20 February 2015
EMA/97288/2015 rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Synflorix

(Pneumococcal polysaccharide conjugate vaccine, adsorbed)

Procedure No. EMEA/H/C/000973

P46 048

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 August 3, 2012 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

The pharmaceutical formulation used in the study is the same as the commercially available.

II.2 Clinical aspects

1. Introduction

The MAH submitted a final report for:

- 10PN-PD-DIT-58: Immunogenicity, safety and reactogenicity of GlaxoSmithKline Biologicals' pneumococcal vaccine 1024850A following primary and booster vaccination of healthy Japanese children.

Only the result for the booster vaccination were submitted in this procedure. The results of the primary vaccination were reported and assessed in procedure EMEA/H/C/973 P 46 012, which was finalised in January 2012.

2. Clinical study

10PN-PD-DIT-58: Immunogenicity, safety and reactogenicity of GlaxoSmithKline Biologicals' pneumococcal vaccine 1024850A following primary and booster vaccination of healthy Japanese children

➢ **Description**

A phase III, randomized, open, controlled study in healthy Japanese children to assess the immunogenicity, safety and reactogenicity of GlaxoSmithKline Biologicals' 10-valent pneumococcal conjugate vaccine when co-administered with DTPa vaccine as a 3-dose primary immunization course at 3, 4 and 5 months of age and followed by a booster vaccination at 17-19 months of age

➢ **Methods**

- Objective(s)

The objectives relevant to this report are highlighted in bold font below.

Primary:

- To compare the immunogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine in healthy Japanese children, one month post-dose III, to the immune responses of the 10-valent pneumococcal conjugate vaccine as observed in the pivotal non-inferiority study 10PN-PD-DIT-001 in Europe*.

Secondary:

- To compare the immunogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine in healthy Japanese children, one month post-dose III, to the historical immunogenicity data *.

- To compare the immunogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine in healthy Japanese children, one month post-dose III, to the immune responses of the 10-valent pneumococcal conjugate.
- To evaluate, one month post-primary* and post-booster vaccination course, the immunogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine when co-administered with DTPa vaccine.
- To evaluate, one month post-primary* and post-booster vaccination course, the immunogenicity of DTPa vaccine when co-administered with GSK Biologicals' 10-valent pneumococcal conjugate vaccine.
- To assess the antibody persistence 12-14 months following the completion of the three-dose primary vaccination course with GSK Biologicals' 10-valent pneumococcal conjugate vaccine when co-administered with DTPa vaccine.
- To assess the antibody persistence 12-14 months following the completion of the three-dose primary vaccination course with DTPa vaccine when co-administered with GSK Biologicals' 10- valent pneumococcal conjugate vaccine.
- To assess the safety and reactogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine when co-administered with DTPa vaccine.

*The objectives related to the primary epoch were presented in the final clinical study report of the primary epoch.

- Study design
  - A multicentre, randomized, open-label, controlled study with two parallel groups.
  - Control: the control group (active comparator) was the group who received only the DTPa vaccine (commercially available in Japan as DPT "KAKETSUKEN" Syringe).
  - Vaccination schedule: 3-dose primary vaccination at 3, 4 and 5 months of age and booster vaccination at 17-19 months of age
  - Blood samples: One blood sample was collected from each subject at four different time points: prior to the first vaccine dose (Pre-Vacc), one month post-dose III (Post-Vacc 3), prior to booster vaccination (Pre-Booster) and one month post-booster dose (Post-Booster).
  - Type of study: Self-contained, except for the immunogenicity objectives for which the studies 10PN-PD-DIT-001, Undeca-Pn-010 (POET), and 10PN-PD-DIT-028 (COMPAS) were used as a reference.

- Study population /Sample size
  - Healthy subjects as established by medical history and clinical examination before entering into the study.
  - Born after a gestation period of 36 to 42 weeks inclusive.
  - Male or female subjects aged between and including 90 and 118 days at the time of the first vaccination.
  - Subjects for whom the investigator/co-investigator believed that their parent(s)/Legally Acceptable Representative(s) (LAR(s)) could and would comply with the requirements of the protocol.
  - Written informed consent was obtained from the parent(s)/LAR(s) of the subject.

  When comparing the local immunogenicity data with the immunogenicity data obtained from the 10PN-PD-DIT-001 study, 200 evaluable subjects would provide at least 98% or 85% power (under equal mean or in case of 1.2-fold decrease in GMC, respectively) to show non-inferiority (limit of 2-fold) of the 10Pn-PD-DiT vaccine in the current study compared to the 10Pn-PD-DiT vaccine in the 10PN-PD-DIT-001 study with respect to ELISA GMC ratios for the 10 vaccine pneumococcal serotypes.
  Considering that up to 17% of the subjects enrolled could be excluded from the ATP cohort for analysis of immunogenicity, 240 subjects were planned to be enrolled.

- Treatments
  The study groups received:
  - 10Pn group: 3 primary doses and one booster dose of 10Pn-PD-DiT co-administered with DTPa vaccine
  - DTPa group: 3 primary doses and one booster dose of DTPa vaccine

Vaccine administration

Vaccination	Visit	Dose	Vaccine	Route	Site	Side[3]
10Pn-PD-DiT[1]	1, 3	1, 3	10Pn-PD-DiT	Intramuscular	Thigh*	Left
	2, 5	2, 4	10Pn-PD-DiT	Intramuscular	Thigh*	Right
DTPa[1,2]	1, 3	1, 3	DTPa	Sub-cutaneous	Upper arm**	Right
	2, 5	2, 4	DTPa	Sub-cutaneous	Upper arm**	Left

[1] Applicable for 10Pn group
[2] Applicable for DTPa group
[3] Side (left/right) of vaccination could be changed by the Investigator/co-investigator upon best medical judgement.
* Thigh was defined as the anterolateral region of the thigh around the midpoint of the line connecting the anterior superior iliac spine with the patella, and slightly lateral to the line.
** Upper arm was defined as the distal one third of the extensor surface of the upper arm (between the acromial process and the olecranon).

