20 February 2015
EMA/99784/2015 rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Synflorix

(Pneumococcal polysaccharide conjugate vaccine, adsorbed)

Procedure No. EMEA/H/C/000973

P46 053

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

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

I. INTRODUCTION

On July 30, 2013 the MAH submitted a completed paediatric study for Synflorix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Synflorix and that there is no consequential regulatory action.

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the study(ies)

The commercial formulation of Synflorix was used in the clinical study.

II.2 Clinical aspects

1. Introduction

The MAH submitted a final report for:

- 10PN-PD-DIT-068; phase III, open, single centre study to assess the safety, reactogenicity and immunogenicity of GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate (10Pn-PD-DiT) vaccine (GSK 1024850A), when either given as a booster dose (at 15-21 months of age) in children previously primed with three doses of 10Pn-PD-DiT vaccine, or when given as a two-dose catch-up immunization (at 15-21 and 17-23 months of age) in unprimed children, all previously enrolled in the 10PN-PD-DIT-032 primary vaccination study in Nigeria.

2. Clinical study

10PN-PD-DIT-068; phase III, open, single centre study to assess the safety, reactogenicity and immunogenicity of GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate (10Pn-PD-DiT) vaccine (GSK 1024850A), when either given as a booster dose (at 15-21 months of age) in children previously primed with three doses of 10Pn-PD-DiT vaccine, or when given as a two-dose catch-up immunization (at 15-21 and 17-23 months of age) in unprimed children, all previously enrolled in the 10PN-PD-DIT-032 primary vaccination study in Nigeria.

- **Description**

- **Methods**

- Objectives

Primary:

- To assess the safety and reactogenicity of the 10Pn-PD-DiT vaccine in terms of occurrence of adverse events with grade 3 intensity after booster vaccination.

Secondary:

- To assess the safety and reactogenicity of the 10Pn-PD-DiT vaccine after administration of any vaccine dose.
- To assess one month post-booster dose, the immunogenicity of the 10Pn-PD-DiT vaccine.
- To assess the immunogenicity of a 2-dose catch-up vaccination with the 10Pn-PD-DiT vaccine in the second year of life.
- To assess the antibody persistence 11 to 18 months after completion of the primary vaccination course with the 10Pn-PD-DiT vaccine in study 10PN-PD-DIT-032.
- To assess the safety and reactogenicity of a booster dose of GSK Biologicals' DTPa vaccine when co-administered with the 10Pn-PD-DiT vaccine at 15-21 months of age.

- Study design

The study was an open study with two parallel groups which included subjects from a single centre. The vaccination schedules were as follows:

- Pn-Pn group: Booster vaccination at 15-21 months of age.
- Zil-Pn group: Two-dose catch-up vaccination at 15-21 months and 17-23 months of age, with an interval of 56-118 days.

A booster dose of DTPa vaccine was co-administered with a booster dose of the 10Pn-PD-DiT vaccine or the first dose of 10Pn-PD-DiT catch-up vaccination (at 15-21 months of age).
Blood sampling: two blood samples were collected in each group.

- Pn-Pn group: prior to and one month post-booster vaccination
- Zil-Pn group: pre-vaccination and one month post-dose 2

Type of study:

- Pn-Pn group: booster vaccination study following primary vaccination study 10PN-PD-DIT-032.
- Zil-Pn group: catch-up vaccination study in children during their second year of life.

Data collection: hard copy Case Report Form (CRF).

- Study population /Sample size

Healthy male or female subjects, between and including 15-21 months of age at the time of Visit 1. Subjects in the Pn-Pn group should have completed the full vaccination course with 10Pn-PD-DiT in the study 10PN-PD-DIT-032. Subjects in the Zil-Pn group were those who were previously enrolled in the control group of the study 10PN-PD-DIT-032.
Written informed consent, signed or thumb printed was to be obtained from the parent(s)/LAR(s) of the subject.
Where parent(s)/LAR(s) were illiterate, the consent form was to be countersigned by a witness.

The sample size was contingent on the number of Nigerian subjects who received three doses of pneumococcal conjugate vaccine in study 10PN-PD-DIT-032 (110521), i.e. 77 planned subjects. Assuming that around 20% of these subjects might not enter this study, one could consider that approximately 60 subjects would receive the booster dose of study vaccine.

- Treatments

Both groups received the same vaccines in this study. The 10Pn-PD-DiT vaccine was administered intramuscularly into the anterolateral region of the thigh. The DTPa vaccine was injected intramuscularly into the left thigh.

- Outcomes/endpoints

Safety and reactogenicity:

- Solicited local and general adverse events (AEs)
  - Occurrence of each solicited local adverse event (any, grade 3) within 4 days (Day 0-Day 3) after each vaccine dose.
  - Occurrence of each solicited general adverse event (any, grade 3, related) within 4 days (Day 0-Day 3) after each vaccine dose.
- Unsolicited adverse events
  - Occurrence of unsolicited adverse events within 31 days (Day 0-Day 30) after each vaccine dose.
- Serious adverse events (SAEs)
  - Occurrence of serious adverse events during the entire study period.

Immunogenicity:

<u>Pn-Pn group</u>

Evaluation of the immune responses to the components of the investigational vaccine prior to and one month after the booster immunization:

- Concentrations of antibodies against vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.
- Opsonophagocytic activity against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F*.
- Concentrations of antibodies against cross-reactive pneumococcal serotypes 6A and 19A.
- Opsonophagocytic activity against cross-reactive pneumococcal serotypes 6A and 19A*
- Concentrations of antibodies against protein D.

Zil-Pn group:

Evaluation of the immune responses to the components of the investigational vaccine, prior to the first dose and one month after Dose 2:

- Concentrations of antibodies against vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.
- Opsonophagocytic activity against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F*.
- Concentrations of antibodies against cross-reactive pneumococcal serotypes 6A and 19A.
- Opsonophagocytic activity against cross-reactive pneumococcal serotypes 6A and 19A*
- Concentrations of antibodies against protein D.

*The OPA testing for pre-booster (primed group) or pre-dose 1 (unprimed group) blood samples initially planned in the study protocol was not performed.

➢ **Results**

- Recruitment/ Number analysed

Study population (Total vaccinated cohort)		
Number of subjects	**Pn-Pn**	**Zil-Pn**
Planned, N	77	38
Total vaccinated cohort, N	68	36
Completed visit 2, n (%) for Primed group	67 (98.5)	-
Completed visit 3, n (%) for Unprimed group	-	36 (100)
Demographics	**Pn-Pn**	**Zil-Pn**
N (Total Vaccinated Cohort)	68	36
Females:Males	29:39	17:19
Mean Age*, months (SD)	16.7 (1.00)	16.4 (0.91)
African heritage / African American, n (%)	68 (100)	36 (100)
Pn-Pn = Primed group receiving booster dose of 10Pn-PD-DiT + DTPa following 3-dose primary vaccination in the 10PN-PD-DIT-032 study Zil-Pn = Unprimed group receiving 2-dose catch-up vaccination with 10Pn-PD-DiT and a dose of DTPa in the second year of life *mean age at first vaccination		

- Immunogenicity results

Immunogenicity analysis was performed on ATP cohort for analysis of antibody persistence or on the ATP cohort for immunogenicity according to the objective. Since, in any group, the percentage of vaccinated subjects with serological data excluded from the ATP cohort for persistence and for immunogenicity was less than 5%, a second analysis based on the Total vaccinated cohort was not performed.

The immune responses measured by 22F-inhibition ELISA results one month after completion of the primary vaccination course, prior to and one month after the booster dose (Pn-Pn group) or prior to dose I and one month after dose II (Zil-Pn group) are detailed in Tables 57 and 58.

Table 57 Seropositivity rates and GMCs for ANTI-1, ANTI-4, ANTI-5, ANTI-6B, ANTI-7F, ANTI-9V, ANTI-14, ANTI-18C, ANTI-19F and ANTI-23F antibodies (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
ANTI-1	Pn-Pn	PIII(M3)	68	68	100	94.7	100	68	100	94.7	100	3.37	2.74	4.16
		PRE-BOOSTER	68	65	95.6	87.6	99.1	42	61.8	49.2	73.3	0.29	0.22	0.40
		POST-BOOSTER	67	67	100	94.6	100	67	100	94.6	100	8.72	6.37	11.93
	Zil-Pn	PIII(M3)	31	5	16.1	5.5	33.7	2	6.5	0.8	21.4	0.03	0.03	0.05
		PRE-VACC	35	8	22.9	10.4	40.1	1	2.9	0.1	14.9	0.03	0.03	0.04
		POST-VACC II	35	35	100	90.0	100	35	100	90.0	100	3.17	2.58	3.89
ANTI-4	Pn-Pn	PIII(M3)	68	68	100	94.7	100	68	100	94.7	100	4.25	3.42	5.28
		PRE-BOOSTER	68	66	97.1	89.8	99.6	52	76.5	64.6	85.9	0.40	0.31	0.50
		POST-BOOSTER	67	67	100	94.6	100	67	100	94.6	100	11.03	9.06	13.42
	Zil-Pn	PIII(M3)	35	7	20.0	8.4	36.9	3	8.6	1.8	23.1	0.04	0.03	0.06
		PRE-VACC	35	13	37.1	21.5	55.1	4	11.4	3.2	26.7	0.06	0.04	0.09
		POST-VACC II	35	35	100	90.0	100	35	100	90.0	100	8.22	6.75	10.02
ANTI-5	Pn-Pn	PIII(M3)	68	68	100	94.7	100	68	100	94.7	100	5.39	4.50	6.46
		PRE-BOOSTER	68	68	100	94.7	100	56	82.4	71.2	90.5	0.49	0.40	0.61
		POST-BOOSTER	67	67	100	94.6	100	67	100	94.6	100	10.34	8.32	12.85
	Zil-Pn	PIII(M3)	32	4	12.5	3.5	29.0	1	3.1	0.1	16.2	0.03	0.02	0.04
		PRE-VACC	35	17	48.6	31.4	66.0	4	11.4	3.2	26.7	0.05	0.04	0.07
		POST-VACC II	35	35	100	90.0	100	35	100	90.0	100	2.87	2.22	3.71
ANTI-6B	Pn-Pn	PIII(M3)	68	66	97.1	89.8	99.6	61	89.7	79.9	95.8	2.06	1.45	2.93
		PRE-BOOSTER	68	67	98.5	92.1	100	59	86.8	76.4	93.8	0.63	0.48	0.83
		POST-BOOSTER	67	67	100	94.6	100	66	98.5	92.0	100	4.31	3.37	5.52
	Zil-Pn	PIII(M3)	35	5	14.3	4.8	30.3	0	0.0	0.0	10.0	0.03	0.03	0.04
		PRE-VACC	35	11	31.4	16.9	49.3	4	11.4	3.2	26.7	0.05	0.03	0.08
		POST-VACC II	35	33	94.3	80.8	99.3	29	82.9	66.4	93.4	0.85	0.52	1.38
ANTI-7F	Pn-Pn	PIII(M3)	68	68	100	94.7	100	68	100	94.7	100	3.91	3.25	4.72
		PRE-BOOSTER	68	68	100	94.7	100	62	91.2	81.8	96.7	0.73	0.57	0.92
		POST-BOOSTER	67	67	100	94.6	100	67	100	94.6	100	10.30	8.57	12.38
	Zil-Pn	PIII(M3)	33	7	21.2	9.0	38.9	1	3.0	0.1	15.8	0.03	0.03	0.04
		PRE-VACC	35	15	42.9	26.3	60.6	4	11.4	3.2	26.7	0.05	0.04	0.08
		POST-VACC II	35	35	100	90.0	100	35	100	90.0	100	6.07	4.89	7.52
ANTI-9V	Pn-Pn	PIII(M3)	68	68	100	94.7	100	68	100	94.7	100	4.08	3.33	5.01
		PRE-BOOSTER	67	67	100	94.6	100	64	95.5	87.5	99.1	1.04	0.78	1.39
		POST-BOOSTER	67	67	100	94.6	100	66	98.5	92.0	100	11.49	9.02	14.65
	Zil-Pn	PIII(M3)	35	11	31.4	16.9	49.3	4	11.4	3.2	26.7	0.04	0.03	0.06
		PRE-VACC	35	15	42.9	26.3	60.6	4	11.4	3.2	26.7	0.06	0.04	0.10
		POST-VACC II	35	35	100	90.0	100	35	100	90.0	100	2.70	2.05	3.55
ANTI-14	Pn-Pn	PIII(M3)	68	68	100	94.7	100	67	98.5	92.1	100	6.31	4.70	8.47
		PRE-BOOSTER	68	68	100	94.7	100	66	97.1	89.8	99.6	1.13	0.87	1.46
		POST-BOOSTER	67	67	100	94.6	100	67	100	94.6	100	14.14	11.74	17.04
	Zil-Pn	PIII(M3)	35	30	85.7	69.7	95.2	10	28.6	14.6	46.3	0.12	0.08	0.18
		PRE-VACC	35	29	82.9	66.4	93.4	11	31.4	16.9	49.3	0.14	0.08	0.23
		POST-VACC II	35	35	100	90.0	100	35	100	90.0	100	10.59	8.70	12.89
ANTI-18C	Pn-Pn	PIII(M3)	68	68	100	94.7	100	68	100	94.7	100	21.62	16.83	27.77
		PRE-BOOSTER	68	68	100	94.7	100	67	98.5	92.1	100	1.62	1.30	2.04
		POST-BOOSTER	67	67	100	94.6	100	67	100	94.6	100	35.33	27.73	45.02

				≥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
	Zil-Pn	PIII(M3)	35	8	22.9	10.4	40.1	2	5.7	0.7	19.2	0.04	0.03	0.06
		PRE-VACC	35	9	25.7	12.5	43.3	4	11.4	3.2	26.7	0.05	0.03	0.09
		POST-VACC II	35	35	100	90.0	100	35	100	90.0	100	25.61	19.70	33.30
ANTI-19F	Pn-Pn	PIII(M3)	68	68	100	94.7	100	67	98.5	92.1	100	9.83	7.35	13.16
		PRE-BOOSTER	67	67	100	94.6	100	59	88.1	77.8	94.7	1.20	0.85	1.71
		POST-BOOSTER	67	67	100	94.6	100	67	100	94.6	100	9.26	7.20	11.91
	Zil-Pn	PIII(M3)	34	24	70.6	52.5	84.9	11	32.4	17.4	50.5	0.10	0.06	0.17
		PRE-VACC	35	24	68.6	50.7	83.1	12	34.3	19.1	52.2	0.14	0.08	0.24
		POST-VACC II	35	35	100	90.0	100	34	97.1	85.1	99.9	7.16	4.27	12.02
ANTI-23F	Pn-Pn	PIII(M3)	68	68	100	94.7	100	66	97.1	89.8	99.6	2.17	1.65	2.85
		PRE-BOOSTER	68	62	91.2	81.8	96.7	48	70.6	58.3	81.0	0.46	0.32	0.68
		POST-BOOSTER	67	66	98.5	92.0	100	66	98.5	92.0	100	6.99	5.21	9.39
	Zil-Pn	PIII(M3)	35	6	17.1	6.6	33.6	1	2.9	0.1	14.9	0.03	0.03	0.04
		PRE-VACC	35	5	14.3	4.8	30.3	1	2.9	0.1	14.9	0.03	0.02	0.04
		POST-VACC II	35	33	94.3	80.8	99.3	31	88.6	73.3	96.8	1.06	0.66	1.70

Table 58 Seropositivity rates and GMCs for ANTI-6A and ANTI-19A antibodies (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
ANTI-6A	Pn-Pn	PIII(M3)	68	58	85.3	74.6	92.7	26	38.2	26.7	50.8	0.14	0.10	0.19
		PRE-BOOSTER	68	54	79.4	67.9	88.3	33	48.5	36.2	61.0	0.19	0.13	0.27
		POST-BOOSTER	67	65	97.0	89.6	99.6	54	80.6	69.1	89.2	0.81	0.56	1.18
	Zil-Pn	PIII(M3)	31	10	32.3	16.7	51.4	0	0.0	0.0	11.2	0.04	0.03	0.04
		PRE-VACC	35	11	31.4	16.9	49.3	6	17.1	6.6	33.6	0.05	0.03	0.07
		POST-VACC II	35	29	82.9	66.4	93.4	18	51.4	34.0	68.6	0.24	0.15	0.40
ANTI-19A	Pn-Pn	PIII(M3)	68	59	86.8	76.4	93.8	41	60.3	47.7	72.0	0.23	0.17	0.31
		PRE-BOOSTER	68	60	88.2	78.1	94.8	33	48.5	36.2	61.0	0.24	0.17	0.36
		POST-BOOSTER	67	65	97.0	89.6	99.6	57	85.1	74.3	92.6	1.33	0.88	2.00
	Zil-Pn	PIII(M3)	31	12	38.7	21.8	57.8	4	12.9	3.6	29.8	0.05	0.03	0.08
		PRE-VACC	35	17	48.6	31.4	66.0	9	25.7	12.5	43.3	0.09	0.05	0.17
		POST-VACC II	35	35	100	90.0	100	31	88.6	73.3	96.8	1.94	1.13	3.33

One month after booster vaccination:

- For each of the vaccine pneumococcal serotypes, all subjects in the Pn-Pn group had antibody concentrations ≥0.2 µg/mL except for serotypes 6B, 9V and 23F (98.5% of subjects had antibody concentrations ≥0.2 µg/mL for these three serotypes) (Table 57).
- For cross-reactive serotypes, the observed percentage of subjects with antibody concentrations ≥0.2 µg/mL was 80.6% for 6A and 85.1% for 19A.
- All subjects had measurable anti-protein D antibody concentrations (≥100 EL.U/mL).
- Robust increases in antibody GMCs were observed from pre- to post-booster for all vaccine pneumococcal serotypes.

One month after the completion of the 2-dose catch-up vaccination:

- For each of the vaccine pneumococcal serotypes, all subjects in the Zil-Pn group had antibody concentrations ≥0.2 µg/mL except for serotypes 6B (82.9% of subjects), 19F (97.1% of subjects) and 23F (88.6% of subjects) (Table 57).
- For cross-reactive serotypes the observed percentage of subjects with antibody concentrations ≥0.2 µg/mL was 51.4% for 6A and 88.6% for 19A.

- 94.3% of the subjects had measurable anti-protein D antibody concentrations (≥100 EL.U/mL).
- Robust increases in antibody GMCs were observed from pre- vaccination to post 2-dose catch-up vaccination for all vaccine pneumococcal serotypes.

The OPA results, one month after completion of the primary vaccination course, and one month after the booster dose (Pn-Pn group) or one month after dose II (Zil-Pn group) are detailed in Tables 61 and 62.

One month after the booster vaccination

- For each of the vaccine pneumococcal serotypes at least 94.0% of subjects in the Pn-Pn group had opsonophagocytic titres ≥8 (Table 61).
- For cross-reactive serotypes 6A and 19A, the observed percentage of subjects with opsonophagocytic titres ≥8 was 82.0% and 77.3%, respectively.

One month after the completion of the 2-dose catch-up vaccination

- For each of the vaccine pneumococcal serotypes at least 91.4% of subjects in the Zil-Pn group had opsonophagocytic titres ≥8 except for serotypes 6B (77.4% of subjects) and 19F (85.3% of subjects) (Table 61).
- For cross-reactive serotypes 6A and 19A, the observed percentage of subjects with opsonophagocytic titres ≥8 was 82.4% and 85.7%, respectively.

Table 61 Seropositivity rates and GMTs for OPSONO-1, OPSONO-4, OPSONO-5, OPSONO-6B, OPSONO-7F, OPSONO-9V, OPSONO-14, OPSONO-18C, OPSONO-19F and OPSONO-23F titres (ATP cohort for immunogenicity)

				≥8				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
OPSONO-1	Pn-Pn	PIII(M3)	31	29	93.5	78.6	99.2	130.2	77.9	217.6
		POST-BOOSTER	66	65	98.5	91.8	100	1667.8	1210.9	2297.0
	Zil-Pn	PIII(M3)	17	1	5.9	0.1	28.7	4.7	3.4	6.5
		POST-VACC II	35	33	94.3	80.8	99.3	103.4	67.7	157.9
OPSONO-4	Pn-Pn	PIII(M3)	31	31	100	88.8	100	964.0	764.8	1215.0
		POST-BOOSTER	65	65	100	94.5	100	3869.1	3122.8	4793.9
	Zil-Pn	PIII(M3)	16	1	6.3	0.2	30.2	5.3	2.9	9.9
		POST-VACC II	35	35	100	90.0	100	1482.9	1211.0	1815.8
OPSONO-5	Pn-Pn	PIII(M3)	31	30	96.8	83.3	99.9	100.6	64.6	156.5
		POST-BOOSTER	67	67	100	94.6	100	679.9	515.9	895.9
	Zil-Pn	PIII(M3)	16	0	0.0	0.0	20.6	4.0	4.0	4.0
		POST-VACC II	35	32	91.4	76.9	98.2	58.7	38.6	89.4
OPSONO-6B	Pn-Pn	PIII(M3)	31	29	93.5	78.6	99.2	895.2	483.0	1659.2
		POST-BOOSTER	66	64	97.0	89.5	99.6	1687.6	1138.7	2501.0
	Zil-Pn	PIII(M3)	17	2	11.8	1.5	36.4	7.9	2.9	20.9
		POST-VACC II	31	24	77.4	58.9	90.4	325.7	118.1	898.6
OPSONO-7F	Pn-Pn	PIII(M3)	31	31	100	88.8	100	2081.0	1434.8	3018.3
		POST-BOOSTER	67	67	100	94.6	100	11045.3	8456.8	14426.3
	Zil-Pn	PIII(M3)	14	9	64.3	35.1	87.2	78.0	19.2	316.2
		POST-VACC II	35	35	100	90.0	100	7980.2	6287.8	10128.1
OPSONO-9V	Pn-Pn	PIII(M3)	31	31	100	88.8	100	930.4	626.5	1381.8
		POST-BOOSTER	66	66	100	94.6	100	5300.1	4329.3	6488.5
	Zil-Pn	PIII(M3)	15	3	20.0	4.3	48.1	8.7	3.5	21.7
		POST-VACC II	35	35	100	90.0	100	6375.3	4779.4	8504.1
OPSONO-14	Pn-Pn	PIII(M3)	31	31	100	88.8	100	1296.3	818.8	2052.1
		POST-BOOSTER	66	66	100	94.6	100	2472.0	1767.3	3457.8
	Zil-Pn	PIII(M3)	15	2	13.3	1.7	40.5	8.3	2.8	24.4
		POST-VACC II	35	35	100	90.0	100	1797.8	1241.4	2603.6
OPSONO-18C	Pn-Pn	PIII(M3)	31	30	96.8	83.3	99.9	783.7	505.1	1215.9
		POST-BOOSTER	67	63	94.0	85.4	98.3	2323.0	1403.1	3846.1
	Zil-Pn	PIII(M3)	17	1	5.9	0.1	28.7	5.5	2.8	10.5
		POST-VACC II	35	35	100	90.0	100	4104.2	2954.5	5701.2
OPSONO-19F	Pn-Pn	PIII(M3)	31	29	93.5	78.6	99.2	375.3	205.7	684.6
		POST-BOOSTER	65	62	95.4	87.1	99.0	683.5	440.0	1062.0
	Zil-Pn	PIII(M3)	17	1	5.9	0.1	28.7	4.9	3.2	7.8
		POST-VACC II	34	29	85.3	68.9	95.0	443.5	203.0	968.8
OPSONO-23F	Pn-Pn	PIII(M3)	30	28	93.3	77.9	99.2	1024.3	512.9	2045.4
		POST-BOOSTER	67	66	98.5	92.0	100	5144.5	3657.4	7236.3
	Zil-Pn	PIII(M3)	14	3	21.4	4.7	50.8	18.1	3.2	103.2
		POST-VACC II	35	32	91.4	76.9	98.2	3081.7	1389.3	6836.1

Table 62 Seropositivity rates and GMTs for OPSONO-6A and OPSONO-19A titres (ATP cohort for immunogenicity)

				≥8				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
OPSONO-6A	Pn-Pn	PIII(M3)	31	8	25.8	11.9	44.6	9.6	5.3	17.3
		POST-BOOSTER	61	50	82.0	70.0	90.6	213.0	121.7	372.9
	Zil-Pn	PIII(M3)	16	3	18.8	4.0	45.6	9.1	3.5	24.0
		POST-VACC II	34	28	82.4	65.5	93.2	313.9	147.6	667.4
OPSONO-19A	Pn-Pn	PIII(M3)	31	14	45.2	27.3	64.0	13.0	7.6	22.2
		POST-BOOSTER	66	51	77.3	65.3	86.7	112.7	66.7	190.5
	Zil-Pn	PIII(M3)	17	0	0.0	0.0	19.5	4.0	4.0	4.0
		POST-VACC II	35	30	85.7	69.7	95.2	341.2	159.0	732.1

Assessor's comment: The responses in the 2-dose catch-up group were in some cases lower than the post-dose 3 responses in the primed group (e.g. ELISA results for serotypes 5 and 6B). The study was not designed or powered for formal comparisons between the groups, and larger studies with that objective were assessed during the approval procedure for Synflorix. The responses to a single booster dose were generally higher compared to the 2-dose catch-up groups, not unexpectedly. Considering the high response rate in terms of percentage of subjects achieving ≥0.2 µg/mL, and the similarity of these rates to those reported in previous studies, the immunogenicity results of this study do not raise further concern that would result in SPC changes.

- Safety results (summary)

Solicited local adverse events:

- In the Pn-Pn group, pain was the most frequently reported solicited local adverse event during the 4-day post-booster vaccination period reported in 36.8% of subjects who received the 10Pn-PD-DiT vaccine. Swelling at the 10Pn-PD-DiT administration site was the only grade 3 solicited local adverse event reported (2.9% of subjects).
- A large swelling reaction was reported for one subject in the Pn-Pn group at the 10-Pn-PD-DiT injection site on Day 1 following booster vaccination. The swelling was at maximum 60 mm diameter, not involving an adjacent joint, and resolved without sequelae within 2 days after onset.
- In the Zil-Pn group, pain was the most frequently reported solicited local adverse event during the 4-day post-vaccination period (30.6% following dose 1 and 13.9% following dose 2 at the 10Pn-PD-DiT administration site). Grade 3 swelling and redness were reported for one subject after dose 1 of the 10Pn-PD-DiT vaccine.

Solicited general adverse events:

- In the Pn-Pn group, fever was the most frequently reported solicited general adverse event during the 4-day post-booster vaccination period (11.8% of subjects). There were no reports of grade 3 solicited general adverse events.
- In the Zil-Pn group, fever was the most frequently reported solicited general adverse event during the 4-day post-vaccination period (4.2% of doses; 8.3% of subjects). For one subject, grade 3 fever (axillary temperature > 39.5 °C) was reported following the first dose of 10Pn-PD-DiT co-administered with DTPa and this was considered by the investigator to be causally related to vaccination.

Unsolicited adverse events:

- In the Pn-Pn group, at least one unsolicited adverse event within the 31-day post-vaccination period, classified by MedDRA Primary System Organ Class and Preferred Term was reported for 45.6% of subjects. A grade 3 unsolicited adverse event (drowning) that also was a serious adverse event, was reported for one subject. None of the reported adverse events were assessed by the investigator to be causally related to vaccination.
- In the Zil-Pn group, for 31.9% of doses (50.0% of subjects), at least one unsolicited adverse event within the 31-day post-vaccination period, classified by MedDRA Primary System Organ Class and Preferred Term was reported. None of them were grade 3 or were assessed by the investigator to be causally related to vaccination.

Serious adverse events:

- In the Pn-Pn group, one fatal event (drowning) was reported for one out of 68 subjects during the entire study period. This event was considered by the investigator as not causally related to vaccination. No non-fatal SAEs were reported in this group.
- No SAE was reported for subjects in the Zil-Pn group.

Withdrawals due to serious adverse events:

- One subject in the Pn-Pn group died due to drowning during the study period.

Assessor's comment: The frequency of adverse events, solicited and unsolicited, do not cause further safety concern compared to previously reported safety results.

3. Discussion on clinical aspects

The current study, which was a booster and catch-up study in Nigerian children 15-21 months of age, does not cause further concern regarding immunogenicity or safety results. Thus, the procedure is considered fulfilled and no further regulatory action is required.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➢ **Overall conclusion**

The procedure is considered fulfilled and no further regulatory action is required.

➢ **Recommendation**

☒ **Fulfilled –**

No further action required

☐ **Not fulfilled:**

IV. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable