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Committee for Medicinal Products for Human Use (CHMP)

Synflorix

(Pneumococcal polysaccharide conjugate vaccine, adsorbed)

Procedure No: EMEA/H/C/000973/P46/040

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

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

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I. INTRODUCTION

On December 2, 2010, 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 submitted a final report for:
Study number: 10PN-PD-DIT-063
Study title: A phase III, controlled, single-blind study to assess the reactogenicity, safety and immunogenicity of a booster dose of GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine or Prevenar™ when co-administered with Hiberix™ at 12-18 months of age in children primed with the same vaccines in study 10PN-PD-DIT-036.

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

In the study Synflorix was administered using the currently approved formulation.

II.2 Clinical aspects

2. Clinical study

Study number: 10PN-PD-DIT-063
Study title: A phase III, controlled, single-blind study to assess the reactogenicity, safety and immunogenicity of a booster dose of GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine or Prevenar™ when co-administered with Hiberix™ at 12-18 months of age in children primed with the same vaccines in study 10PN-PD-DIT-036

- **Description**

This study was conducted by 14 principal investigators in Korea.

- **Methods**

Objective(s)

Primary:

- To assess the reactogenicity of a booster dose of the 10Pn-PD-DiT vaccine in terms of the occurrence of adverse events (AEs) with grade 3 intensity, when co-administered with Hiberix at 12-18 months of age in children primed with the same vaccines at 2, 4 and 6 months of age in study 10PN-PD-DIT-036.

Secondary:

- To assess the safety and reactogenicity of a booster dose of the 10Pn-PD-DiT vaccine when co-administered with Hiberix at 12-18 months of age in children primed with the same vaccines at 2, 4 and 6 months of age in study 10PN-PD-DIT-036.
- To assess the immunogenicity of a booster dose of the 10Pn-PD-DiT vaccine when co-administered with Hiberix at 12-18 months of age in children primed with the same vaccines at 2, 4 and 6 months of age in study 10PN-PD-DIT-036.

Study design

- This was a phase III, multi-centre, single-blind, controlled study with 2 parallel groups:
  - 10Pn group: subjects previously primed with 3 doses of the 10Pn-PD-DiT vaccine and with Hiberix in study 10PN-PD-DIT-036 and receiving a booster dose of 10Pn-PD-DiT and Hiberix at 12-18 months of age.
  - Prev group: subjects previously primed with 3 doses of Prevenar and with Hiberix in study 10PN-PD-DIT-036 and receiving a booster dose of Prevenar and Hiberix at 12-18 months of age.
- Control: Prev group.

- Vaccination schedule: a booster dose of either 10Pn-PD-DiT or Prevenar co-administered with Hiberix at 12-18 months of age.
- One blood sample was collected one month post-booster vaccination.
- Type of study: booster vaccination study of primary vaccination study 10PN-PD-DIT-036.

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, 12-18 months of age at the time of the booster vaccination.
- Subjects who received three doses of pneumococcal conjugate vaccine in study 10PN-PD-DIT-036.
- Written informed consent obtained from the parent(s) or guardian(s) of the child/ward.
- Healthy subjects as established by medical history and clinical examination before entering into the study.

The sample size was contingent on the number of subjects who received three doses of pneumococcal conjugate vaccine in study 10PN-PD-DIT-036. Assuming that around 20% of these subjects did not enter this study, it could be considered that approximately 400 subjects (300 in group 10Pn and 100 subjects in group Prev) received the booster dose of study vaccines.
This sample size had at least 80% power to detect a difference between the considered 10Pn group and Prev group in terms of percentage of subjects with grade 3 adverse event.

Number of subjects:	**Total**	**10Pn**	**Prev**
Planned:	503	374	129
Enrolled:	450	337	113
Completed:	427	319	108
Total vaccinated cohort	448	335	113
According-To-Protocol (ATP) cohort for analysis of safety	439	332	107
ATP cohort for analysis of immunogenicity	419	317	102

Treatments

The formulations for the 10Pn-PD-DiT, Hiberix and Prevenar vaccines are in Table 3.

Table 3 Vaccines, formulation, lot numbers and allocation

Vaccine	Formulation (per dose)	Lot number	Group
(Study vaccine) GSK Biologicals' 10Pn-PD-DiT vaccine	Protein D carrier: 1 μg of each capsular PS for serotypes 1, 5, 6B, 7F, 9V, 14 and 23F and 3 μg for serotype 4 conjugated to PD. Tetanus toxoid carrier: 3 μg of capsular PS of serotype 18C conjugated to TT. Diphtheria toxoid carrier: 3 μg of capsular PS of serotype 19F conjugated to DT. Protein carrier content: 9-16 μg PD, 3-6 μg DT, 5-10 μg TT. 0.5 mg aluminium (Al^{3+}) as aluminium phosphate adjuvant. Sodium chloride, water for injections.	ASPNA007C	10Pn
(Co-administered vaccine) GSK Biologicals' Hib vaccine (Hiberix)	Polyribosyl-Ribitol-Phosphate (PRP): 10 μg Tetanus toxoid: 20-40 μg Lactose: 10 mg	AHIBC032A	10Pn Prev
	Diluent Sodium chloride 4.5 mg Water for injection 0.5 mL	AD02B136A3	
(Control vaccine) Pfizer's Prevenar vaccine	Each dose contains 2 μg of pneumococcal polysaccharide serotypes: 4, 9V, 14, 18C, 19F, 23F, and 4 μg of pneumococcal polysaccharide serotype 6B conjugated to CRM197 and adsorbed on aluminium phosphate: 0.5 mg; sodium chloride, water for injections.	DEXTA333AZ (manufacturer Lot n° 37102)	Prev

Outcomes/endpoints

Primary endpoint

- Occurrence of grade 3 adverse events (solicited and unsolicited) within 31 days (Day 0 - Day 30) after booster vaccination.

Secondary endpoints

- Occurrence of each solicited adverse event, within 4 days after booster vaccination.
  - Local (any, grade 3) adverse events.
  - General (any, grade 3, related) adverse events.
- Occurrence of unsolicited adverse events within 31 days after booster vaccination.
- Occurrence of serious adverse events after booster vaccination up to study end (Visit 1 to Visit 2).

Immunogenicity:

Evaluation of the immune responses to components of the investigational vaccine, one month after booster vaccination:

- Concentrations of antibodies against vaccine pneumococcal serotypes.
- Opsonophagocytic activity against vaccine pneumococcal serotypes.
- 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.

Evaluation of the immune response to the co-administered vaccine, one month after booster vaccination:

- Antibody concentrations against polyribosyl-ribitol-phosphate (PRP).

Statistical Methods

Statistical analyses were performed according to the protocol.

Demography:

- Demographic characteristics (age in months, gender, race) of each study cohort were tabulated as a whole and per group.
- The mean age in months (plus range and standard deviation) of the enrolled subjects, as a whole, and per group, was calculated.
- Distribution of enrolled subjects among the study centres was tabulated as a whole and per group.
- In addition, a summary of the tracking log-sheet that documented outcomes of the contacts made with subjects for enrolment in this study was provided.

Safety /reactogenicity:

Descriptive analysis:

- The number and percentages of subjects reporting solicited and/or unsolicited local and general adverse events during the 31-day (Days 0-30) follow-up period after booster vaccination was calculated with 95% confidence interval (CI), according to the type of symptom, the intensity and relationship to vaccination.
- The number and percentages of subjects reporting each local and each general solicited symptom reported during the 4-day (Days 0-3) follow-up period after booster vaccination was calculated with 95% CI, according to the type of symptom, the intensity and relationship to vaccination.
- The number and percentages of subjects with an unsolicited symptom reported within the 31-day (Days 0-30) follow-up period after booster vaccination were classified according to the Medical Dictionary for Regulatory Activities (MedDRA), with 95% CI according to the intensity and relationship to vaccination.
- The proportion of AEs resulting in a medically attended visit was also be tabulated.
- Prevalence of concomitant antipyretic/medication during the 4-day (Days 0-3) follow-up period after booster vaccination was computed with 95% CI.
- Serious adverse events, large swelling reactions and withdrawal due to serious adverse event(s) were described in detail.

Immunogenicity:

Descriptive analysis:

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

➢ Results

- Recruitment/ Number analysed

The study cohort composition of the primary vaccination study 10PN-PD-DIT-036 and of the present booster vaccination study 10PN-PD-DIT-063 BST: 036 is shown in Table 11.

Table 11 Study cohort composition for booster and primary phases (Primary Total vaccinated cohort)

Primary : 10PN-PD-DIT-036 (110808)		Booster : 10PN-PD-DIT-063 BST:036 (112933)	
Group	n	Group	n
10Pn	374	10Pn	335
Prev	129	Prev	113

10Pn = 10Pn-PD-DiT + Hiberix

Prev = Prevenar + Hiberix

n primary = number of subjects (Primary Total vaccinated cohort)

n booster = number of subjects (Total vaccinated cohort)

Fifty three subjects (37 from the 10Pn group and 16 from the Prev group) did not participate in the booster vaccination study for the following reasons:

- 18 subjects (12 in the 10Pn group and 6 in the Prev group) were not eligible.
- 19 subjects (15 in the 10Pn group and 4 in the Prev group) were lost to follow-up.
- 6 subjects (4 in the 10Pn group and 2 in the Prev group) did not fill in a tracking document (so missing information for them).
- 10 subjects (6 in the 10Pn group and 4 in the Prev group) did not want to participate (not because of AE or SAE).

- Baseline data

Demography:

In the Total vaccinated cohort, the mean age at booster vaccination was 13.6 months (standard deviation of 1.05), 99.8% of subjects were Asian (East Asian heritage) and 50.7% of subjects were female.

Efficacy results

Immunogenicity:

Immunogenicity analysis was performed on the ATP cohort (primary analysis) and on the Total vaccinated cohort. The immunogenicity results for the Total vaccinated cohort were consistent with those for ATP cohort for immunogenicity.

Booster immune response to the pneumococcal antigens - descriptive analysis results:

- One month post-booster vaccination, for each of the 7 common serotypes contained in 10Pn-PD-DiT and Prevenar, at least 97.5% of subjects in the 10Pn group and at least 98.0% of subjects in the Prev group had antibody concentrations ≥ 0.2 µg/mL. For each of the 3 additional serotypes (1, 5, 7F), the observed percentage of subjects in the 10Pn group with antibody concentrations ≥ 0.2 µg/mL was 100% for serotype 5 and 99.7% for serotypes 1 and 7F.
- A trend towards higher antibody GMCs was observed one month post-booster vaccination compared to the post-primary vaccination in both groups, for each of the serotypes for which subjects were primed.
- One month post-booster vaccination, the observed antibody GMCs were higher in the Prev group compared to the 10Pn group (no overlap of 95% CIs) for each of the 7 common serotypes except for serotype 18C and 19F. For serotype 18C, the antibody GMC was in the same range in both groups and for serotype 19F, the antibody GMC was higher in the 10Pn group compared to the Prev group (no overlap of 95% CI). This trend was consistent with what was observed in the primary vaccination study 10PN-PD-DIT-036.

Table 25 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)	317	317	100	98.8	100	317	100	98.8	100	3.42	3.14	3.74
		POST-BOOSTER	317	316	99.7	98.3	100	316	99.7	98.3	100	4.03	3.66	4.43
	Prev	PIII(M5)	102	34	33.3	24.3	43.4	7	6.9	2.8	13.6	0.04	0.03	0.05
		POST-BOOSTER	100	56	56.0	45.7	65.9	11	11.0	5.6	18.8	0.06	0.05	0.07
ANTI-4	10Pn	PIII(M5)	317	317	100	98.8	100	316	99.7	98.3	100	4.01	3.66	4.39
		POST-BOOSTER	317	317	100	98.8	100	317	100	98.8	100	5.77	5.25	6.34
	Prev	PIII(M5)	102	102	100	96.4	100	102	100	96.4	100	5.17	4.48	5.98
		POST-BOOSTER	102	102	100	96.4	100	102	100	96.4	100	12.19	10.11	14.69
ANTI-5	10Pn	PIII(M5)	317	317	100	98.8	100	317	100	98.8	100	4.54	4.24	4.85
		POST-BOOSTER	317	317	100	98.8	100	317	100	98.8	100	5.51	5.08	5.98
	Prev	PIII(M5)	102	68	66.7	56.6	75.7	15	14.7	8.5	23.1	0.07	0.06	0.08
		POST-BOOSTER	102	97	95.1	88.9	98.4	39	38.2	28.8	48.4	0.19	0.16	0.23
ANTI-6B	10Pn	PIII(M5)	317	310	97.8	95.5	99.1	293	92.4	88.9	95.1	1.41	1.24	1.59
		POST-BOOSTER	317	314	99.1	97.3	99.8	309	97.5	95.1	98.9	2.78	2.48	3.12
	Prev	PIII(M5)	102	102	100	96.4	100	101	99.0	94.7	100	2.15	1.83	2.52
		POST-BOOSTER	102	102	100	96.4	100	102	100	96.4	100	7.09	5.82	8.63
ANTI-7F	10Pn	PIII(M5)	317	317	100	98.8	100	317	100	98.8	100	4.01	3.69	4.36
		POST-BOOSTER	317	316	99.7	98.3	100	316	99.7	98.3	100	5.39	4.97	5.85
	Prev	PIII(M5)	102	20	19.6	12.4	28.6	4	3.9	1.1	9.7	0.03	0.03	0.04
		POST-BOOSTER	102	47	46.1	36.2	56.2	14	13.7	7.7	22.0	0.06	0.04	0.07
ANTI-9V	10Pn	PIII(M5)	317	316	99.7	98.3	100	316	99.7	98.3	100	3.38	3.06	3.72
		POST-BOOSTER	317	317	100	98.8	100	317	100	98.8	100	4.99	4.55	5.46
	Prev	PIII(M5)	102	102	100	96.4	100	101	99.0	94.7	100	4.79	4.04	5.67
		POST-BOOSTER	102	102	100	96.4	100	102	100	96.4	100	12.72	10.86	14.88
ANTI-14	10Pn	PIII(M5)	317	317	100	98.8	100	314	99.1	97.3	99.8	5.48	4.92	6.09
		POST-BOOSTER	316	316	100	98.8	100	316	100	98.8	100	7.73	7.09	8.43
	Prev	PIII(M5)	102	102	100	96.4	100	102	100	96.4	100	8.35	7.03	9.93
		POST-BOOSTER	102	102	100	96.4	100	102	100	96.4	100	22.22	18.96	26.03
ANTI-18C	10Pn	PIII(M5)	317	317	100	98.8	100	316	99.7	98.3	100	5.93	5.26	6.69
		POST-BOOSTER	317	317	100	98.8	100	317	100	98.8	100	13.14	11.90	14.52
	Prev	PIII(M5)	102	102	100	96.4	100	102	100	96.4	100	4.81	4.00	5.77
		POST-BOOSTER	102	102	100	96.4	100	102	100	96.4	100	14.53	12.10	17.44
ANTI-19F	10Pn	PIII(M5)	317	317	100	98.8	100	313	98.7	96.8	99.7	7.52	6.70	8.43
		POST-BOOSTER	317	315	99.4	97.7	99.9	313	98.7	96.8	99.7	16.89	14.87	19.20
	Prev	PIII(M5)	102	102	100	96.4	100	102	100	96.4	100	2.73	2.38	3.13
		POST-BOOSTER	101	101	100	96.4	100	101	100	96.4	100	4.82	3.97	5.85
ANTI-23F	10Pn	PIII(M5)	317	314	99.1	97.3	99.8	305	96.2	93.5	98.0	2.02	1.81	2.27
		POST-BOOSTER	317	316	99.7	98.3	100	313	98.7	96.8	99.7	3.75	3.37	4.16
	Prev	PIII(M5)	102	101	99.0	94.7	100	100	98.0	93.1	99.8	3.56	2.87	4.41
		POST-BOOSTER	102	101	99.0	94.7	100	100	98.0	93.1	99.8	14.81	11.61	18.89

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

- One month post-booster vaccination, for each of the 7 common serotypes contained in 10Pn-PD-DiT and Prevenar, at least 94.7% of subjects in the 10Pn group and at least 97.7% of

subjects in the Prev group had OPA titres ≥ 8. For each of the 3 additional serotypes (1, 5, 7F), at least 94.6% of subjects in the 10Pn group had OPA titres ≥ 8.

- A trend towards higher OPA GMTs or comparable OPA GMTs (for serotype 5 and 6B in the 10Pn group) was observed one month post-booster compared to post-primary vaccination in both groups for each of the serotypes for which subjects were primed.
- The observed post-booster OPA GMTs were higher in the Prev group compared to the 10Pn group (no overlap of 95% CIs) for each of the 7 common serotypes except for serotype 19F for which OPA GMT was higher in the 10Pn group compared to the Prev group (no overlap of 95% CI). This trend was consistent with what was observed in the primary vaccination study 10PN-PD-DIT-036.

Table 26 **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)	147	136	92.5	87.0	96.2	192.6	148.7	249.4
		POST-BOOSTER	148	140	94.6	89.6	97.6	363.7	275.3	480.5
	Prev	PIII(M5)	47	6	12.8	4.8	25.7	6.1	4.3	8.7
		POST-BOOSTER	47	3	6.4	1.3	17.5	4.7	3.9	5.6
OPSONO-4	10Pn	PIII(M5)	146	143	97.9	94.1	99.6	621.5	519.8	743.2
		POST-BOOSTER	149	148	99.3	96.3	100	1058.0	893.9	1252.3
	Prev	PIII(M5)	48	48	100	92.6	100	1528.0	1156.2	2019.4
		POST-BOOSTER	45	45	100	92.1	100	3717.0	2759.3	5007.0
OPSONO-5	10Pn	PIII(M5)	150	146	97.3	93.3	99.3	235.6	196.6	282.5
		POST-BOOSTER	150	146	97.3	93.3	99.3	233.9	189.8	288.3
	Prev	PIII(M5)	47	4	8.5	2.4	20.4	5.0	4.0	6.4
		POST-BOOSTER	46	0	0.0	0.0	7.7	4.0	4.0	4.0
OPSONO-6B	10Pn	PIII(M5)	148	140	94.6	89.6	97.6	616.1	472.6	803.1
		POST-BOOSTER	150	142	94.7	89.8	97.7	546.5	415.9	718.0
	Prev	PIII(M5)	48	48	100	92.6	100	1568.0	1136.2	2163.9
		POST-BOOSTER	46	45	97.8	88.5	99.9	3826.8	2518.0	5815.9
OPSONO-7F	10Pn	PIII(M5)	149	149	100	97.6	100	4056.4	3484.2	4722.6
		POST-BOOSTER	145	145	100	97.5	100	5467.5	4698.1	6363.0
	Prev	PIII(M5)	46	32	69.6	54.2	82.3	159.8	74.4	343.6
		POST-BOOSTER	46	43	93.5	82.1	98.6	1038.2	609.9	1767.2
OPSONO-9V	10Pn	PIII(M5)	150	149	99.3	96.3	100	1082.1	918.4	1274.9
		POST-BOOSTER	151	151	100	97.6	100	1707.5	1497.6	1946.8
	Prev	PIII(M5)	48	47	97.9	88.9	99.9	1918.9	1274.3	2889.6
		POST-BOOSTER	44	44	100	92.0	100	5204.0	3842.8	7047.4
OPSONO-14	10Pn	PIII(M5)	150	148	98.7	95.3	99.8	1244.6	1034.9	1496.8
		POST-BOOSTER	150	150	100	97.6	100	1814.6	1577.4	2087.5
	Prev	PIII(M5)	48	48	100	92.6	100	2395.4	1665.4	3445.3
		POST-BOOSTER	46	46	100	92.3	100	3958.4	2888.1	5425.4
OPSONO-18C	10Pn	PIII(M5)	144	129	89.6	83.4	94.1	165.0	126.1	215.9
		POST-BOOSTER	147	147	100	97.5	100	607.9	498.2	741.6
	Prev	PIII(M5)	48	46	95.8	85.7	99.5	361.9	217.4	602.5
		POST-BOOSTER	45	45	100	92.1	100	1723.3	1196.4	2482.3
OPSONO-19F	10Pn	PIII(M5)	149	143	96.0	91.4	98.5	359.2	277.2	465.5
		POST-BOOSTER	149	147	98.7	95.2	99.8	1284.5	1027.2	1606.3
	Prev	PIII(M5)	46	41	89.1	76.4	96.4	77.9	48.8	124.4
		POST-BOOSTER	44	43	97.7	88.0	99.9	277.3	171.6	448.2
OPSONO-23F	10Pn	PIII(M5)	149	146	98.0	94.2	99.6	1619.3	1326.5	1976.7
		POST-BOOSTER	149	148	99.3	96.3	100	2702.9	2234.9	3268.9
	Prev	PIII(M5)	48	47	97.9	88.9	99.9	8525.2	5329.8	13636.2
		POST-BOOSTER	44	43	97.7	88.0	99.9	29918.6	17115.7	52298.1

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

- One month post-booster vaccination, 99.4% of subjects had measurable anti-protein D antibodies concentrations (≥ 100 EL.U/mL) in the 10Pn group. A trend towards lower anti-protein D antibody GMC was observed post-booster vaccination compared to post-primary vaccination in the 10Pn group.

Booster immune response to the co-administered Hib polysaccharide PRP antigen - descriptive analysis results

One month post-booster vaccination, all subjects in both groups had seroprotective anti-PRP antibody concentrations (≥1.0 µg/mL). A trend toward higher anti-PRP antibody GMCs was observed in the 10Pn group compared to the Prev group.

Safety results

The safety analysis was performed on the Total vaccinated cohort (primary analysis) and on the ATP cohort. The results for the ATP cohort for safety were in line with those for the Total vaccinated cohort.

Overall incidence of adverse events:

- During the 31-day post-booster vaccination period, 76.8% and 77.9% of subjects in the 10Pn and Prev groups respectively reported at least one AE (solicited and unsolicited, local and general).
- Regarding the primary endpoint, 12.7% and 11.5% of subjects in the 10Pn and Prev groups respectively reported at least one grade 3 AE (solicited and unsolicited, local and general). Local grade 3 AEs (11.4% and 10.6% of subjects in the 10Pn and Prev groups respectively) tended to be more frequent than general grade 3 AEs (2.1% and 1.8% of subjects in the 10Pn and Prev groups respectively).

Table 18 Incidence and nature of symptoms (solicited and unsolicited) reported during the 31-day (Days 0-30) post-vaccination period (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
10Pn	332	255	76.8	71.9	81.2	332	217	65.4	60.0	70.5	332	184	55.4	49.9	60.8
Prev	113	88	77.9	69.1	85.1	113	70	61.9	52.3	70.9	113	66	58.4	48.8	67.6

10Pn = 10Pn-PD-DiT + Hiberix

Prev = Prevenar + Hiberix

N= number of subjects with the documented dose

n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Solicited local adverse events:

- Redness was the most frequently reported solicited local AE during the 4-day post-booster vaccination period in both groups (42.8% of subjects in the 10Pn group and 48.7% in the Prev group).
- Observed incidences of any solicited local AEs were within the same ranges in both groups.
- Low incidences of grade 3 pain and swelling were reported, ranging from 0.0% (for pain) to 4.2% (for swelling), whatever the group. Although grade 3 redness seemed to be reported more frequently, the incidences were within the same range in both groups (9.0% and 10.6% of subjects in the 10Pn and Prev groups, respectively).
- Four subjects reported large swelling reactions following booster vaccination (all in the 10Pn group). Two of the four large swelling reactions were reported at the Hiberix injection site and 2 at the 10Pn- PD-DiT injection site. All the large swelling reactions were localized swelling at the injection site, not involving the adjacent joints and all resolved without sequelae.

Table 21 Incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort)

			10Pn					Prev				
						95% CI					95% CI	
Symptom	Product	Type	N	n	%	LL	UL	N	n	%	LL	UL
Pain	Total	All	332	120	36.1	31.0	41.6	113	39	34.5	25.8	44.0
		Grade 3	332	7	2.1	0.9	4.3	113	0	0.0	0.0	3.2
		Medical advice	332	2	0.6	0.1	2.2	113	0	0.0	0.0	3.2
	10Pn-PD-DiT	All	332	110	33.1	28.1	38.5	-	-	-	-	-
		Grade 3	332	7	2.1	0.9	4.3	-	-	-	-	-
		Medical advice	332	1	0.3	0.0	1.7	-	-	-	-	-
	Prevenar	All	-	-	-	-	-	113	37	32.7	24.2	42.2
		Grade 3	-	-	-	-	-	113	0	0.0	0.0	3.2
		Medical advice	-	-	-	-	-	113	0	0.0	0.0	3.2
	Hiberix	All	332	89	26.8	22.1	31.9	113	30	26.5	18.7	35.7
		Grade 3	332	5	1.5	0.5	3.5	113	0	0.0	0.0	3.2
		Medical advice	332	1	0.3	0.0	1.7	113	0	0.0	0.0	3.2
Redness (mm)	Total	All	332	142	42.8	37.4	48.3	113	55	48.7	39.2	58.3
		>20.0mm	332	40	12.0	8.7	16.0	113	14	12.4	6.9	19.9
		>30.0mm	332	30	9.0	6.2	12.6	113	12	10.6	5.6	17.8
		Medical advice	332	2	0.6	0.1	2.2	113	0	0.0	0.0	3.2
	10Pn-PD-DiT	All	332	128	38.6	33.3	44.0	-	-	-	-	-
		>20.0mm	332	35	10.5	7.5	14.4	-	-	-	-	-
		>30.0mm	332	22	6.6	4.2	9.9	-	-	-	-	-
		Medical advice	332	1	0.3	0.0	1.7	-	-	-	-	-
	Prevenar	All	-	-	-	-	-	113	51	45.1	35.8	54.8
		>20.0mm	-	-	-	-	-	113	13	11.5	6.3	18.9
		>30.0mm	-	-	-	-	-	113	11	9.7	5.0	16.8
		Medical advice	-	-	-	-	-	113	0	0.0	0.0	3.2
	Hiberix	All	332	106	31.9	26.9	37.2	113	39	34.5	25.8	44.0
		>20.0mm	332	19	5.7	3.5	8.8	113	3	2.7	0.6	7.6
		>30.0mm	332	15	4.5	2.6	7.3	113	3	2.7	0.6	7.6
		Medical advice	332	1	0.3	0.0	1.7	113	0	0.0	0.0	3.2
Swelling (mm)	Total	All	332	97	29.2	24.4	34.4	113	35	31.0	22.6	40.4
		>20.0mm	332	21	6.3	4.0	9.5	113	6	5.3	2.0	11.2
		>30.0mm	332	14	4.2	2.3	7.0	113	3	2.7	0.6	7.6
		Medical advice	332	2	0.6	0.1	2.2	113	0	0.0	0.0	3.2
	10Pn-PD-DiT	All	332	86	25.9	21.3	31.0	-	-	-	-	-
		>20.0mm	332	17	5.1	3.0	8.1	-	-	-	-	-
		>30.0mm	332	10	3.0	1.5	5.5	-	-	-	-	-
		Medical advice	332	1	0.3	0.0	1.7	-	-	-	-	-
	Prevenar	All	-	-	-	-	-	113	34	30.1	21.8	39.4
		>20.0mm	-	-	-	-	-	113	5	4.4	1.5	10.0
		>30.0mm	-	-	-	-	-	113	2	1.8	0.2	6.2
		Medical advice	-	-	-	-	-	113	0	0.0	0.0	3.2
	Hiberix	All	332	60	18.1	14.1	22.6	113	22	19.5	12.6	28.0
		>20.0mm	332	10	3.0	1.5	5.5	113	1	0.9	0.0	4.8
		>30.0mm	332	6	1.8	0.7	3.9	113	1	0.9	0.0	4.8
		Medical advice	332	1	0.3	0.0	1.7	113	0	0.0	0.0	3.2

10Pn = 10Pn-PD-DiT + Hiberix
Prev = Prevenar + Hiberix
N= number of subjects with the documented dose
n/%= number/percentage of subjects reporting at least once the symptom
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

Solicited general adverse events:

- Irritability was the most frequently reported solicited general AE in both groups (42.5% of subjects in the 10Pn group and 37.2% in the Prev group).
- Observed incidences of any solicited general AEs were within the same ranges in both groups.
- A low incidence of grade 3 solicited general AEs was reported and ranged from 0.0% to 1.8% (for irritability) whatever the group. Grade 3 fever (axillary temperature > 39.5°C) was reported by one subject in the Prev group.
  Note: Tympanic measurement was the preferred route of temperature measurement. The statistical tables are standardized and present the axillary measurement. From the point of view of the validity of data, temperature values measured using tympanic route are considered equivalent to those measured using the axillary route.
- A low incidence of grade 3 solicited general AEs considered as causally related to vaccination by the investigator, was reported and ranged from 0.0% to 1.5% (for irritability) whatever the group.

Table 22 Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort)

		10Pn					Prev				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Drowsiness	All	332	75	22.6	18.2	27.5	113	21	18.6	11.9	27.0
	Grade 3	332	0	0.0	0.0	1.1	113	0	0.0	0.0	3.2
	Related	332	55	16.6	12.7	21.0	113	14	12.4	6.9	19.9
	Grade 3 & Related	332	0	0.0	0.0	1.1	113	0	0.0	0.0	3.2
	Medical advice	332	1	0.3	0.0	1.7	113	1	0.9	0.0	4.8
Fever(Axillary) (°C)	All	332	46	13.9	10.3	18.0	113	20	17.7	11.2	26.0
	>38.0°C	332	23	6.9	4.4	10.2	113	7	6.2	2.5	12.3
	>38.5°C	332	8	2.4	1.0	4.7	113	3	2.7	0.6	7.6
	>39.0°C	332	2	0.6	0.1	2.2	113	2	1.8	0.2	6.2
	>39.5°C	332	0	0.0	0.0	1.1	113	1	0.9	0.0	4.8
	Related	332	26	7.8	5.2	11.3	113	15	13.3	7.6	20.9
	>39.5°C & Related	332	0	0.0	0.0	1.1	113	1	0.9	0.0	4.8
	Medical advice	332	10	3.0	1.5	5.5	113	6	5.3	2.0	11.2
Irritability	All	332	141	42.5	37.1	48.0	113	42	37.2	28.3	46.8
	Grade 3	332	6	1.8	0.7	3.9	113	1	0.9	0.0	4.8
	Related	332	102	30.7	25.8	36.0	113	32	28.3	20.2	37.6
	Grade 3 & Related	332	5	1.5	0.5	3.5	113	1	0.9	0.0	4.8
	Medical advice	332	2	0.6	0.1	2.2	113	1	0.9	0.0	4.8
Loss of appetite	All	332	71	21.4	17.1	26.2	113	29	25.7	17.9	34.7
	Grade 3	332	2	0.6	0.1	2.2	113	0	0.0	0.0	3.2
	Related	332	48	14.5	10.9	18.7	113	22	19.5	12.6	28.0
	Grade 3 & Related	332	1	0.3	0.0	1.7	113	0	0.0	0.0	3.2
	Medical advice	332	2	0.6	0.1	2.2	113	1	0.9	0.0	4.8

10Pn = 10Pn-PD-DiT + Hiberix
Prev = Prevenar + Hiberix
N= number of subjects with the documented dose
n/%= number/percentage of subjects reporting at least once the symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Unsolicited adverse events:

- Upper respiratory tract infection was the most frequently reported unsolicited AE in both groups.
- 35.2% and 36.3% of subjects in the 10Pn and Prev groups, respectively, reported at least one unsolicited AE.

- 3.6% and 4.4% of subjects in the 10Pn and Prev groups, respectively, reported at least one unsolicited AE considered by the investigator to be causally related to the vaccination.
- Only one subject (0.3%) in the 10Pn group reported a grade 3 unsolicited AE (i.e. vomiting) which was considered by the investigator to be causally related to the vaccination.

Serious adverse events:

- No fatal events were reported during the study period.
- Twelve subjects reported at least one SAE during the study period: 8 out of 335 vaccinated subjects (2.4%) in the 10Pn group and 4 out of 113 vaccinated subjects (3.5%) in the Prev group.
- None of the reported SAEs were considered by the investigator to be causally related to vaccination and all SAEs resolved without sequelae.

Withdrawals due to adverse events /serious adverse events:

No subject was withdrawn from the study due to a non-serious AE or a SAE.

3. Discussion on clinical aspects

MAH Conclusions:

- The observed incidences of grade 3 AEs (solicited and unsolicited, local and general) as well as the incidences of any solicited local and general AEs were within the same ranges in both groups.
- Incidences of reported grade 3 local symptoms, ranged from 0.0% (for pain) to 10.6% (for redness), whatever the group.
- Low incidences of grade 3 solicited general AEs were reported, ranging from 0.0% to 1.8% whatever the group. No grade 3 fever (axillary temperature > 39.5°C) was reported in subjects boosted with 10Pn-PD-DiT vaccine.
- Only one subject (0.3%) in the 10Pn group reported a grade 3 unsolicited AEs, which was considered by the investigator to be causally related to the vaccination.
- 8 out of 335 vaccinated subjects (2.4%) in the 10Pn group and 4 out of 113 vaccinated subjects (3.5%) in the Prev group reported at least one SAE during the study period. None of the reported SAEs were considered by the investigator to be causally related to vaccination and all SAEs resolved without sequelae. No fatal events were reported during the entire study period.
- One month post-booster vaccination, in the group boosted with 10Pn-PD-DiT, at least 97.5% of subjects had antibody concentrations ≥0.2 µg/mL and at least 94.6% of subjects had OPA titres ≥8 for each of the 10 pneumococcal vaccine serotypes. These percentages were at least 98.0% and 97.7% of subjects in the group boosted with Prevenar for each of the 7 common pneumococcal serotypes.
- The observed antibody GMCs and OPA GMTs were higher for subjects boosted with Prevenar compared to 10Pn-PD-DiT (no overlap of 95% CIs), for each of the 7 common pneumococcal serotypes except for serotype 18C (for which the antibody GMC was in the same range in both groups) and 19F (for which the antibody GMC and OPA GMT were higher in subjects boosted with 10Pn-PD-DiT compared to Prevenar). This trend was consistent with what was observed in the primary vaccination study 10PN-PD-DIT-036.
- One month post-booster vaccination, 99.4% of subjects boosted with 10Pn-PD-DiT had measurable anti-protein D antibody concentrations (≥100 EL.U/mL).
- In both groups, all subjects reached seroprotective anti-PRP antibody concentrations ≥1.0 µg/mL, one month post-booster vaccination.
- The 10Pn-PD-DiT vaccine was immunogenic and well tolerated when given as a booster (fourth) dose at 12-18 months of age co-administered with Hiberix in Korean children primed with the same vaccines.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The results of study 063 are in generally in accordance with what has been reported from other booster studies although no pre-booster responses were measured in this study.

- **Recommendation** *Note: please tick the appropriate box*

☐ **Fulfilled –**

No further action required