Other vaccinations
Administration of a vaccine not foreseen by the study protocol during the period starting from 30 days before the first dose of study vaccine and ending on the last study visit, with the exception of Hib, HBV, BCG, OPV, Japanese encephalitis, MR, varicella, mumps and flu vaccines. The Hib, HBV, Japanese encephalitis and flu vaccines could be administered up to 7 days before or at least 7 days after each dose of study vaccine. Administration of Hib and HBV vaccines concomitantly with the study vaccines at Visit 1 (Month 0), Visit 2 (Month 1), Visit 3 (Month 2) and 5 (Month 14-16) was allowed. To comply with the Japanese immunization schedule, administration of BCG, OPV, MR, varicella and mumps vaccines was allowed according to local recommendations (up to 28 days before or at least 7 days after the administration of inactivated vaccines such as DTPa or 10Pn-PD-DiT vaccines).
Administration of any pneumococcal vaccine other than the 10Pn-PD-DiT vaccine during the entire study period except for the DTPa group for whom vaccination with a licensed pneumococcal vaccine by catch-up schedule will be allowed only if the 2 vaccine doses are administered between Visits 4 and 5, i.e. from the second blood sampling time point (Visit 4) onwards and up to 7 days before the booster dose of the DTPa vaccine.

- Outcomes/endpoints
  Primary outcome
  Immunogenicity:
    - Evaluation of immune responses to components of the investigational vaccine, one month after primary immunization.
        - Concentrations of antibodies against vaccine pneumococcal serotypes.

  Secondary Outcome/Efficacy Variables:
  This report presents data related to the booster epoch. Results related to the primary epoch were presented in the final clinical study report of the primary epoch.

  Immunogenicity:
- Evaluation of immune responses to components of the study vaccines for additional parameters one month after primary immunization and prior to and one month after booster immunization.
    - Concentrations of antibodies against vaccine pneumococcal serotypes.
    - Opsonophagocytic activity (OPA) against vaccine pneumococcal serotypes.
    - Concentrations of antibodies against cross-reactive pneumococcal serotypes 6A and 19A.
    - OPA against cross-reactive pneumococcal serotypes 6A and 19A.
    - Concentrations of antibodies against protein D (PD).
    - Antibody concentrations against diphtheria toxoid (DT), tetanus toxoid (TT), pertussis toxoid (PT) and filamentous haemagglutinin (FHA).

  Safety /reactogenicity:
- Solicited local and general adverse events (AEs)

- Occurrence of each solicited local AE (any, grade 3) within 8 days (Day 0 - Day 7) after each vaccine dose.
- Occurrence of each solicited general AE (any, grade 3, related to vaccination) within 8 days (Day 0 - Day 7) after each vaccine dose.

- Unsolicited adverse events
  - Occurrence of unsolicited AE within 31 days (Day 0 - Day 30) after each vaccination.
- Serious adverse events (SAEs)
  - Occurrence of SAEs from dose 1 up to study end.

- Statistical Methods

Demography:

The analysis of demographics was performed for the booster epoch.

- Distribution of vaccinated subjects among the study centres, withdrawal status and deviations from protocol/adapted intervals were tabulated.
- Demographic characteristics (age, gender, geographic ancestry) of each study cohort were tabulated.
- Summary of study continuation for subjects enrolled in the primary epoch of the study and those who participated in the present booster epoch of the study was tabulated.

Immunogenicity (including post-primary persistence)

Since Haemophilus influenzae type b and hepatitis B virus vaccines were allowed during the study under specific conditions, analyses of anti-polyribosyl-ribitol phosphate (PRP) and anti-hepatitis B surface antigen (HBs) immune responses were performed.

Descriptive analysis:

For each treatment group, at each time point that a blood sample result was available:

- Geometric mean concentrations (GMCs)/Geometric mean titres (GMTs) with 95% confidence intervals (CIs) were tabulated for each serotype/antigen.
- Seropositivity/seroprotection rates with exact 95% CIs were calculated for each appropriate serotype/antigen.
- Percentage of subjects with antibody concentrations ≥ 0.20 µg/mL was calculated for pneumococcal serotypes (1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F).
- The distribution of antibody concentrations/titres for each serotype/antigen was displayed using tables and/or reverse cumulative distribution curves.

Safety

Analysis of safety relative to the booster epoch covered analysis of safety endpoints collected following the booster dose and SAEs from dose 1 up to study end.

Descriptive analysis:

- The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the 31-day (Day 0 – Day 30) postvaccination follow-up period was tabulated with exact 95% CI. The same calculations were performed for AEs rated as grade 3 and general AEs with causal relationship to vaccination.
- The percentage of subjects reporting each individual solicited local and general AE during the 8- day (Day 0 - Day 7) solicited post-vaccination follow-up period was tabulated with exact 95% CI. In addition, the same tabulations were performed during the 4-day (Day 0 - Day 3) solicited postvaccination follow-up period.
- The same tabulation was performed for grade 3 solicited AEs and for solicited AEs with causal relationship to vaccination. For redness and swelling, grade 2 or 3 AEs were also tabulated.
- Occurrence of fever was reported per 0.5°C cumulative increments as well as the occurrence of axillary temperature > 39.5°C and the occurrence of axillary temperature > 39.5°C with causal relationship to vaccination.
- The proportion of subjects with at least one report of unsolicited AE classified by the Medical Dictionary for Regulatory Activities (MedDRA) and reported up to 30 days after booster vaccination was tabulated with exact 95% CI. The same tabulation was performed for grade 3 unsolicited AEs and for unsolicited AEs with a relationship to vaccination.
- The proportion of AEs resulting in a medically attended visit was also tabulated.
- The number and percentage of subjects who took concomitant antipyretic/medication at least once during the 8-day (Day 0 - Day 7) solicited post-vaccination follow-up

period was tabulated for each group with exact 95% CI. In addition, the same tabulation was performed during the 4-day (Day 0 - Day 3) solicited post-vaccination follow-up period.

- Serious adverse events (SAEs), large swelling reactions and withdrawals due to adverse event(s) were tabulated.

➢ **Results**

- Recruitment/ Number analysed

Out of the 360 subjects enrolled in the primary epoch of the study, a total of 349 participated in the booster epoch of the study (229 subjects in the 10Pn group and 120 subjects in the DTPa group).

Study population (Total vaccinated cohort for booster epoch)		
Number of subjects	**10Pn**	**DTPa**
Planned, N	240	120
Randomised*, N (Total Vaccinated Cohort for booster epoch)	228	120
Completed, n (%)	226 (99.1)	120 (100)
Demographics	**10Pn**	**DTPa**
N (Total Vaccinated Cohort for booster epoch)	228	120
Females: Males	110:118	57:63
Mean Age at booster dose, months (Standard deviation)	17.9 (0.78)	17.9 (0.66)
Asian - Japanese heritage, n (%)	228 (100)	119 (99.2)
*Subjects were randomised at the time of the primary epoch. 10Pn = Primed and boosted with 10Pn-PD-DiT + DTPa vaccines DTPa = Primed and boosted with DTPa vaccine n/% = number / percentage of subjects		

- Immunogenicity results

<u>Immune response to vaccine pneumococcal serotypes (ELISA)</u>

The results for the ELISA immune responses to vaccine pneumococcal serotypes, one month after completion of a 3-dose primary vaccination course, prior to and one month after the booster dose are detailed in table 20.

Table 20 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 of immunogenicity for booster epoch)

				≥ 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	10Pn	PIII(M3)	216	216	100	98.3	100	216	100	98.3	100	6.63	5.92	7.44
		PRE-BOOSTER	216	216	100	98.3	100	197	91.2	86.6	94.6	0.80	0.69	0.92
		POST-BOOSTER	214	214	100	98.3	100	214	100	98.3	100	7.81	6.91	8.82
	DTPa_Pr	PIII(M3)	111	33	29.7	21.4	39.1	2	1.8	0.2	6.4	0.04	0.03	0.04
		PRE-BOOSTER	113	37	32.7	24.2	42.2	4	3.5	1.0	8.8	0.04	0.03	0.04
		POST-BOOSTER	114	51	44.7	35.4	54.3	5	4.4	1.4	9.9	0.04	0.04	0.05
	DTPa_w_Pr	PIII(M3)	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	0.03	-	-
		PRE-BOOSTER	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	0.03	-	-
		POST-BOOSTER	1	1	100	2.5	100	1	100	2.5	100	0.24	-	-
ANTI-4	10Pn	PIII(M3)	216	216	100	98.3	100	216	100	98.3	100	6.61	5.88	7.41
		PRE-BOOSTER	215	213	99.1	96.7	99.9	192	89.3	84.4	93.1	0.81	0.70	0.93
		POST-BOOSTER	213	213	100	98.3	100	213	100	98.3	100	12.89	11.41	14.56
	DTPa_Pr	PIII(M3)	112	11	9.8	5.0	16.9	0	0.0	0.0	3.2	0.03	0.03	0.03
		PRE-BOOSTER	114	114	100	96.8	100	106	93.0	86.6	96.9	0.85	0.71	1.02
		POST-BOOSTER	114	114	100	96.8	100	106	93.0	86.6	96.9	0.78	0.64	0.94
	DTPa_w_Pr	PIII(M3)	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	0.03	-	-
		PRE-BOOSTER	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	0.03	-	-
		POST-BOOSTER	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	0.03	-	-
ANTI-5	10Pn	PIII(M3)	216	216	100	98.3	100	216	100	98.3	100	6.64	6.00	7.35
		PRE-BOOSTER	216	216	100	98.3	100	206	95.4	91.7	97.8	1.22	1.05	1.41
		POST-BOOSTER	214	214	100	98.3	100	214	100	98.3	100	8.81	7.87	9.86
	DTPa_Pr	PIII(M3)	111	52	46.8	37.3	56.6	4	3.6	1.0	9.0	0.05	0.04	0.06
		PRE-BOOSTER	114	82	71.9	62.7	79.9	23	20.2	13.2	28.7	0.08	0.07	0.10
		POST-BOOSTER	114	103	90.4	83.4	95.1	40	35.1	26.4	44.6	0.15	0.12	0.17
	DTPa_w_Pr	PIII(M3)	1	1	100	2.5	100	0	0.0	0.0	97.5	0.07	-	-
		PRE-BOOSTER	1	1	100	2.5	100	0	0.0	0.0	97.5	0.05	-	-
		POST-BOOSTER	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	0.03	-	-
ANTI-6B	10Pn	PIII(M3)	216	207	95.8	92.2	98.1	200	92.6	88.2	95.7	1.77	1.47	2.13
		PRE-BOOSTER	215	209	97.2	94.0	99.0	194	90.2	85.5	93.9	0.93	0.79	1.10
		POST-BOOSTER	214	210	98.1	95.3	99.5	209	97.7	94.6	99.2	3.66	3.14	4.27
	DTPa_Pr	PIII(M3)	113	22	19.5	12.6	28.0	2	1.8	0.2	6.2	0.03	0.03	0.03
		PRE-BOOSTER	114	106	93.0	86.6	96.9	72	63.2	53.6	72.0	0.34	0.27	0.44
		POST-BOOSTER	114	105	92.1	85.5	96.3	72	63.2	53.6	72.0	0.33	0.25	0.42
	DTPa_w_Pr	PIII(M3)	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	0.03	-	-
		PRE-BOOSTER	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	0.03	-	-
		POST-BOOSTER	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	0.03	-	-

				≥ 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-7F	10Pn	PIII(M3)	216	216	100	98.3	100	216	100	98.3	100	6.16	5.51	6.88
		PRE-BOOSTER	215	215	100	98.3	100	214	99.5	97.4	100	1.48	1.32	1.65
		POST-BOOSTER	214	214	100	98.3	100	214	100	98.3	100	10.68	9.66	11.81
	DTPa_Pr	PIII(M3)	112	24	21.4	14.2	30.2	1	0.9	0.0	4.9	0.03	0.03	0.04
		PRE-BOOSTER	114	49	43.0	33.7	52.6	9	7.9	3.7	14.5	0.05	0.04	0.05
		POST-BOOSTER	114	85	74.6	65.6	82.3	28	24.6	17.0	33.5	0.09	0.08	0.11
	DTPa_w_Pr	PIII(M3)	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	0.03	-	-
		PRE-BOOSTER	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	0.03	-	-
		POST-BOOSTER	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	0.03	-	-
ANTI-9V	10Pn	PIII(M3)	216	215	99.5	97.4	100	215	99.5	97.4	100	5.44	4.80	6.16
		PRE-BOOSTER	212	212	100	98.3	100	209	98.6	95.9	99.7	1.81	1.61	2.03
		POST-BOOSTER	214	214	100	98.3	100	214	100	98.3	100	12.79	11.49	14.23
	DTPa_Pr	PIII(M3)	111	15	13.5	7.8	21.3	0	0.0	0.0	3.3	0.03	0.03	0.03
		PRE-BOOSTER	114	114	100	96.8	100	104	91.2	84.5	95.7	1.01	0.83	1.25
		POST-BOOSTER	114	114	100	96.8	100	106	93.0	86.6	96.9	0.96	0.79	1.17
	DTPa_w_Pr	PIII(M3)	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	0.03	-	-
		PRE-BOOSTER	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	0.03	-	-
		POST-BOOSTER	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	0.03	-	-
ANTI-14	10Pn	PIII(M3)	216	216	100	98.3	100	216	100	98.3	100	10.31	8.99	11.83
		PRE-BOOSTER	216	216	100	98.3	100	213	98.6	96.0	99.7	2.37	2.04	2.74
		POST-BOOSTER	214	214	100	98.3	100	214	100	98.3	100	15.72	13.97	17.69
	DTPa_Pr	PIII(M3)	112	71	63.4	53.8	72.3	21	18.8	12.0	27.2	0.07	0.06	0.08
		PRE-BOOSTER	114	114	100	96.8	100	114	100	96.8	100	3.17	2.74	3.67
		POST-BOOSTER	114	114	100	96.8	100	114	100	96.8	100	2.92	2.53	3.38
	DTPa_w_Pr	PIII(M3)	1	1	100	2.5	100	1	100	2.5	100	0.27	-	-
		PRE-BOOSTER	1	1	100	2.5	100	0	0.0	0.0	97.5	0.09	-	-
		POST-BOOSTER	1	1	100	2.5	100	0	0.0	0.0	97.5	0.16	-	-
ANTI-18C	10Pn	PIII(M3)	216	216	100	98.3	100	216	100	98.3	100	16.85	14.57	19.50
		PRE-BOOSTER	215	215	100	98.3	100	212	98.6	96.0	99.7	2.18	1.89	2.51
		POST-BOOSTER	213	213	100	98.3	100	213	100	98.3	100	34.90	31.05	39.23
	DTPa_Pr	PIII(M3)	113	35	31.0	22.6	40.4	4	3.5	1.0	8.8	0.04	0.03	0.04
		PRE-BOOSTER	114	112	98.2	93.8	99.8	112	98.2	93.8	99.8	0.94	0.79	1.11
		POST-BOOSTER	114	112	98.2	93.8	99.8	109	95.6	90.1	98.6	0.77	0.65	0.92
	DTPa_w_Pr	PIII(M3)	1	1	100	2.5	100	0	0.0	0.0	97.5	0.08	-	-
		PRE-BOOSTER	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	0.03	-	-
		POST-BOOSTER	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	0.03	-	-
ANTI-19F	10Pn	PIII(M3)	214	214	100	98.3	100	213	99.5	97.4	100	17.64	15.72	19.79
		PRE-BOOSTER	215	215	100	98.3	100	215	100	98.3	100	2.92	2.50	3.41
		POST-BOOSTER	214	214	100	98.3	100	214	100	98.3	100	28.72	25.29	32.63
	DTPa_Pr	PIII(M3)	110	55	50.0	40.3	59.7	14	12.7	7.1	20.4	0.06	0.05	0.07
		PRE-BOOSTER	114	111	97.4	92.5	99.5	83	72.8	63.7	80.7	0.51	0.38	0.68
		POST-BOOSTER	114	111	97.4	92.5	99.5	89	78.1	69.4	85.3	0.68	0.51	0.91
	DTPa_w_Pr	PIII(M3)	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	0.03	-	-
		PRE-BOOSTER	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	0.03	-	-
		POST-BOOSTER	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	0.03	-	-
ANTI-23F	10Pn	PIII(M3)	216	210	97.2	94.1	99.0	204	94.4	90.5	97.1	2.20	1.84	2.63
		PRE-BOOSTER	213	208	97.7	94.6	99.2	187	87.8	82.6	91.9	1.14	0.93	1.39
		POST-BOOSTER	214	213	99.5	97.4	100	212	99.1	96.7	99.9	7.68	6.68	8.83
	DTPa_Pr	PIII(M3)	111	29	26.1	18.2	35.3	4	3.6	1.0	9.0	0.04	0.03	0.04
		PRE-BOOSTER	114	106	93.0	86.6	96.9	87	76.3	67.4	83.8	0.55	0.42	0.73
		POST-BOOSTER	114	113	99.1	95.2	100	97	85.1	77.2	91.1	0.88	0.70	1.12

				≥ 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
	DTPa_w_Pr	PIII(M3)	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	0.03	-	-
		PRE-BOOSTER	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	0.03	-	-
		POST-BOOSTER	1	0	0.0	0.0	97.5	0	0.0	0.0	97.5	0.03	-	-

10Pn = Primed and boosted with 10Pn-PD-DiT + DTPa vaccines
DTPa_Pr = Primed and boosted with DTPa vaccine with at least one dose of Prevenar given before pre-booster blood sample
DTPa_w_Pr = Primed and boosted with DTPa vaccine with no Prevenar vaccination given before pre-booster blood sample
GMC = geometric mean antibody concentration
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) = one month after dose 3
PRE-BOOSTER = prior to booster dose
POST-BOOSTER = one month after booster dose

Immune response to vaccine pneumococcal serotypes (OPA)

The results for the OPA immune responses to vaccine pneumococcal serotypes, one month after completion of a 3-dose primary vaccination course, prior to and one month after the booster dose are detailed in table 24.

Table 24 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 (ATP cohort of immunogenicity for booster epoch)

				≥ 8				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
OPSONO-1	10Pn	PIII(M3)	210	208	99.0	96.6	99.9	615.0	503.6	751.1
		PRE-BOOSTER	214	139	65.0	58.2	71.3	45.9	34.9	60.4
		POST-BOOSTER	214	214	100	98.3	100	2320.7	1941.8	2773.6
	DTPa_Pr	PIII(M3)	107	9	8.4	3.9	15.4	4.9	4.2	5.7
		PRE-BOOSTER	113	4	3.5	1.0	8.8	4.5	4.0	5.1
		POST-BOOSTER	112	5	4.5	1.5	10.1	4.7	4.1	5.5
	DTPa_w_Pr	PIII(M3)	1	0	0.0	0.0	97.5	4.0	-	-
		PRE-BOOSTER	1	0	0.0	0.0	97.5	4.0	-	-
		POST-BOOSTER	1	0	0.0	0.0	97.5	4.0	-	-
OPSONO-4	10Pn	PIII(M3)	208	207	99.5	97.4	100	1194.3	1046.9	1362.5
		PRE-BOOSTER	205	149	72.7	66.0	78.7	58.3	43.6	77.9
		POST-BOOSTER	214	214	100	98.3	100	3863.1	3319.7	4495.5
	DTPa_Pr	PIII(M3)	107	2	1.9	0.2	6.6	4.1	3.9	4.3
		PRE-BOOSTER	105	74	70.5	60.8	79.0	79.0	49.3	126.7
		POST-BOOSTER	109	75	68.8	59.2	77.3	69.3	43.1	111.5
	DTPa_w_Pr	PIII(M3)	1	0	0.0	0.0	97.5	4.0	-	-
		PRE-BOOSTER	1	1	100	2.5	100	371.0	-	-
		POST-BOOSTER	1	1	100	2.5	100	493.0	-	-
OPSONO-5	10Pn	PIII(M3)	211	210	99.5	97.4	100	345.8	293.6	407.3
		PRE-BOOSTER	212	155	73.1	66.6	79.0	22.9	19.1	27.6
		POST-BOOSTER	214	214	100	98.3	100	686.7	583.8	807.9
	DTPa_Pr	PIII(M3)	107	3	2.8	0.6	8.0	4.3	4.0	4.6
		PRE-BOOSTER	113	2	1.8	0.2	6.2	4.2	3.9	4.5
		POST-BOOSTER	112	6	5.4	2.0	11.3	4.7	4.1	5.3
	DTPa_w_Pr	PIII(M3)	1	0	0.0	0.0	97.5	4.0	-	-
		PRE-BOOSTER	1	0	0.0	0.0	97.5	4.0	-	-
		POST-BOOSTER	1	0	0.0	0.0	97.5	4.0	-	-
OPSONO-6B	10Pn	PIII(M3)	209	201	96.2	92.6	98.3	1996.1	1614.5	2468.0
		PRE-BOOSTER	212	185	87.3	82.0	91.4	191.2	141.9	257.5
		POST-BOOSTER	214	210	98.1	95.3	99.5	1682.9	1379.1	2053.7
	DTPa_Pr	PIII(M3)	108	7	6.5	2.6	12.9	5.1	4.2	6.1
		PRE-BOOSTER	110	69	62.7	53.0	71.8	118.5	66.3	211.7
		POST-BOOSTER	110	74	67.3	57.7	75.9	119.0	68.5	206.9
	DTPa_w_Pr	PIII(M3)	1	0	0.0	0.0	97.5	4.0	-	-
		PRE-BOOSTER	1	0	0.0	0.0	97.5	4.0	-	-
		POST-BOOSTER	1	0	0.0	0.0	97.5	4.0	-	-
OPSONO-7F	10Pn	PIII(M3)	203	203	100	98.2	100	7735.0	6663.4	8978.8
		PRE-BOOSTER	209	209	100	98.3	100	2244.8	1921.9	2621.9
		POST-BOOSTER	214	214	100	98.3	100	14144.3	12109.3	16521.4
	DTPa_Pr	PIII(M3)	103	60	58.3	48.1	67.9	67.4	41.2	110.4
		PRE-BOOSTER	111	107	96.4	91.0	99.0	1014.7	743.8	1384.1
		POST-BOOSTER	112	108	96.4	91.1	99.0	1165.6	855.7	1587.8
	DTPa_w_Pr	PIII(M3)	1	0	0.0	0.0	97.5	4.0	-	-
		PRE-BOOSTER	1	1	100	2.5	100	588.0	-	-
		POST-BOOSTER	1	1	100	2.5	100	1278.0	-	-

				≥ 8				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
OPSONO-9V	10Pn	PIII(M3)	206	206	100	98.2	100	4054.0	3535.5	4648.6
		PRE-BOOSTER	213	211	99.1	96.6	99.9	520.0	437.3	618.5
		POST-BOOSTER	214	214	100	98.3	100	4693.7	4099.0	5374.6
	DTPa_Pr	PIII(M3)	101	7	6.9	2.8	13.8	4.9	4.2	5.8
		PRE-BOOSTER	113	111	98.2	93.8	99.8	1081.6	803.3	1456.4
		POST-BOOSTER	112	108	96.4	91.1	99.0	958.8	680.0	1351.8
	DTPa_w_Pr	PIII(M3)	1	0	0.0	0.0	97.5	4.0	-	-
		PRE-BOOSTER	1	1	100	2.5	100	4595.0	-	-
		POST-BOOSTER	1	1	100	2.5	100	367.0	-	-
OPSONO-14	10Pn	PIII(M3)	204	204	100	98.2	100	3488.7	3042.9	3999.7
		PRE-BOOSTER	211	209	99.1	96.6	99.9	673.1	573.1	790.6
		POST-BOOSTER	213	213	100	98.3	100	6209.0	5299.3	7274.8
	DTPa_Pr	PIII(M3)	96	13	13.5	7.4	22.0	6.7	5.1	8.9
		PRE-BOOSTER	111	111	100	96.7	100	826.7	669.3	1021.0
		POST-BOOSTER	112	111	99.1	95.1	100	819.1	651.4	1030.1
	DTPa_w_Pr	PIII(M3)	1	0	0.0	0.0	97.5	4.0	-	-
		PRE-BOOSTER	1	0	0.0	0.0	97.5	4.0	-	-
		POST-BOOSTER	1	0	0.0	0.0	97.5	4.0	-	-
OPSONO-18C	10Pn	PIII(M3)	204	197	96.6	93.1	98.6	960.4	788.5	1169.8
		PRE-BOOSTER	207	146	70.5	63.8	76.6	26.3	21.1	32.6
		POST-BOOSTER	214	214	100	98.3	100	2181.0	1900.1	2503.4
	DTPa_Pr	PIII(M3)	100	4	4.0	1.1	9.9	4.7	3.9	5.6
		PRE-BOOSTER	112	43	38.4	29.4	48.1	11.5	8.2	16.0
		POST-BOOSTER	109	47	43.1	33.7	53.0	12.7	9.1	17.7
	DTPa_w_Pr	PIII(M3)	1	0	0.0	0.0	97.5	4.0	-	-
		POST-BOOSTER	1	0	0.0	0.0	97.5	4.0	-	-
OPSONO-19F	10Pn	PIII(M3)	206	203	98.5	95.8	99.7	1337.1	1103.4	1620.2
		PRE-BOOSTER	204	178	87.3	81.9	91.5	83.4	64.7	107.6
		POST-BOOSTER	212	211	99.5	97.4	100	3496.3	2938.8	4159.6
	DTPa_Pr	PIII(M3)	107	3	2.8	0.6	8.0	4.4	3.9	4.9
		PRE-BOOSTER	110	48	43.6	34.2	53.4	21.1	13.5	32.9
		POST-BOOSTER	108	51	47.2	37.5	57.1	20.9	13.7	31.8
	DTPa_w_Pr	PIII(M3)	1	1	100	2.5	100	19.0	-	-
		PRE-BOOSTER	1	0	0.0	0.0	97.5	4.0	-	-
		POST-BOOSTER	1	1	100	2.5	100	191.0	-	-
OPSONO-23F	10Pn	PIII(M3)	205	197	96.1	92.5	98.3	4296.4	3353.0	5505.1
		PRE-BOOSTER	209	172	82.3	76.4	87.2	600.5	417.6	863.4
		POST-BOOSTER	214	212	99.1	96.7	99.9	7057.2	5896.6	8446.1
	DTPa_Pr	PIII(M3)	101	9	8.9	4.2	16.2	6.2	4.5	8.3
		PRE-BOOSTER	111	89	80.2	71.5	87.1	1048.0	561.5	1956.1
		POST-BOOSTER	111	94	84.7	76.6	90.8	1758.3	949.4	3256.5

				≥ 8				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
	DTPa_w_Pr	PIII(M3)	1	0	0.0	0.0	97.5	4.0	-	-
		PRE-BOOSTER	1	0	0.0	0.0	97.5	4.0	-	-
		POST-BOOSTER	1	0	0.0	0.0	97.5	4.0	-	-

10Pn = Primed and boosted with 10Pn-PD-DiT + DTPa vaccines
DTPa_Pr = Primed and boosted with DTPa vaccine with at least one dose of Prevenar given before pre-booster blood sample
DTPa_w_Pr = Primed and boosted with DTPa vaccine with no Prevenar vaccination given before pre-booster blood sample
GMT = geometric mean titre
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) = one month after dose 3
PRE-BOOSTER = prior to booster dose
POST-BOOSTER = one month after booster dose

Assessor's comment: The ELISA and OPA responses to the booster dose were generally higher (9 serotypes) or very similar to the post-primary responses. This is in agreement with previously reported results.

Immune response to cross-reactive serotypes 6A and 19A (ELISA and OPA)
Twelve to fourteen months following primary vaccination (prior to booster vaccination with 10Pn-PD-DiT in the 10Pn group):
The percentage of subjects with antibody concentrations ≥0.2 µg/mL was 78.9% for cross-reactive serotype 6A and 74.3% for cross-reactive serotype 19A.
The percentage of subjects with OPA titres ≥8 was 79.1% for cross-reactive serotype 6A and 33.8% for cross-reactive serotype 19A.

One month following booster vaccination with 10Pn-PD-DiT in the 10Pn group:
The percentage of subjects with antibody concentrations ≥0.2 µg/mL was 95.3% for cross-reactive serotype 6A and 95.8% for cross-reactive serotype 19A.
The percentage of subjects with OPA titres ≥8 was 92.9% for cross-reactive serotype 6A and 89.6% for cross-reactive serotype 19A.

Immune response to DTPa antigens
The results for the DTPa antigens, one month after completion of a 3-dose primary vaccination course, prior to and one month after the booster dose are detailed in tables 33 and 34.

- Safety results

The safety analysis was performed on the Total vaccinated cohort for booster epoch (primary analysis). Solicited local reactions are presented in Table 82 and solicited general reactions in Table 85.

Table 82 Incidence of solicited local symptoms reported during the 8-day (Days 0-7) post-vaccination period (Total vaccinated cohort for booster epoch)

			10Pn					DTPa				
						95 % CI					95 % CI	
Symptom	Product	Type	N	n	%	LL	UL	N	n	%	LL	UL
Pain	Total	All	228	134	58.8	52.1	65.2	120	47	39.2	30.4	48.5
		Grade 3	228	12	5.3	2.7	9.0	120	0	0.0	0.0	3.0
		Medical advice	228	8	3.5	1.5	6.8	120	1	0.8	0.0	4.6
	10Pn-PD-DiT	All	228	114	50.0	43.3	56.7	-	-	-	-	-
		Grade 3	228	12	5.3	2.7	9.0	-	-	-	-	-
		Medical advice	228	4	1.8	0.5	4.4	-	-	-	-	-
	DTPa	All	226	99	43.8	37.2	50.5	120	47	39.2	30.4	48.5
		Grade 3	226	1	0.4	0.0	2.4	120	0	0.0	0.0	3.0
		Medical advice	226	6	2.7	1.0	5.7	120	1	0.8	0.0	4.6
Redness (mm)	Total	All	228	197	86.4	81.3	90.6	120	102	85.0	77.3	90.9
		>20	228	99	43.4	36.9	50.1	120	30	25.0	17.5	33.7
		>30	228	72	31.6	25.6	38.0	120	20	16.7	10.5	24.6
		Medical advice	228	15	6.6	3.7	10.6	120	1	0.8	0.0	4.6
	10Pn-PD-DiT	All	228	178	78.1	72.1	83.3	-	-	-	-	-
		>20	228	64	28.1	22.3	34.4	-	-	-	-	-
		>30	228	52	22.8	17.5	28.8	-	-	-	-	-
		Medical advice	228	4	1.8	0.5	4.4	-	-	-	-	-
	DTPa	All	226	182	80.5	74.8	85.5	120	102	85.0	77.3	90.9
		>20	226	71	31.4	25.4	37.9	120	30	25.0	17.5	33.7
		>30	226	43	19.0	14.1	24.8	120	20	16.7	10.5	24.6
		Medical advice	226	12	5.3	2.8	9.1	120	1	0.8	0.0	4.6
Swelling (mm)	Total	All	228	180	78.9	73.1	84.1	120	90	75.0	66.3	82.5
		>20	228	92	40.4	33.9	47.0	120	29	24.2	16.8	32.8
		>30	228	65	28.5	22.7	34.8	120	18	15.0	9.1	22.7
		Medical advice	228	15	6.6	3.7	10.6	120	1	0.8	0.0	4.6
	10Pn-PD-DiT	All	228	154	67.5	61.0	73.6	-	-	-	-	-
		>20	228	57	25.0	19.5	31.1	-	-	-	-	-
		>30	228	41	18.0	13.2	23.6	-	-	-	-	-
		Medical advice	228	6	2.6	1.0	5.6	-	-	-	-	-
	DTPa	All	226	160	70.8	64.4	76.6	120	90	75.0	66.3	82.5
		>20	226	66	29.2	23.4	35.6	120	29	24.2	16.8	32.8
		>30	226	45	19.9	14.9	25.7	120	18	15.0	9.1	22.7
		Medical advice	226	11	4.9	2.5	8.5	120	1	0.8	0.0	4.6

10Pn = Primed and boosted with 10Pn-PD-DiT + DTPa vaccines

DTPa = Primed and boosted with DTPa vaccine

N= number of subjects with the documented dose

n/%= number/percentage of subjects reporting the symptom at least once

Total : n/%= number/percentage of subjects with at least one local symptom whatever the number of injections

95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Table 85 Incidence of solicited general symptoms reported during the 8-day (Days 0-7) post-vaccination period (Total vaccinated cohort for booster epoch)

		10Pn					DTPa				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Drowsiness	All	228	69	30.3	24.4	36.7	120	30	25.0	17.5	33.7
	Grade 3	228	3	1.3	0.3	3.8	120	3	2.5	0.5	7.1
	Related	228	19	8.3	5.1	12.7	120	7	5.8	2.4	11.6
	Grade 3 & Related	228	2	0.9	0.1	3.1	120	0	0.0	0.0	3.0
	Medical advice	228	7	3.1	1.2	6.2	120	0	0.0	0.0	3.0
Fever (Axillary) (°C)	All	228	90	39.5	33.1	46.1	120	24	20.0	13.3	28.3
	>38.0	228	42	18.4	13.6	24.1	120	13	10.8	5.9	17.8
	>38.5	228	24	10.5	6.9	15.3	120	7	5.8	2.4	11.6
	>39.0	228	13	5.7	3.1	9.6	120	4	3.3	0.9	8.3
	>39.5*	228	6	2.6	1.0	5.6	120	0	0.0	0.0	3.0
	Related	228	41	18.0	13.2	23.6	120	11	9.2	4.7	15.8
	>39.5* & Related	228	1	0.4	0.0	2.4	120	0	0.0	0.0	3.0
	Medical advice	228	29	12.7	8.7	17.8	120	6	5.0	1.9	10.6
Irritability	All	228	90	39.5	33.1	46.1	120	35	29.2	21.2	38.2
	Grade 3	228	8	3.5	1.5	6.8	120	2	1.7	0.2	5.9
	Related	228	36	15.8	11.3	21.2	120	10	8.3	4.1	14.8
	Grade 3 & Related	228	3	1.3	0.3	3.8	120	0	0.0	0.0	3.0
	Medical advice	228	8	3.5	1.5	6.8	120	1	0.8	0.0	4.6
Loss of appetite	All	228	48	21.1	15.9	26.9	120	17	14.2	8.5	21.7
	Grade 3	228	4	1.8	0.5	4.4	120	1	0.8	0.0	4.6
	Related	228	12	5.3	2.7	9.0	120	2	1.7	0.2	5.9
	Grade 3 & Related	228	1	0.4	0.0	2.4	120	0	0.0	0.0	3.0
	Medical advice	228	6	2.6	1.0	5.6	120	0	0.0	0.0	3.0

10Pn = Primed and boosted with 10Pn-PD-DiT + DTPa vaccines
DTPa = Primed and boosted with DTPa vaccine
N= number of subjects with the documented dose
n/%= number/percentage of subjects reporting the symptom at least once
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
*One subject from 10Pn group had temperature of 40.6°C (on Day 7) which was assessed by the investigator to be causally related to vaccination

Unsolicited symptoms: During the 31-day post-booster vaccination period, at least one unsolicited AE was reported for 57.9% and 55.0% of subjects in the 10Pn and DTPa groups, respectively. Unsolicited AEs considered by the investigator to be causally related to vaccination were reported for 17.5% and 7.5% of subjects in the 10Pn and DTPa groups, respectively, with injection site induration as the most frequently reported symptom in both groups. Grade 3 unsolicited AEs were reported for 2.2% and 1.7% of subjects in the 10Pn and DTPa groups, respectively. None of the grade 3 AEs was assessed by the investigator to be causally related to vaccination.

Serious adverse events:
During the booster vaccination phase of the study (from Visit 5 up to Visit 6, period of approximately 1 month), at least one SAE was reported for 5 subjects (4 subjects in the 10Pn group and 1 subject in

the DTPa group). None of them were fatal or assessed by the investigator to be causally related to vaccination. All SAEs were recovered/resolved without sequelae.
During the entire study period (from study start up to Visit 6, period of approximately 15 months), 75 SAEs were reported for 47 subjects (28 subjects in the 10Pn group and 19 subject in the DTPa group). One fatal SAE (i.e. sudden infant death syndrome) was reported for a subject in the 10Pn group, 9 days after dose 2 of primary vaccination. None of the SAEs were considered by the investigator to be causally related to vaccination.

Assessor's comment: As seen in previous studies the systemic reactions increased in frequency when Synflorix was given concomitantly with DTPa. No new safety signal was detected in this study.

3. Discussion on clinical aspects
The current submission contains the booster results of study 10PN-DIT-058. The results of the primary vaccination were assessed previously (EMEA/H/C/973 P 46 012). The presented immunogenicity data are generally in agreement with already presented data, and no additional concerns have been raised by these data. Likewise, the safety data are generally in line with previous data and no new safety signals are raised by this study.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The submitted study is not considered to change the overall benefit risk balance of Synflorix, and no further regulatory action is required.

- **Recommendation**

☒ **Fulfilled –**

No further action required

☐ **Not fulfilled:**

IV. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable