EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Synflorix

(Pneumococcal polysaccharide conjugate vaccine, adsorbed)

Procedure No. EMEA/H/C/000973

P46 041

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

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I. INTRODUCTION

On April 11, 2011, 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.

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-036 Primary vaccination course in children receiving the pneumococcal vaccine GSK 1024850A or Prevenar. co-administered with Hiberix.

2. Clinical study

10PN-PD-DIT-036 Primary vaccination course in children receiving the pneumococcal vaccine GSK 1024850A or Prevenar co-administered with Hiberix.

- **Description**

- **Methods**

  - Objectives
    Primary:
    To demonstrate that GSK Biologicals. 10-valent pneumococcal conjugate vaccine administered as a three-dose primary vaccination course in Korea is non-inferior to Prevenar for the immune response against at least 7 of the pneumococcal serotypes contained in the 10-valent pneumococcal conjugate vaccine.
    Criteria for non-inferiority:
    For each of the 7 Prevenar serotypes, non-inferiority will be demonstrated if the upper limit of the 2-sided 96.5% CI (adjusted 1-sided alpha = 0.0175) of the difference between groups (Prevenar minus 10Pn-PD-DiT), in terms of percentage of subjects with pneumococcal antibody concentrations ≥ 0.2 µg/mL, is lower than 10%.
    For each of the 3 non-Prevenar serotypes (i.e., 1, 5 and 7F), non-inferiority will be demonstrated if the upper limit of the 96.5% CI of the difference between the aggregate response for the 7 Prevenar serotypes and 10Pn-PD-DiT group, in terms of percentage of subjects with pneumococcal antibody concentrations ≥ 0.2 µg/mL, is lower than 10%.
    Secondary:
    To assess safety and reactogenicity of GSK Biologicals. 10-valent pneumococcal conjugate vaccine, coadministered with GSK Biologicals. Hiberix vaccine in Korea.

  - Study design
    Phase III, multi-centre, single-blind study with two parallel groups:
    10Pn-PD-DiT group ("10Pn" in results tables and figures): receiving 10Pn-PD-DiT coadministered with Hiberix
    Prevenar group ("Prev" in results tables and figures): receiving Prevenar co-administered with Hiberix

- Treatment allocation: (3:1)
- Vaccination schedules: 2, 4 and 6 months of age
- Three dose primary vaccination course starting at 6 to 12 weeks (42-90 days) of age, administered at least 1 week after national routine immunization with allowable intervals of 49-83 days between the study vaccination doses.
- Control: Prevenar
- One blood sample was collected one month post-dose III.

- Study population /Sample size

Diagnosis and criteria for inclusion:

- Subjects for whom the investigator believed that their parent(s)/guardian(s) could and would comply with the requirements of the protocol.
- Male or female between, and including, 6-12 weeks (42 to 90 days) of age at the time of the first vaccination.
- Written informed consent obtained from the parent(s) or guardian(s) of the subject.
- Free of obvious health problems as established by medical history and clinical examination before entering into the study.
- Born after a gestation period of 36 to 42 weeks inclusive, with a birth weight of at least 2.5 kg.

Number of subjects:	**Total**	**10Pn**	**Prev**
Planned:	500	375	125
Enrolled:	503	374	129
Completed:	489	364	125
Total vaccinated cohort for analysis of safety	503	374	129
ATP cohort for analysis of immunogenicity	467	344	123

- Treatments

Vaccine	**Schedule**
10Pn-PD-DiT *(Study vaccine)*	2, 4, 6 months of age
Prevenar *(Control vaccine)*	2, 4, 6 months of age
Hiberix *(Study co-administered vaccine)*	2, 4, 6 months of age

- Outcomes/endpoints
  Laboratory assays

Antigen	Assay method	Test Kit/ Manufacturer	Assay unit	Assay cut-off	Laboratory
10 pneumococcal vaccine serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F)	[redacted]	in-house	µg/mL	0.05	[redacted]
10 pneumococcal vaccine serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F)		in-house	dilution for 50% killing	8	
Pneumococcal cross-reactive serotypes 6A and 19A		in-house	µg/mL	0.05	
Pneumococcal cross-reactive serotypes 6A and 19A		in-house	dilution for 50% killing	8	
Protein D		in-house	EL.U/mL	100	
PRP		in-house	µg/mL	0.15	

[1]Or multiplex techniques

- Statistical Methods

Demography:
Demographic characteristics (age in weeks, gender, race) of each study cohort were tabulated per group.
Distribution of enrolled subjects among the study centres, withdrawal status and deviations from protocol/adapted intervals were tabulated as a whole and per group.

Immunogenicity:
Confirmatory inferential analysis:
For each of the 7 Prevenar serotypes, standardized asymptotic 96.5% CIs for the difference between groups (Prevenar minus 10Pn-PD-DiT), in percentage of subjects with pneumococcal antibody concentrations ≥ 0.20 µg/mL, one month post-dose III, were computed using StatXact 7.0.
For each of the 3 additional non-Prevenar serotypes, bootstrap 96.5% CIs for the difference between the aggregate response for the 7 Prevenar serotypes in the Prevenar group and the responses for serotypes 1, 5 and 7F in the 10Pn-PD-DiT group, in percentage of subjects with pneumococcal antibody concentrations ≥ 0.20 µg/mL, one month post-dose III, were computed.

The primary objective was reached if the upper limits of the 96.5% CIs for the difference between groups (Prevenar minus 10Pn-PD-DiT and aggregate response for the 7 Prevenar serotypes in the Prevenar group minus responses for serotypes 1, 5 and 7F in 10Pn-PD-DiT group) was below 10% for at least 7 serotypes.

Descriptive analysis:
Geometric mean concentrations/titres (GMCs/GMTs), seropositivity/seroprotection rates were calculated with their 95% CI for each group, each antigen/serotype, one month post-dose III.
Distribution of antibody concentrations/titres was displayed using tables and/or reverse cumulative curves for each group, each antigen/serotype, one month post-dose III.

Safety /reactogenicity:
Descriptive analysis:
Incidence of solicited and/or unsolicited local and general adverse events during the 31-day postvaccination follow-up period was calculated with 95% CI, after each vaccine dose and overall, according to the type of symptom, the intensity and relationship to vaccination.
Incidence of each local and each general solicited symptom reported during the 4-day postvaccination follow-up period was calculated with 95% CI, after each vaccine dose and overall, according to the type of symptom, the intensity and relationship to vaccination.
The percentages of subjects/doses with an unsolicited symptom reported within the 31-day postvaccination follow-up period were summarized according to the Medical Dictionary for Regulatory Activities (MedDRA), with 95% CI according to the intensity and relationship to vaccination.
Prevalence of concomitant antipyretic/medication during the 4-day post-vaccination follow-up period was computed with 95% CI, after each vaccine dose and overall.
Serious adverse events and withdrawals due to adverse event(s) reported during the entire study period were described in detail.

➢ **Results**

- Recruitment/ Number analysed
  Table 11 presents the number of subjects vaccinated, completed and withdrawn from the study with the reasons for withdrawal.

Table 11 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Total vaccinated cohort)

	10Pn	Prev	Total
Number of subjects vaccinated	374	129	503
Number of subjects completed	364	125	489
Number of subjects withdrawn	10	4	14
Reasons for withdrawal :			
Serious Adverse Event	0	1	1
Non-serious adverse event	0	0	0
Protocol violation	0	0	0
Consent withdrawal (not due to an adverse event)	6	3	9
Migrated/moved from study area	4	0	4
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0
Lost to follow-up (subjects with complete vaccination course)	0	0	0
Others	0	0	0

10Pn = 10Pn-PD-DiT + Hiberix
Prev = Prevenar + Hiberix

Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come for the last visit

- Immunogenicity results
  For each of the 7 Prevenar serotypes (4, 6B, 9V, 14, 18C, 19F and 23F), the difference between groups (Prev minus 10Pn), in terms of percentage of subjects with pneumococcal antibody concentrations ≥ 0.2 µg/mL, one month post-dose III, and its 96.5% CI are shown in Table 14.
  For each of the 3 additional non-Prevenar serotypes (1, 5 and 7F), the difference between the aggregate response of the 7 Prevenar serotypes in the Prev group and the responses for serotypes 1, 5 and 7F in the 10Pn group, in terms of percentage of subjects with pneumococcal antibody concentrations ≥ 0.2 µg/mL, one month post-dose III, and its bootstrap 96.5% CI are shown in Table 15.
  The upper limits of these 96.5% CIs for the difference between groups, in terms of percentage of subjects with pneumococcal antibody concentrations ≥ 0.2 µg/mL, were below the pre-defined limit for non-inferiority of 10% for all serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F).
  The GMCs of antibodies against the vaccine pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F), measured by 22F-inhibition ELISA, and the percentage of subjects with pneumococcal antibody concentrations ≥ the cut-off of the assay of 0.05 µg/mL and ≥ the threshold value of 0.2 µg/mL, one month post-dose III are presented in Table 16.

Table 14 **Difference between groups (Prev minus 10Pn) in percentage of subjects with ELISA pneumococcal antibody concentrations greater or equal to 0.2 microgram/mL, one month after dose III, for pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F and 23F (ATP cohort for immunogenicity)**

					Difference in % ≥ 0.2 µg/mL (Prev minus 10Pn)		
	10Pn		Prev			96.5 % CI	
Antibody	N	%	N	%	%	LL	UL
ANTI-4	344	99.7	123	100	0.29	-3.21	1.81
ANTI-6B	344	92.4	123	98.4	5.93	0.92	9.86
ANTI-9V	344	99.7	123	99.2	-0.52	-4.66	1.10
ANTI-14	344	99.4	123	100	0.58	-2.92	2.28
ANTI-18C	344	99.7	123	100	0.29	-3.21	1.81
ANTI-19F	344	98.8	123	100	1.16	-2.34	3.15
ANTI-23F	344	96.2	123	98.4	2.15	-2.65	5.34

10Pn = 10Pn-PD-DiT + Hiberix; Prev = Prevenar + Hiberix

N = number of subjects with available results; % = percentage of subjects with ELISA pneumococcal antibody concentrations ≥ 0.2 µg/mL

96.5% CI = 96.5% Standardized asymptotic confidence interval; LL = Lower Limit, UL = Upper Limit.

Table 15 **Difference between the aggregate response for the 7 Prevenar serotypes in the Prev group and responses for serotypes 1, 5 and 7F in the 10Pn group in percentage of subjects with ELISA pneumococcal antibody concentrations greater or equal to 0.2 microgram/mL, one month after dose III (ATP cohort for immunogenicity)**

					Difference in % ≥ 0.2 µg/mL (aggregate Prev minus 10Pn)		
	10Pn		Aggregate Prev response			96.5 % CI	
Antibody	N	%	N	%	%	LL	UL
ANTI-1	344	100	861	99.4	-0.58	-0.95	-0.18
ANTI-5	344	100	861	99.4	-0.58	-0.95	-0.18
ANTI-7F	344	100	861	99.4	-0.58	-0.95	-0.18

10Pn = 10Pn-PD-DiT + Hiberix

Prev = Prevenar + Hiberix

N = number of subjects with available results

% = percentage of subjects with ELISA pneumococcal antibody concentrations ≥ 0.2 µg/mL.

Aggregate Prev response % = percentage of pneumococcal antibody concentrations ≥ 0.2 µg/mL for the combined 7 Prevenar serotypes (4, 6B, 9V, 14, 18C, 19F, 23F)

96.5% CI = 96.5% Efron's percentile confidence interval (boostrap method); LL = Lower Limit, UL = Upper Limit

Table 16 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	10Pn	PIII(M5)	344	344	100	98.9	100	344	100	98.9	100	3.41	3.14	3.71
	Prev	PIII(M5)	123	44	35.8	27.3	44.9	7	5.7	2.3	11.4	0.04	0.04	0.05
ANTI-4	10Pn	PIII(M5)	344	344	100	98.9	100	343	99.7	98.4	100	4.00	3.67	4.35
	Prev	PIII(M5)	123	123	100	97.0	100	123	100	97.0	100	5.35	4.66	6.15
ANTI-5	10Pn	PIII(M5)	344	344	100	98.9	100	344	100	98.9	100	4.52	4.24	4.83
	Prev	PIII(M5)	123	85	69.1	60.1	77.1	18	14.6	8.9	22.1	0.07	0.06	0.08
ANTI-6B	10Pn	PIII(M5)	344	337	98.0	95.9	99.2	318	92.4	89.1	95.0	1.40	1.24	1.58
	Prev	PIII(M5)	123	122	99.2	95.6	100	121	98.4	94.2	99.8	2.07	1.75	2.44
ANTI-7F	10Pn	PIII(M5)	344	344	100	98.9	100	344	100	98.9	100	4.08	3.77	4.41
	Prev	PIII(M5)	123	22	17.9	11.6	25.8	4	3.3	0.9	8.1	0.03	0.03	0.04
ANTI-9V	10Pn	PIII(M5)	344	343	99.7	98.4	100	343	99.7	98.4	100	3.39	3.09	3.71
	Prev	PIII(M5)	123	123	100	97.0	100	122	99.2	95.6	100	5.09	4.34	5.96
ANTI-14	10Pn	PIII(M5)	344	344	100	98.9	100	342	99.4	97.9	99.9	5.54	5.02	6.12
	Prev	PIII(M5)	123	123	100	97.0	100	123	100	97.0	100	8.51	7.27	9.95
ANTI-18C	10Pn	PIII(M5)	344	344	100	98.9	100	343	99.7	98.4	100	5.80	5.17	6.52
	Prev	PIII(M5)	123	123	100	97.0	100	123	100	97.0	100	5.13	4.31	6.11
ANTI-19F	10Pn	PIII(M5)	344	344	100	98.9	100	340	98.8	97.0	99.7	7.41	6.67	8.23
	Prev	PIII(M5)	123	123	100	97.0	100	123	100	97.0	100	2.77	2.45	3.13
ANTI-23F	10Pn	PIII(M5)	344	340	98.8	97.0	99.7	331	96.2	93.6	98.0	1.96	1.75	2.19
	Prev	PIII(M5)	123	122	99.2	95.6	100	121	98.4	94.2	99.8	3.94	3.26	4.77

10Pn = 10Pn-PD-DiT + Hiberix; Prev = Prevenar + Hiberix

For each of the 7 Prevenar serotypes (4, 6B, 9V, 14, 18C, 19F and 23F), the difference between groups (Prev minus 10Pn), in terms of percentage of subjects with OPA titres ≥8, one month post-dose III, and its 95% CI are shown in Supplement 5.
For each of the 3 additional non-Prevenar serotypes (1, 5 and 7F), the difference between the aggregate response of the 7 Prevenar serotypes in the Prev group and the responses for serotypes 1, 5 and 7F in the 10Pn group, in terms of percentage of subjects with OPA titres ≥ 8, one month post-dose III, and its bootstrap 95% CI are shown in Supplement 6.

The GMTs of opsonophagocytic activity against the vaccine pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F), and the percentage of subjects with OPA titres ≥8, one month post-dose III are presented in Table 17.

Supplement 5 Difference between groups (Prev minus 10Pn) in percentage of subjects with Opsonophagocytic activity greater or equal to 8, one month after dose III, for pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F and 23F (ATP cohort for immunogenicity)

					Difference in % ≥ 8 (Prev minus 10Pn)		
	10Pn		Prev			95% CI	
Antibody	N	%	N	%	%	LL	UL
OPSONO-4	161	98.1	63	100	1.86	-3.94	5.35
OPSONO-6B	162	93.8	63	100	6.17	0.30	11.00
OPSONO-9V	165	99.4	63	98.4	-0.98	-7.91	2.01
OPSONO-14	165	98.8	63	98.4	-0.38	-7.33	3.03
OPSONO-18C	159	89.3	63	96.8	7.52	-0.89	13.99
OPSONO-19F	164	97.0	61	90.2	-6.79	-17.04	-0.38
OPSONO-23F	164	97.6	63	98.4	0.85	-6.17	4.86

10Pn = 10Pn-PD-DiT + Hiberix
Prev = Prevenar + Hiberix

N = number of subjects with available results
% = percentage of subjects with opsonophagocytic activity ≥ 8
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 6 Difference between the aggregate response for the 7 Prevenar serotypes and responses for serotypes 1, 5 and 7F in the 10Pn group in percentage of subjects with Opsonophagocytic activity greater or equal to 8, one month after dose III (ATP cohort for immunogenicity)

					Difference in % ≥ 8 (Aggregate Prev minus 10Pn)		
	10Pn		Aggregate Prev response			95 % CI	
Antibody	N	%	N	%	%	LL	UL
OPSONO-1	162	92.6	439	97.5	4.90	1.35	8.27
OPSONO-5	165	97.6	439	97.5	-0.08	-2.45	2.13
OPSONO-7F	164	100	439	97.5	-2.51	-3.77	-1.08

10Pn = 10Pn-PD-DiT + Hiberix
Prev = Prevenar + Hiberix

N = number of subjects with available results
% = percentage of subjects with Opsonophagocytic activity ≥ 8
Aggregate Prev response % = percentage of opsonophagocytic titres ≥ 8 for the combined 7 Prevenar serotypes (4, 6B, 9V, 14, 18C, 19F and 23F)
95% CI = 95% Efron's percentile confidence interval (boostrap method) ; LL = Lower Limit, UL = Upper Limit

Table 17 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 for immunogenicity)

				≥ 8				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
OPSONO-1	10Pn	PIII(M5)	162	150	92.6	87.4	96.1	187.8	146.7	240.6
	Prev	PIII(M5)	62	8	12.9	5.7	23.9	6.3	4.6	8.8
OPSONO-4	10Pn	PIII(M5)	161	158	98.1	94.7	99.6	631.9	535.5	745.7
	Prev	PIII(M5)	63	63	100	94.3	100	1457.0	1153.5	1840.3
OPSONO-5	10Pn	PIII(M5)	165	161	97.6	93.9	99.3	238.1	199.9	283.5
	Prev	PIII(M5)	62	6	9.7	3.6	19.9	5.3	4.2	6.6
OPSONO-6B	10Pn	PIII(M5)	162	152	93.8	88.9	97.0	597.0	459.3	776.0
	Prev	PIII(M5)	63	63	100	94.3	100	1456.0	1116.8	1898.3
OPSONO-7F	10Pn	PIII(M5)	164	164	100	97.8	100	3968.4	3422.1	4601.8
	Prev	PIII(M5)	59	40	67.8	54.4	79.4	152.2	76.6	302.5
OPSONO-9V	10Pn	PIII(M5)	165	164	99.4	96.7	100	1051.4	902.7	1224.7
	Prev	PIII(M5)	63	62	98.4	91.5	100	1901.3	1364.2	2650.0
OPSONO-14	10Pn	PIII(M5)	165	163	98.8	95.7	99.9	1248.3	1046.6	1489.0
	Prev	PIII(M5)	63	62	98.4	91.5	100	2168.8	1510.5	3114.2
OPSONO-18C	10Pn	PIII(M5)	159	142	89.3	83.4	93.6	156.9	121.0	203.4
	Prev	PIII(M5)	63	61	96.8	89.0	99.6	389.0	257.2	588.3
OPSONO-19F	10Pn	PIII(M5)	164	159	97.0	93.0	99.0	357.6	282.1	453.2
	Prev	PIII(M5)	61	55	90.2	79.8	96.3	74.8	51.2	109.5
OPSONO-23F	10Pn	PIII(M5)	164	160	97.6	93.9	99.3	1488.7	1224.5	1810.1
	Prev	PIII(M5)	63	62	98.4	91.5	100	9336.4	6464.4	13484.4

10Pn = 10Pn-PD-DiT + Hiberix; Prev = Prevenar + Hiberix
GMT = geometric mean titre
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M5) = one month after dose III

MAH's Immunogenicity conclusions

- The primary non-inferiority objective of the study was reached as the upper limits of the 96.5% CIs for the difference between groups (Prev minus 10Pn and aggregate response for the 7 Prevenar serotype in the Prev group minus the responses for serotypes 1, 5 and 7F in the 10Pn group), in terms of percentage of subjects with antibody concentrations ≥ 0.2 µg/mL, were below the pre-defined limit for noninferiority of 10% for all pneumococcal serotypes contained in the 10Pn-PD-DiT vaccine.
- In the group that received 10Pn-PD-DiT vaccine, one month post-dose III, for each of the vaccine pneumococcal serotypes, at least 96.2% of subjects had pneumococcal antibody concentrations ≥ 0.2 µg/mL, except for serotype 6B (92.4%) and at least 97.0% of subjects had OPA titres ≥ 8, except for serotypes 1 (92.6%), 6B (93.8%) and 18C (89.3%). All subjects except one (99.7%) had measurable antibodies against protein D (≥ 100 EL.U/mL).
- For each of the 7 common pneumococcal serotypes, one month post-dose III, the observed antibody GMCs and OPA GMTs were higher in the Prev group compared to the 10Pn group except for serotype 19F for which the antibody GMC and OPA GMT was higher in the 10Pn group and for serotype 18C for which the antibody GMC was in the same range for the two groups.
- One month post-dose III, all subjects had seroprotective levels of antibodies against the Hib polysaccharide PRP antigen (≥0.15 µg/mL) in the co-administered Hiberix vaccine in both groups. Higher anti-PRP antibody GMC was observed in the 10Pn group compared to the Prev group.

Assessor's comment: The immune responses to the 10Pn vaccine were well in line with previously presented results, and non-inferior to the responses to Prevenar.

- Safety result

Adverse events
The overall incidence of AEs (solicited and unsolicited), reported during the 31-day postvaccination period, following each dose, overall/dose and overall/subject is presented in Table 24.
The incidence of each solicited local AE, within the 4-day post-vaccination period, overall/dose is shown in Table 26. The incidence of solicited general AEs, within the 4-day post-vaccination period, overall/dose is shown in Table 27.

Table 24 Incidence and nature of symptoms (solicited and unsolicited) reported during the 31-day (Days 0-30) post-vaccination period, following each dose and overall (Total vaccinated cohort)

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	10Pn	371	342	92.2	89.0	94.7	371	314	84.6	80.6	88.2	371	261	70.4	65.4	75.0
	Prev	129	114	88.4	81.5	93.3	129	97	75.2	66.8	82.4	129	91	70.5	61.9	78.2
Dose 2	10Pn	366	300	82.0	77.6	85.8	366	260	71.0	66.1	75.6	366	200	54.6	49.4	59.8
	Prev	128	102	79.7	71.7	86.3	128	83	64.8	55.9	73.1	127	74	58.3	49.2	67.0
Dose 3	10Pn	365	282	77.3	72.6	81.5	364	217	59.6	54.4	64.7	365	196	53.7	48.4	58.9
	Prev	126	106	84.1	76.6	90.0	126	86	68.3	59.4	76.3	126	73	57.9	48.8	66.7
Overall/dose	10Pn	1102	924	83.8	81.5	86.0	1101	791	71.8	69.1	74.5	1102	657	59.6	56.7	62.5
	Prev	383	322	84.1	80.0	87.6	383	266	69.5	64.6	74.0	382	238	62.3	57.2	67.2
Overall/subject	10Pn	371	360	97.0	94.8	98.5	371	350	94.3	91.5	96.5	371	292	78.7	74.2	82.8
	Prev	129	126	97.7	93.4	99.5	129	119	92.2	86.2	96.2	129	104	80.6	72.7	87.0

10Pn = 10Pn-PD-DiT + Hiberix
Prev = Prevenar + Hiberix

For each dose and overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
For overall/dose:
N= number of documented doses
n/%= number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Table 26 Incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period, overall/dose (Total vaccinated cohort)

			10Pn					Prev				
						95 % CI					95 % CI	
Symptom	Product	Type	N	n	%	LL	UL	N	n	%	LL	UL
Pain	Total	All	1102	364	33.0	30.3	35.9	382	136	35.6	30.8	40.6
		Grade 3	1102	16	1.5	0.8	2.3	382	2	0.5	0.1	1.9
		Medical advice	1102	0	0.0	0.0	0.3	382	0	0.0	0.0	1.0
	10Pn-PD-DiT	All	1102	346	31.4	28.7	34.2	-	-	-	-	-
		Grade 3	1102	16	1.5	0.8	2.3	-	-	-	-	-
		Medical advice	1102	0	0.0	0.0	0.3	-	-	-	-	-
	Prevenar	All	-	-	-	-	-	382	131	34.3	29.5	39.3
		Grade 3	-	-	-	-	-	382	1	0.3	0.0	1.4
		Medical advice	-	-	-	-	-	382	0	0.0	0.0	1.0
	Hiberix	All	1102	245	22.2	19.8	24.8	382	100	26.2	21.8	30.9
		Grade 3	1102	8	0.7	0.3	1.4	382	1	0.3	0.0	1.4
		Medical advice	1102	0	0.0	0.0	0.3	382	0	0.0	0.0	1.0
Redness (mm)	Total	All	1102	507	46.0	43.0	49.0	382	186	48.7	43.6	53.8
		> 20.0	1102	78	7.1	5.6	8.8	382	23	6.0	3.9	8.9
		> 30.0	1102	22	2.0	1.3	3.0	382	10	2.6	1.3	4.8
		Medical advice	1102	0	0.0	0.0	0.3	382	0	0.0	0.0	1.0
	10Pn-PD-DiT	All	1102	480	43.6	40.6	46.5	-	-	-	-	-
		> 20.0	1102	65	5.9	4.6	7.5	-	-	-	-	-
		> 30.0	1102	20	1.8	1.1	2.8	-	-	-	-	-
		Medical advice	1102	0	0.0	0.0	0.3	-	-	-	-	-
	Prevenar	All	-	-	-	-	-	382	178	46.6	41.5	51.7
		> 20.0	-	-	-	-	-	382	22	5.8	3.6	8.6
		> 30.0	-	-	-	-	-	382	10	2.6	1.3	4.8
		Medical advice	-	-	-	-	-	382	0	0.0	0.0	1.0
	Hiberix	All	1102	336	30.5	27.8	33.3	382	120	31.4	26.8	36.3
		> 20.0	1102	35	3.2	2.2	4.4	382	6	1.6	0.6	3.4
		> 30.0	1102	8	0.7	0.3	1.4	382	3	0.8	0.2	2.3
		Medical advice	1102	0	0.0	0.0	0.3	382	0	0.0	0.0	1.0
Swelling (mm)	Total	All	1102	348	31.6	28.8	34.4	382	128	33.5	28.8	38.5
		> 20.0	1102	64	5.8	4.5	7.4	382	13	3.4	1.8	5.7
		> 30.0	1102	29	2.6	1.8	3.8	382	5	1.3	0.4	3.0
		Medical advice	1102	0	0.0	0.0	0.3	382	0	0.0	0.0	1.0
	10Pn-PD-DiT	All	1102	326	29.6	26.9	32.4	-	-	-	-	-
		> 20.0	1102	56	5.1	3.9	6.5	-	-	-	-	-
		> 30.0	1102	25	2.3	1.5	3.3	-	-	-	-	-
		Medical advice	1102	0	0.0	0.0	0.3	-	-	-	-	-
	Prevenar	All	-	-	-	-	-	382	118	30.9	26.3	35.8
		> 20.0	-	-	-	-	-	382	13	3.4	1.8	5.7
		> 30.0	-	-	-	-	-	382	5	1.3	0.4	3.0
		Medical advice	-	-	-	-	-	382	0	0.0	0.0	1.0
	Hiberix	All	1102	195	17.7	15.5	20.1	382	64	16.8	13.1	20.9
		> 20.0	1102	20	1.8	1.1	2.8	382	2	0.5	0.1	1.9
		> 30.0	1102	8	0.7	0.3	1.4	382	1	0.3	0.0	1.4
		Medical advice	1102	0	0.0	0.0	0.3	382	0	0.0	0.0	1.0

10Pn = 10Pn-PD-DiT + Hiberix
Prev = Prevenar + Hiberix

N= number of documented doses; n/%= number/percentage of doses followed by at least one type of symptom
Total : n/%= number/percentage of subjects/doses with at least one local symptom whatever the number of injections.

Table 27 Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period, overall/dose (Total vaccinated cohort)

		10Pn					Prev				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Drowsiness	All	1101	350	31.8	29.0	34.6	383	113	29.5	25.0	34.3
	Grade 3	1101	2	0.2	0.0	0.7	383	0	0.0	0.0	1.0
	Related	1101	153	13.9	11.9	16.1	383	59	15.4	11.9	19.4
	Grade 3 & Related	1101	0	0.0	0.0	0.3	383	0	0.0	0.0	1.0
	Medical advice	1101	0	0.0	0.0	0.3	383	0	0.0	0.0	1.0
Fever/(Axillary) (°C)	All	1101	137	12.4	10.6	14.5	383	43	11.2	8.2	14.8
	> 38.0	1101	36	3.3	2.3	4.5	383	7	1.8	0.7	3.7
	> 38.5	1101	12	1.1	0.6	1.9	383	2	0.5	0.1	1.9
	> 39.0	1101	2	0.2	0.0	0.7	383	1	0.3	0.0	1.4
	> 39.5	1101	0	0.0	0.0	0.3	383	0	0.0	0.0	1.0
	Related	1101	91	8.3	6.7	10.1	383	24	6.3	4.1	9.2
	> 39.5°C & Related	1101	0	0.0	0.0	0.3	383	0	0.0	0.0	1.0
	Medical advice	1101	8	0.7	0.3	1.4	383	3	0.8	0.2	2.3
Irritability	All	1101	539	49.0	46.0	52.0	383	188	49.1	44.0	54.2
	Grade 3	1101	28	2.5	1.7	3.7	383	9	2.3	1.1	4.4
	Related	1101	277	25.2	22.6	27.8	383	97	25.3	21.0	30.0
	Grade 3 & Related	1101	16	1.5	0.8	2.3	383	5	1.3	0.4	3.0
	Medical advice	1101	1	0.1	0.0	0.5	383	0	0.0	0.0	1.0
Loss of appetite	All	1101	277	25.2	22.6	27.8	383	100	26.1	21.8	30.8
	Grade 3	1101	2	0.2	0.0	0.7	383	1	0.3	0.0	1.4
	Related	1101	121	11.0	9.2	13.0	383	57	14.9	11.5	18.8
	Grade 3 & Related	1101	1	0.1	0.0	0.5	383	1	0.3	0.0	1.4
	Medical advice	1101	2	0.2	0.0	0.7	383	1	0.3	0.0	1.4

10Pn = 10Pn-PD-DiT + Hiberix
Prev = Prevenar + Hiberix

N= number of documented doses
n/%= number/percentage of doses followed by at least one type of symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

29.3% and 24.0% of injected doses in the 10Pn and Prev groups, respectively, were followed by at least one unsolicited AE.
The most frequently reported unsolicited AE was upper respiratory tract infection in the 10Pn group (4.6% of doses) and nasopharyngitis in the Prev group (5.5% of doses). The observed percentage of doses followed by at least one unsolicited AE considered by the investigator to be causally related to vaccination was 2.5% in the 10Pn group and 2.1% in the Prev group (see Table 28). Injection site induration was the most frequently
reported unsolicited AE considered by the investigator to be causally related to
vaccination (1.2% of doses in the 10Pn group and 1.0% of doses in the Prev group).

No fatal adverse events were reported during the entire study period.

In total, 65 subjects reported at least one SAE:
56 subjects out of the 374 vaccinated subjects in the 10Pn group (15%)
9 subjects out of the 129 vaccinated subjects in the Prev group (7%)
Three subjects reported at least one SAE considered by the investigator to be causally related to vaccination (2 in the 10Pn group and 1 in the Prev group, 2 cases of pyrexia and 1 case of anorexia, see below).
One subject in the Prev group (subject number 811) withdrew because of SAEs experienced during the vaccination course. This subject developed anorexia on the same day the subject received the second dose of Prevenar co-administered with Hiberix. One day after, the subject developed upper respiratory tract infection and was hospitalized. Anorexia was considered by the investigator to be causally related to vaccination. Both SAEs resolved without sequelae on day 5 after vaccination. Seven days after the second dose of Prevenar co-administered with Hiberix, the same subject was hospitalized for

gastroenteritis. The event was not considered by the investigator to be causally related to vaccination and resolved without sequelae, 9 days after onset. The decision to withdraw the subject was made by the parents.

All SAEs resolved without sequelae.

MAH's Safety conclusions

- The observed incidences of solicited and unsolicited AEs were within the same ranges for the 10Pn-PD-DiT vaccine and Prevenar, both co-administered with Hiberix vaccine.
- The most frequently reported solicited local and general AE was redness and irritability, respectively, in both groups.
- There was no increase in the incidence of solicited AEs following consecutive 10Pn- PD-DiT doses during the 3-dose primary vaccination course.
- A low overall/dose incidence of grade 3 solicited local and general AEs (maximum 2.6% and 2.5%, respectively, whatever the group) and grade 3 solicited general AEs considered by the investigator to be causally related to vaccination (maximum 1.5%, whatever the group). No grade 3 fever (axillary temperature > 39.5°C) was reported during the 4-day post-vaccination period in both groups.
- 29.3% and 24.0% of injected doses in the 10Pn and the Prev groups respectively, were followed by at least one unsolicited AE.
- A low percentage of doses were followed by grade 3 unsolicited AEs (maximum 0.4% whatever the group) or by unsolicited AEs considered by the investigator to be causally related to vaccination (maximum 2.5% whatever the group). There was no unsolicited grade 3 AE considered by the investigator to be causally related to 10Pn- PD-DiT vaccination reported.

Assessor's comment: No new safety signal was detected in this study, and the incidence of adverse events was generally in agreement with previous studies.

3. Discussion on clinical aspects

The submitted clinical study report confirms previously reported immunogenicity and safety results. Thus, in conclusion the MAH has fulfilled the requirements and no further regulatory action is required.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**
- **Recommendation**

☒ **Fulfilled –**

No further action required

☐ **Not fulfilled:**

IV. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable