blood sampling 1 month after the third dose; Post-BS1 = Blood sampling 1 month after booster dose 1

Safety results

During the study period from month 8 to month 26, only SAEs judged to be related to vaccination, fatal SAEs and potential immune-mediated disorders (pIMD) were to be reported. As the Synflorix booster dose was co-administered with an Infanrix/Hib booster dose, no safety data on Synflorix booster dose alone is being reported.

Over the period from month 8 up to month 26, no subjects reported SAEs judged to be related to vaccination by the investigator and no pIMD was reported.

Over the period from month 8 up to month 26, fatal SAEs were reported for one subject from the RERo[P] group, two subjects from the HEP[Ro] group and one subject from the HERo[P] group.

CHMP comment:

Over the period included in this report, fatal SAEs were reported by four subjects in different groups. No SAEs were judged as related to vaccination and no pIMDs were identified. As Synflorix was not administered alone, it is difficult to draw any conclusions on the safety profile of the single vaccine.

Overall, the safety data did not raise any unforeseen safety issues.

1.2.3. Discussion on clinical aspects

The booster dose of Synflorix in subjects who initially received Synflorix with RTS,S/AS01E (REP[Ro]) or a licensed hepatitis B vaccine (HEP[Ro]) was immunogenic and elicited increases in antibody GMC and OPA GMT for the majority of vaccine pneumococcal serotypes (ATP cohort for immunogenicity).

In terms of safety, over the period from Month 8 up to Month 26, fatal SAEs were reported by four subjects (one in the RERo[P] group, two in the HEP[Ro] group and one in the HERo[P] group). No SAEs related to vaccination and no pIMDs were identified.

2. Rapporteur's overall conclusion and recommendation

Overall conclusion

This article 46 submission is considered satisfactory and no further regulatory action regarding Synflorix is required.

Recommendation

☒ **Fulfilled:**