20 February 2015
EMA/85312/2015 rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Synflorix

(Pneumococcal polysaccharide conjugate vaccine, adsorbed)

Procedure No. EMEA/H/C/000973

P46 042 and 043

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 2011-07-08, the MAH submitted completed paediatric studies 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 studies do 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 studies

The formulation used in the clinical studies was the same as for the marketed product.

II.2 Clinical aspects

1. Introduction

The MAH submitted final reports for:

- **10PN-PD-DIT-009;** A phase II, observer-blind follow-up study with two groups to assess the reactogenicity and immunogenicity of GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine (GSK1024850A), when either given as a booster dose in primed children or as a twodose catch-up immunization in unprimed children.
- **10PN-PD-DIT-016**; Not assessed in this report.
- **10PN-PD-DIT-018;** A phase IIIb, observer-blind, controlled study to assess the safety, reactogenicity and immunogenicity of GlaxoSmithKline (GSK) Biologicals. 10-valent pneumococcal conjugate vaccine or Prevenar when given as a booster dose between 12-18 months of age in children previously vaccinated in the primary study 10PN-PD-DIT-012 (107007) with either GSK Biologicals. 10-valent pneumococcal conjugate vaccine or Prevenar.
- **10PN-PD-DIT-029;** A phase III, single group, open study to assess the immunogenicity, safety and reactogenicity of GlaxoSmithKline (GSK) Biologicals. 10-valent pneumococcal conjugate vaccine in Mexico when co-administered with GSK Biologicals. Infanrix hexa (DTPa-HBV-IPV/Hib) vaccine as a 3-dose primary immunization course at 2, 4 and 6 months of age and GSK Biologicals. Rotarix vaccine (HRV) as a 2-dose primary immunization course at 2 and 4 months of age.
- **10PN-PD-DIT-031;** Primary vaccination course in children receiving the pneumococcal vaccine GSK 1024850A, Infanrix hexa and Rotarix.
- **10PN-PD-DIT-014**; Not assessed in this report.
- **10PN-PD-DIT-046**; Not assessed in this report.
- **10PN-PD-DIT-061**; Not assessed in this report.
- **10PN-PD-DIT-032;** A phase III, randomized, open, controlled study to assess the immunogenicity, safety and reactogenicity of GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine as a 3-dose primary immunization course at 6, 10 and 14 weeks of age in Sub-Saharan Africa, coadministered with GSK Biologicals' DTPw-HBV/Hib and OPV vaccines.
- **10PN-PD-DIT-037**; A phase III, randomized, single-blind, controlled study to assess the immunogenicity, safety and reactogenicity of GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine as a 3-dose primary immunization course at 6, 10 and 14 weeks of age in India, co-administered with GSK Biologicals' Tritanrix-HepB/Hib (DTPw-HBV/Hib) vaccine.
- **10PN-PD-DIT-048**; A phase III, multi-centre, double-blind, randomised study to assess the noninferiority of a commercial lot of GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate (10Pn-PD-DiT) vaccine compared to a clinical phase III vaccine lot, when given as a threedose primary immunization course.

Studies 014, 016, 061 and 046 were submitted and assessed previously as part of other regulatory procedures and will not be discussed further in this AR.

2. Clinical studies

10PN-PD-DIT-009; A phase II, observer-blind follow-up study with two groups to assess the reactogenicity and immunogenicity of GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine (GSK1024850A), when either given as a booster dose in primed children or as a two-dose catch-up immunization in unprimed children

➢ **Description**

A phase II, observer-blind follow-up study with two groups to assess the reactogenicity and immunogenicity of GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine (GSK1024850A), when either given as a booster dose (at 20-23 months of age) in children previously primed with three doses of the study vaccine, or when given as a two-dose catch-up immunization (at 18-21 and 20-23 months of age) in unprimed children, all previously enrolled in the 10PN-PD-DIT-005 primary vaccination study. The study was conducted in Chile.

➢ **Methods**

- Objective(s)

Primary:

- To assess the reactogenicity of study vaccines in terms of the occurrence of adverse events with intensity grade 3.

Secondary:

- To assess the safety and reactogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine after the administration of any vaccine dose.
- To assess, 12 to 15 months after completion of the 3-dose primary vaccination course, the persistence of antibodies induced by GSK Biologicals' 10-valent pneumococcal conjugate vaccine.
- To assess, one month post-booster, the immunogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine in subjects primed with GSK Biologicals' 10-valent pneumococcal conjugate vaccine.
- To assess, one month after the second catch-up dose, the immunogenicity of GSK Biologicals' 10- valent pneumococcal conjugate vaccine in subjects primed with hepatitis A vaccine.
- To assess, three months after the hepatitis A dose, the immunogenicity of hepatitis A vaccine, when co-administered with DTPa-HBV-IPV/Hib vaccine, in subjects unprimed with hepatitis A vaccine.

- Study design

Observer-blind follow-up study with two groups:

- Primed 10V group (referred as 'HAV-Pn' in result tables and figures): approximately 120 subjects received hepatitis A + DTPa-HBV-IPV/Hib (dose 1) and 10Pn-PD-DiT (dose 2).
- Unprimed 10V group (referred as 'Pn-Pn' in result tables and figures): approximately 120 subjects received 10Pn-PD-DiT + DTPa-HBV-IPV/Hib (catch-up dose 1) and 10Pn-PD-DiT (catch-up dose 2).

Booster vaccination study of the primary vaccination study 10PN-PD-DIT-005 (106208) at 18-21 and 20-23 months of age, with at least 2 months between the 2 vaccinations.
Two blood samples were collected: prior to dose 1 and one month post-dose 2.

- Study population /Sample size

Diagnosis and criteria for inclusion:

- Male or female between, and including 18-21 months of age at the time of vaccination.
- Subjects who received 3 doses of study or control vaccines in the primary vaccination study 10PNPD- DIT-005 (106208).
- Written informed consent obtained from the parents or guardians of the subject.
- Free of obvious health problems as established by medical history and clinical examination before entering into the study.

Sample size
The sample size was contingent on the number of subjects eligible after the primary course. In the primary vaccination study 10PN-PD-DIT-005 (106208), 240 subjects (120 subjects per group) were planned to be enrolled. Assuming that approximately 10% of these subjects might not enter the booster study, one could consider approximately 216 subjects receiving the booster doses (108 subjects in each group).

- Treatments

Visit	Vaccination	Dose	Vaccine group[1]	Route[2]	Site[3]	Side[4]
1	Infanrix hexa	Dose 1	Primed 10V group	IM	T/D	L
	Havrix		Primed 10V group	IM	T/D	R
	Infanrix hexa		Unprimed 10V group	IM	T/D	L
	10Pn-PD-DiT		Unprimed 10V group	IM	T/D	R
2	10Pn-PD-DiT	Dose 2	Primed 10V group	IM	T/D	R
	10Pn-PD-DiT		Unprimed 10V group	IM	T/D	R

[1]Vaccine / Control
[2]Intramuscular (IM)
[3]Thigh (T)/Deltoid (D)
[4]Left (L)/ Right (R)

- Outcomes/endpoints

Primary endpoint
Occurrence of grade 3 adverse events (solicited and unsolicited) within 4 days (day 0 - day 3) after the administration of any study vaccine dose.
Secondary endpoints
Safety and Reactogenicity
Occurrence of solicited local adverse events (any and grade 3) within 4 days (day 0- day 3) after the administration of each of the study vaccine doses.
Occurrence of solicited general adverse events (any and grade 3) within 4 days (day 0-day 3) after the administration of each of the study vaccine doses.
Occurrence of unsolicited adverse events within 31 days (day 0-day 30) after the administration of the study vaccine doses.
Occurrence of serious adverse events throughout the active phase of the study (from the first study dose up to Visit 3).
Occurrence of serious adverse events throughout the entire study period (from the first study dose up to the end of the extended safety follow-up (phone contact)).
Immunogenicity
Prior to any vaccination and one month after administration of dose 2:

- Antibody concentrations against pneumococcal serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.
- Anti-pneumococcal serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F antibody concentrations ≥0.20 µg/mL.
- Opsonophagocytic activity against pneumococcal serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.
- Antibody concentrations against protein D.
- Anti-HAV antibody concentrations.

Seropositivity status, defined as:

- Anti-pneumococcal serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F antibody concentrations ≥ 0.05 µg/mL.
- Opsonophagocytic activity against pneumococcal serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F ≥ 8.
- Anti-PD antibody concentrations ≥ 100 EL.U/mL.
- Anti-HAV antibody concentrations ≥ 15 mIU/mL.

- Statistical Methods

Safety/reactogenicity:

Descriptive analyses:

- 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 adverse event, the intensity and relationship to vaccination;
- Incidence of each local and each general solicited adverse events 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 adverse events, the intensity and relationship to vaccination;
- The percentages of subjects with an unsolicited adverse events 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 (SAEs), large swelling reactions and withdrawals due to adverse event(s) reported during the active phase of the study (Visit 1 to Visit 3) were described in detail;
- SAEs recorded throughout the entire study period starting from Visit 1 up to the end of the extended 6 months safety follow-up were described in detail.

Immunogenicity:

Descriptive analyses:

- Geometric mean antibody concentrations/titres (GMCs/GMTs) with 95% CIs were tabulated for each appropriate serotype/antigen at each applicable blood sampling time point.
- Seropositivity rates with exact 95% CIs were calculated for each appropriate serotype/antigen at each applicable blood sampling time point.
- The distribution of antibody concentrations/titres was displayed by using tables and/or reverse cumulative distribution curves for each appropriate serotype/antigen at each applicable blood sampling time point.
- Geometric mean of ratios of opsonophagocytic titres/ELISA antibody concentrations with 95% CIs was tabulated for each appropriate pneumococcal serotype at each applicable blood sampling time point.

➢ **Results**

- Recruitment/ Number analysed

Demography:

Out of the 163 enrolled subjects, 155 completed the study. The mean age at the first visit (dose 1) was 18.3 months. Overall, 50.9% of the subjects were female and 99.4% were White/Caucasian.

- Efficacy results

Immunogenicity:

The analysis was performed on the ATP cohort of antibody persistence or on the ATP cohort of immunogenicity according to the objective. Data on OPA analysis and the immune response to the hepatitis A vaccine need to be interpreted with caution because of the relatively small sample size of the groups. The results are summarized in Table 31 and 32 below.

Persistence:

At least 88.9% of subjects in the HAV-Pn group remained seropositive (antibody concentrations ≥ 0.05 µg/mL) to each of the vaccine pneumococcal serotypes indicative for persistence of the antibodies to the pneumococcal vaccine antigens 15 to 18 months after completion of the three-dose primary vaccination course.

Before administration of dose 1 in the booster vaccination study, the percentage of subjects in the 10Pn group with opsonophagocytic activity ≥ 8 was at least 86.4% for serotypes 7F, 9V, 14 and 23F and between 38.9% and 65.0% for serotypes 1, 4, 5, 6B and 18C.

All subjects in the Pn-Pn group remained seropositive for antibodies against hepatitis A indicative for persistence of the immune response to the hepatitis A vaccine 15 to 18 months after completion of the three-dose primary vaccination course (data not shown in this AR).

Booster response to the pneumococcal vaccine:

One month following the 2-dose catch-up vaccination in the Pn-Pn group, the percentage of subjects with pneumococcal antibody concentrations ≥ 0.2 µg/mL was high (over 94.0%) and in the same range compared to the HAV-Pn group for most serotypes except serotype 6B

(84.3% in the Pn-Pn group and 97.4% in the HAV-Pn group). The antibody GMCs were lower for serotypes 1, 5, 6B, 9V, 14, 19F and 23F in the Pn-Pn group compared to the HAV-Pn group (no overlap of 95% CIs). There was also a trend for lower GMCs for the other vaccine pneumococcal serotypes in the Pn-Pn group compared to the HAV-Pn group.
For the HAV-Pn group, for each of the vaccine pneumococcal serotypes, one month postdose 2, at least 96.2% of subjects had opsonophagocytic activity ≥8, except for serotype 6B (91.7%).
One month post-dose 2, at least 95.2% of the subjects in the Pn-Pn group had opsonophagocytic activity ≥ 8 except for serotypes 6B (48.1%), 1 (52.0%) and 5 (84.0%) and this percentage was lower for serotypes 1 and 6B compared to the HAV-Pn group (no overlap of 95% CIs). The OPA GMTs were lower for serotypes 1, 4, 5, 6B and 19F in the Pn-Pn group compared to the HAV-Pn group (no overlap of 95% CIs).

Table 31 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	HAV-Pn	PIII(M5)	81	81	100	95.5	100	81	100	95.5	100	2.31	1.93	2.77
		PRE-BOOSTER	79	72	91.1	82.6	96.4	43	54.4	42.8	65.7	0.20	0.16	0.25
		POST-BOOSTER	78	78	100	95.4	100	78	100	95.4	100	4.28	3.54	5.18
	Pn-Pn	PIII(M5)	70	8	11.4	5.1	21.3	2	2.9	0.3	9.9	0.03	0.03	0.04
		PRE-BOOSTER	72	14	19.4	11.1	30.5	1	1.4	0.0	7.5	0.03	0.03	0.04
		POST-BOOSTER	70	70	100	94.9	100	70	100	94.9	100	2.38	1.94	2.93
ANTI-4	HAV-Pn	PIII(M5)	81	80	98.8	93.3	100	80	98.8	93.3	100	3.29	2.67	4.05
		PRE-BOOSTER	75	72	96.0	88.8	99.2	45	60.0	48.0	71.1	0.27	0.21	0.33
		POST-BOOSTER	77	77	100	95.3	100	77	100	95.3	100	7.81	6.37	9.57
	Pn-Pn	PIII(M5)	66	3	4.5	0.9	12.7	0	0.0	0.0	5.4	0.03	0.02	0.03
		PRE-BOOSTER	73	11	15.1	7.8	25.4	3	4.1	0.9	11.5	0.03	0.03	0.04
		POST-BOOSTER	70	70	100	94.9	100	70	100	94.9	100	5.88	4.99	6.94
ANTI-5	HAV-Pn	PIII(M5)	81	81	100	95.5	100	81	100	95.5	100	3.17	2.70	3.73
		PRE-BOOSTER	76	74	97.4	90.8	99.7	58	76.3	65.2	85.3	0.36	0.30	0.44
		POST-BOOSTER	78	78	100	95.4	100	77	98.7	93.1	100	4.07	3.26	5.10
	Pn-Pn	PIII(M5)	70	20	28.6	18.4	40.6	4	5.7	1.6	14.0	0.04	0.03	0.05
		PRE-BOOSTER	70	29	41.4	29.8	53.8	7	10.0	4.1	19.5	0.05	0.04	0.07
		POST-BOOSTER	70	70	100	94.9	100	70	100	94.9	100	2.14	1.79	2.57
ANTI-6B	HAV-Pn	PIII(M5)	81	78	96.3	89.6	99.2	74	91.4	83.0	96.5	1.23	0.93	1.62
		PRE-BOOSTER	76	71	93.4	85.3	97.8	55	72.4	60.9	82.0	0.51	0.36	0.73
		POST-BOOSTER	78	77	98.7	93.1	100	76	97.4	91.0	99.7	3.24	2.42	4.35
	Pn-Pn	PIII(M5)	72	22	30.6	20.2	42.5	3	4.2	0.9	11.7	0.04	0.03	0.05
		PRE-BOOSTER	73	6	8.2	3.1	17.0	1	1.4	0.0	7.4	0.03	0.03	0.03
		POST-BOOSTER	70	67	95.7	88.0	99.1	59	84.3	73.6	91.9	0.71	0.53	0.95
ANTI-7F	HAV-Pn	PIII(M5)	81	81	100	95.5	100	81	100	95.5	100	4.42	3.77	5.18
		PRE-BOOSTER	70	70	100	94.9	100	60	85.7	75.3	92.9	0.57	0.46	0.72
		POST-BOOSTER	78	78	100	95.4	100	77	98.7	93.1	100	5.43	4.50	6.55
	Pn-Pn	PIII(M5)	72	21	29.2	19.0	41.1	2	2.8	0.3	9.7	0.04	0.03	0.05
		PRE-BOOSTER	68	15	22.1	12.9	33.8	8	11.8	5.2	21.9	0.04	0.03	0.05
		POST-BOOSTER	70	70	100	94.9	100	70	100	94.9	100	3.97	3.42	4.61
ANTI-9V	HAV-Pn	PIII(M5)	81	81	100	95.5	100	80	98.8	93.3	100	2.81	2.30	3.44
		PRE-BOOSTER	78	78	100	95.4	100	71	91.0	82.4	96.3	0.60	0.49	0.73
		POST-BOOSTER	79	79	100	95.4	100	79	100	95.4	100	6.89	5.74	8.28
	Pn-Pn	PIII(M5)	73	9	12.3	5.8	22.1	5	6.8	2.3	15.3	0.03	0.03	0.04
		PRE-BOOSTER	72	12	16.7	8.9	27.3	6	8.3	3.1	17.3	0.04	0.03	0.05
		POST-BOOSTER	70	70	100	94.9	100	69	98.6	92.3	100	2.22	1.81	2.73
ANTI-14	HAV-Pn	PIII(M5)	81	81	100	95.5	100	81	100	95.5	100	4.40	3.50	5.54
		PRE-BOOSTER	76	74	97.4	90.8	99.7	69	90.8	81.9	96.2	0.96	0.71	1.31
		POST-BOOSTER	79	79	100	95.4	100	79	100	95.4	100	10.75	8.27	13.98
	Pn-Pn	PIII(M5)	72	47	65.3	53.1	76.1	15	20.8	12.2	32.0	0.09	0.07	0.11
		PRE-BOOSTER	71	49	69.0	56.9	79.5	20	28.2	18.1	40.1	0.12	0.08	0.18
		POST-BOOSTER	70	70	100	94.9	100	70	100	94.9	100	4.81	3.99	5.78

ANTI-18C	HAV-Pn	PIII(M5)	81	80	98.8	93.3	100	80	98.8	93.3	100	6.63	5.21	8.43
		PRE-BOOSTER	77	76	98.7	93.0	100	68	88.3	79.0	94.5	0.64	0.51	0.81
		POST-BOOSTER	78	78	100	95.4	100	78	100	95.4	100	14.33	11.45	17.93
	Pn-Pn	PIII(M5)	68	13	19.1	10.6	30.5	4	5.9	1.6	14.4	0.03	0.03	0.04
		PRE-BOOSTER	73	18	24.7	15.3	36.1	5	6.8	2.3	15.3	0.04	0.03	0.05
		POST-BOOSTER	70	70	100	94.9	100	70	100	94.9	100	12.73	10.52	15.40
ANTI-19F	HAV-Pn	PIII(M5)	81	81	100	95.5	100	81	100	95.5	100	10.44	8.78	12.40
		PRE-BOOSTER	80	80	100	95.5	100	76	95.0	87.7	98.6	1.35	0.99	1.84
		POST-BOOSTER	78	78	100	95.4	100	78	100	95.4	100	13.93	11.10	17.50
	Pn-Pn	PIII(M5)	70	34	48.6	36.4	60.8	12	17.1	9.2	28.0	0.07	0.05	0.09
		PRE-BOOSTER	72	29	40.3	28.9	52.5	19	26.4	16.7	38.1	0.07	0.05	0.11
		POST-BOOSTER	70	70	100	94.9	100	70	100	94.9	100	8.70	7.20	10.51
ANTI-23F	HAV-Pn	PIII(M5)	81	79	97.5	91.4	99.7	75	92.6	84.6	97.2	1.71	1.28	2.28
		PRE-BOOSTER	76	73	96.1	88.9	99.2	59	77.6	66.6	86.4	0.54	0.39	0.74
		POST-BOOSTER	78	78	100	95.4	100	78	100	95.4	100	4.29	3.42	5.38
	Pn-Pn	PIII(M5)	70	16	22.9	13.7	34.4	4	5.7	1.6	14.0	0.04	0.03	0.05
		PRE-BOOSTER	71	15	21.1	12.3	32.4	3	4.2	0.9	11.9	0.04	0.03	0.04
		POST-BOOSTER	70	70	100	94.9	100	66	94.3	86.0	98.4	1.08	0.85	1.36

HAV-Pn = Dose 1: Havrix + DTPa-HBV-IPV/Hib / Dose2: 10Pn-PD-DiT (primed with 10Pn-PD-DiT)
Pn-Pn = Dose 1: 10Pn-PD-DiT + DTPa-HBV-IPV/Hib / Dose2: 10Pn-PD-DiT (primed with Havrix)
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)
PRE-BOOSTER = Pre-vaccination blood sample (booster phase)
POST-BOOSTER (HAV-Pn group) = one month after booster dose (booster phase)
POST-BOOSTER (Pn-Pn group) = one month after catch-up dose II (booster phase)

Table 32 **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	HAV-Pn	PIII(M5)	33	26	78.8	61.1	91.0	85.2	40.0	181.1
		PRE-BOOSTER	28	12	42.9	24.5	62.8	10.6	6.5	17.1
		POST-BOOSTER	25	25	100	86.3	100	647.0	310.2	1349.6
	Pn-Pn	PIII(M5)	32	1	3.1	0.1	16.2	4.6	3.5	6.0
		PRE-BOOSTER	25	1	4.0	0.1	20.4	4.5	3.6	5.6
		POST-BOOSTER	25	13	52.0	31.3	72.2	17.5	9.0	34.1
OPSONO-4	HAV-Pn	PIII(M5)	32	32	100	89.1	100	603.0	438.2	829.7
		PRE-BOOSTER	17	7	41.2	18.4	67.1	21.0	6.9	63.8
		POST-BOOSTER	24	24	100	85.8	100	1693.8	1083.4	2647.9
	Pn-Pn	PIII(M5)	32	1	3.1	0.1	16.2	4.2	3.8	4.6
		PRE-BOOSTER	19	1	5.3	0.1	26.0	4.3	3.7	5.1
		POST-BOOSTER	18	18	100	81.5	100	585.4	343.9	996.4
OPSONO-5	HAV-Pn	PIII(M5)	33	31	93.9	79.8	99.3	147.4	91.3	238.1
		PRE-BOOSTER	19	13	68.4	43.4	87.4	22.0	10.6	45.6
		POST-BOOSTER	20	20	100	83.2	100	297.0	171.4	514.4
	Pn-Pn	PIII(M5)	30	1	3.3	0.1	17.2	4.5	3.5	5.7
		PRE-BOOSTER	23	1	4.3	0.1	21.9	4.5	3.5	5.9
		POST-BOOSTER	25	21	84.0	63.9	95.5	33.5	19.2	58.5
OPSONO-6B	HAV-Pn	PIII(M5)	33	31	93.9	79.8	99.3	600.9	343.1	1052.5
		PRE-BOOSTER	22	12	54.5	32.2	75.6	26.3	9.2	74.9
		POST-BOOSTER	24	22	91.7	73.0	99.0	1043.4	425.9	2555.9
	Pn-Pn	PIII(M5)	29	4	13.8	3.9	31.7	8.2	4.1	16.7
		PRE-BOOSTER	25	3	12.0	2.5	31.2	7.2	3.4	15.1
		POST-BOOSTER	27	13	48.1	28.7	68.1	54.6	16.7	178.8
OPSONO-7F	HAV-Pn	PIII(M5)	32	32	100	89.1	100	4089.5	2637.8	6340.0
		PRE-BOOSTER	17	16	94.1	71.3	99.9	1157.2	467.4	2864.9
		POST-BOOSTER	25	25	100	86.3	100	3994.8	2872.7	5555.1
	Pn-Pn	PIII(M5)	18	12	66.7	41.0	86.7	193.6	45.2	829.2
		PRE-BOOSTER	12	4	33.3	9.9	65.1	37.9	3.8	380.2
		POST-BOOSTER	26	26	100	86.8	100	4159.6	2572.7	6725.3
OPSONO-9V	HAV-Pn	PIII(M5)	33	33	100	89.4	100	1364.6	878.9	2118.7
		PRE-BOOSTER	20	20	100	83.2	100	512.2	318.1	824.6
		POST-BOOSTER	23	23	100	85.2	100	2515.9	1667.1	3796.8
	Pn-Pn	PIII(M5)	28	3	10.7	2.3	28.2	6.1	3.7	9.9
		PRE-BOOSTER	17	11	64.7	38.3	85.8	57.4	19.1	172.7
		POST-BOOSTER	23	22	95.7	78.1	99.9	1494.3	700.6	3187.2
OPSONO-14	HAV-Pn	PIII(M5)	33	31	93.9	79.8	99.3	736.5	414.0	1310.5
		PRE-BOOSTER	16	14	87.5	61.7	98.4	308.6	95.8	993.7
		POST-BOOSTER	21	21	100	83.9	100	2380.5	1269.3	4464.4
	Pn-Pn	PIII(M5)	26	5	19.2	6.6	39.4	8.8	4.4	17.5
		PRE-BOOSTER	11	5	45.5	16.7	76.6	25.7	5.9	111.4
		POST-BOOSTER	25	25	100	86.3	100	1828.1	1243.1	2688.3
OPSONO-18C	HAV-Pn	PIII(M5)	31	30	96.8	83.3	99.9	295.4	194.9	447.7
		PRE-BOOSTER	29	12	41.4	23.5	61.1	10.7	6.0	19.1
		POST-BOOSTER	26	25	96.2	80.4	99.9	830.8	438.6	1573.8
	Pn-Pn	PIII(M5)	17	1	5.9	0.1	28.7	4.4	3.6	5.4
		PRE-BOOSTER	28	3	10.7	2.3	28.2	6.5	3.4	12.3
		POST-BOOSTER	27	27	100	87.2	100	704.8	389.6	1275.0

OPSONO-19F	HAV-Pn	PIII(M5)	31	30	96.8	83.3	99.9	609.8	340.5	1092.1
		PRE-BOOSTER	22	17	77.3	54.6	92.2	33.6	15.6	72.1
		POST-BOOSTER	20	20	100	83.2	100	1283.6	693.1	2377.2
	Pn-Pn	PIII(M5)	18	0	0.0	0.0	18.5	4.0	4.0	4.0
		PRE-BOOSTER	23	2	8.7	1.1	28.0	4.6	3.8	5.6
		POST-BOOSTER	21	20	95.2	76.2	99.9	237.4	115.0	490.1
OPSONO-23F	HAV-Pn	PIII(M5)	33	31	93.9	79.8	99.3	928.3	472.0	1825.5
		PRE-BOOSTER	21	18	85.7	63.7	97.0	442.7	170.2	1151.0
		POST-BOOSTER	25	25	100	86.3	100	3718.5	2577.2	5365.2
	Pn-Pn	PIII(M5)	29	5	17.2	5.8	35.8	8.1	4.2	15.6
		PRE-BOOSTER	16	8	50.0	24.7	75.3	93.4	15.9	549.7
		POST-BOOSTER	25	25	100	86.3	100	3203.1	2234.7	4591.0

HAV-Pn = Dose 1: Havrix + DTPa-HBV-IPV/Hib / Dose2: 10Pn-PD-DiT (primed with 10Pn-PD-DiT)
Pn-Pn = Dose 1: 10Pn-PD-DiT + DTPa-HBV-IPV/Hib / Dose2: 10Pn-PD-DiT (primed with Havrix)

Assessor's comment: The OPA GMTs to serotypes 1, 4, 5, 6B and 19F after two catch-up doses were considerably lower than the responses to a single booster dose in the previously primed infants. The percentage of subjects with OPA titers ≥8 were also low for serotypes 1 and 6B. Similarly low OPA responses to serotypes 1 and 5 were seen in study 013, assessed in the original MAA. The OPA responder rates after the primary three doses in group HAV-Pn were considerably higher for serotypes 1, 5 and 6B compared to the response rate after 2 catch-up doses the Pn-Pn group. However, the sample size is small and the 95% CI are wide in all cases, which preclude any firm conclusions. The MAH already has a FUM to evaluate the booster response following a 2-dose catch-up vaccination.

- Safety results

Safety/reactogenicity:

The safety analysis was performed on the Total vaccinated cohort.

Redness in the HAV-Pn group and pain in the Pn-Pn group were the most frequently reported grade 3 solicited local adverse events (maximum 15.3%) whereas pain was the most frequently reported in both groups, regardless the injection site (51.5% and 66.0%, respectively).

No increase in the overall incidence of local adverse events was observed in the Pn-Pn group with consecutive doses of the 10Pn-PD-DiT vaccine during the catch-up vaccination course.

The observed percentage of doses followed by at least one unsolicited adverse event, classified by the MedDRA Primary System Organ Class and Preferred Term, was 35.3% in the HAV-Pn group and 41.3% in the Pn-Pn group. The most frequently reported unsolicited adverse event in both groups was bronchitis.

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

			HAV-Pn					Pn-Pn				
						95 % CI					95 % CI	
Symptom	Product	Type	N	n	%	LL	UL	N	n	%	LL	UL
Pain	Total	All	165	85	51.5	43.6	59.4	150	99	66.0	57.8	73.5
		Grade 3	165	10	6.1	2.9	10.9	150	23	15.3	10.0	22.1
		Medical advice	165	2	1.2	0.1	4.3	150	2	1.3	0.2	4.7
	10Pn-PD-DiT	All	82	42	51.2	39.9	62.4	150	90	60.0	51.7	67.9
		Grade 3	82	8	9.8	4.3	18.3	150	19	12.7	7.8	19.1
		Medical advice	82	0	0.0	0.0	4.4	150	2	1.3	0.2	4.7
	DTPa-HBV-IPV/Hib	All	83	41	49.4	38.2	60.6	78	59	75.6	64.6	84.7
		Grade 3	83	2	2.4	0.3	8.4	78	15	19.2	11.2	29.7
		Medical advice	83	2	2.4	0.3	8.4	78	2	2.6	0.3	9.0
	Havrix	All	83	29	34.9	24.8	46.2	-	-	-	-	-
		Grade 3	83	0	0.0	0.0	4.3	-	-	-	-	-
		Medical advice	83	1	1.2	0.0	6.5	-	-	-	-	-
Redness (mm)	Total	All	165	69	41.8	34.2	49.7	150	72	48.0	39.8	56.3
		>20.0 mm	165	26	15.8	10.6	22.2	150	18	12.0	7.3	18.3
		>30.0 mm	165	24	14.5	9.5	20.9	150	14	9.3	5.2	15.2
		Medical advice	165	4	2.4	0.7	6.1	150	3	2.0	0.4	5.7
	10Pn-PD-DiT	All	82	27	32.9	22.9	44.2	150	55	36.7	29.0	44.9
		>20.0 mm	82	6	7.3	2.7	15.2	150	11	7.3	3.7	12.7
		>30.0 mm	82	4	4.9	1.3	12.0	150	6	4.0	1.5	8.5
		Medical advice	82	0	0.0	0.0	4.4	150	3	2.0	0.4	5.7
	DTPa-HBV-IPV/Hib	All	83	40	48.2	37.1	59.4	78	42	53.8	42.2	65.2
		>20.0 mm	83	20	24.1	15.4	34.7	78	13	16.7	9.2	26.8
		>30.0 mm	83	20	24.1	15.4	34.7	78	13	16.7	9.2	26.8
		Medical advice	83	4	4.8	1.3	11.9	78	3	3.8	0.8	10.8
	Havrix	All	83	17	20.5	12.4	30.8	-	-	-	-	-
		>20.0 mm	83	1	1.2	0.0	6.5	-	-	-	-	-
		>30.0 mm	83	0	0.0	0.0	4.3	-	-	-	-	-
		Medical advice	83	1	1.2	0.0	6.5	-	-	-	-	-
Swelling (mm)	Total	All	165	58	35.2	27.9	43.0	150	62	41.3	33.4	49.7
		>20.0 mm	165	20	12.1	7.6	18.1	150	19	12.7	7.8	19.1
		>30.0 mm	165	16	9.7	5.6	15.3	150	14	9.3	5.2	15.2
		Medical advice	165	4	2.4	0.7	6.1	150	4	2.7	0.7	6.7
	10Pn-PD-DiT	All	82	23	28.0	18.7	39.1	150	47	31.3	24.0	39.4
		>20.0 mm	82	2	2.4	0.3	8.5	150	12	8.0	4.2	13.6
		>30.0 mm	82	1	1.2	0.0	6.6	150	8	5.3	2.3	10.2
		Medical advice	82	0	0.0	0.0	4.4	150	3	2.0	0.4	5.7
	DTPa-HBV-IPV/Hib	All	83	33	39.8	29.2	51.1	78	39	50.0	38.5	61.5
		>20.0 mm	83	18	21.7	13.4	32.1	78	16	20.5	12.2	31.2
		>30.0 mm	83	15	18.1	10.5	28.0	78	12	15.4	8.2	25.3
		Medical advice	83	4	4.8	1.3	11.9	78	4	5.1	1.4	12.6
	Havrix	All	83	10	12.0	5.9	21.0	-	-	-	-	-
		>20.0 mm	83	0	0.0	0.0	4.3	-	-	-	-	-
		>30.0 mm	83	0	0.0	0.0	4.3	-	-	-	-	-
		Medical advice	83	0	0.0	0.0	4.3	-	-	-	-	-

Pn-Pn = Dose 1: 10Pn-PD-DiT + DTPa-HBV-IPV/Hib / Dose2: 10Pn-PD-DiT (primed with Havrix)
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.
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

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

		HAV-Pn					Pn-Pn				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Drowsiness	All	165	44	26.7	20.1	34.1	150	44	29.3	22.2	37.3
	Grade 3	165	2	1.2	0.1	4.3	150	1	0.7	0.0	3.7
	Related	165	38	23.0	16.8	30.2	150	40	26.7	19.8	34.5
	Grade 3 & Related	165	2	1.2	0.1	4.3	150	1	0.7	0.0	3.7
	Medical advice	165	2	1.2	0.1	4.3	150	1	0.7	0.0	3.7
Fever (Rectally) (°C)	All	165	36	21.8	15.8	28.9	150	45	30.0	22.8	38.0
	>38.5°C	165	14	8.5	4.7	13.8	150	22	14.7	9.4	21.4
	>39.0°C	165	10	6.1	2.9	10.9	150	11	7.3	3.7	12.7
	>39.5°C	165	4	2.4	0.7	6.1	150	3	2.0	0.4	5.7
	>40.0°C	165	1	0.6	0.0	3.3	150	1	0.7	0.0	3.7
	Related	165	33	20.0	14.2	26.9	150	41	27.3	20.4	35.2
	>40.0°C & Related	165	1	0.6	0.0	3.3	150	1	0.7	0.0	3.7
	Medical advice	165	2	1.2	0.1	4.3	150	2	1.3	0.2	4.7
Irritability	All	165	78	47.3	39.5	55.2	150	87	58.0	49.7	66.0
	Grade 3	165	3	1.8	0.4	5.2	150	12	8.0	4.2	13.6
	Related	165	74	44.8	37.1	52.8	150	82	54.7	46.3	62.8
	Grade 3 & Related	165	3	1.8	0.4	5.2	150	12	8.0	4.2	13.6
	Medical advice	165	2	1.2	0.1	4.3	150	1	0.7	0.0	3.7
Loss of appetite	All	165	46	27.9	21.2	35.4	150	44	29.3	22.2	37.3
	Grade 3	165	5	3.0	1.0	6.9	150	6	4.0	1.5	8.5
	Related	165	38	23.0	16.8	30.2	150	36	24.0	17.4	31.6
	Grade 3 & Related	165	5	3.0	1.0	6.9	150	5	3.3	1.1	7.6
	Medical advice	165	1	0.6	0.0	3.3	150	2	1.3	0.2	4.7

HAV-Pn = Dose 1: Havrix + DTPa-HBV-IPV/Hib / Dose2: 10Pn-PD-DiT (primed with 10Pn-PD-DiT)
Pn-Pn = Dose 1: 10Pn-PD-DiT + DTPa-HBV-IPV/Hib / Dose2: 10Pn-PD-DiT (primed with Havrix)

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

Table 23 **Percentage of doses with unsolicited symptoms with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period, classified by MEDDRA Primary System Organ Class and Preferred Term (Total vaccinated cohort)**

		HAV-Pn N = 167				Pn-Pn N = 155			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
At least one symptom		15	9.0	5.1	14.4	8	5.2	2.3	9.9
Gastrointestinal disorders (10017947)	Vomiting (10047700)	3	1.8	0.4	5.2	0	0.0	0.0	2.4
General disorders and administration site conditions (10018065)	Injection site erythema (10022061)	1	0.6	0.0	3.3	0	0.0	0.0	2.4
	Injection site haematoma (10022066)	0	0.0	0.0	2.2	1	0.6	0.0	3.5
	Injection site haemorrhage (10022067)	1	0.6	0.0	3.3	0	0.0	0.0	2.4
	Injection site induration (10022075)	7	4.2	1.7	8.4	7	4.5	1.8	9.1
	Injection site pruritus (10022093)	2	1.2	0.1	4.3	0	0.0	0.0	2.4
	Injection site rash (10022094)	1	0.6	0.0	3.3	0	0.0	0.0	2.4
	Injection site warmth (10022112)	1	0.6	0.0	3.3	0	0.0	0.0	2.4
Infections and infestations (10021881)	Injection site cellulitis (10050057)	1	0.6	0.0	3.3	0	0.0	0.0	2.4

HAV-Pn = Dose 1: Havrix + DTPa-HBV-IPV/Hib / Dose2: 10Pn-PD-DiT (primed with 10Pn-PD-DiT)
Pn-Pn = Dose 1: 10Pn-PD-DiT + DTPa-HBV-IPV/Hib / Dose2: 10Pn-PD-DiT (primed with Havrix)

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of administered doses
n/% = number/percentage of doses with the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

- MAH's conclusions
- Redness in the HAV-Pn group and pain in the Pn-Pn group were the most frequently reported grade 3 solicited local adverse events (maximum 15.3%). A low overall/dose incidence of most grade 3 solicited general adverse events (reported following maximum 5 doses and 12 doses in the HAV-Pn and Pn-Pn group, respectively) as well as those assessed by the investigator as causally related to vaccination was observed in both groups. The incidence of grade 3 unsolicited adverse events was low in both groups (reported following 4 doses and 3 doses in the HAV-Pn and Pn-Pn group, respectively) and none of these was considered as causally related to vaccination.
- No fatal SAEs were reported. One subject of the HAV-Pn group reported a SAE during the active phase of the study. The SAE was assessed by the investigator not to be causally related to the vaccination and resolved without sequelae.
- A high persistence of the immune response to the pneumococcal vaccine antigens and the hepatitis A vaccine 15 to 18 months after completion of the three-dose primary vaccination course was observed in the Pn group and HAV group, respectively.
- The immune response to the 10Pn-PD-DiT vaccine, one month following the 2-dose catch-up vaccination in the Pn-Pn group, was in the same range compared to the response observed one month following booster vaccination in group HAV-Pn for most serotypes except serotypes 1 and 6B for which a lower percentage of subjects with opsonophagocytic activity ≥8 was observed. All subjects in each group had measurable antibodies against protein D (≥100 EL.U/mL).
- Three months after the administration of the hepatitis A vaccine in the HAV-Pn group, 94.7% of subjects were seropositive.

- The 10Pn-PD-DiT booster vaccination following a 3-dose primary vaccination course as well as a 2-dose catch-up vaccination in Chilean children in the second year of life were shown to be generally well tolerated and immunogenic.

Assessor's comments: See also specific comment on immunogenicity above. The MAH's safety conclusions are endorsed. The relatively low OPA responses to some serotypes, as seen in the original MAA, enhances the concern that two catch-up doses may require a booster dose to provide protection. The MAH has a post-approval commitment to study booster vaccinations following the catch-up schedule.

10PN-PD-DIT-018; A phase IIIb, observer-blind, controlled study to assess the safety, reactogenicity and immunogenicity of GlaxoSmithKline (GSK) Biologicals. 10-valent pneumococcal conjugate vaccine or Prevenar when given as a booster dose between 12-18 months of age in children previously vaccinated in the primary study 10PN-PD-DIT-012 (107007) with either GSK Biologicals. 10-valent pneumococcal conjugate vaccine or Prevenar.

➢ **Description**

Phase III, multicentre, multi-country, double-blind (observer-blind), controlled study with 2 parallel groups that received the primary vaccination according to two different schedules (6-10-14 weeks of age schedule or 2-4-6 months of age schedule):

- 10Pn-PD-DiT group received GSK Biologicals. 10-valent pneumococcal conjugate vaccine
- Prevenar group received Prevenar

➢ **Methods**

- Objective(s)

Primary:

- To demonstrate that a booster dose of GSK Biologicals 10-valent pneumococcal conjugate vaccine is non-inferior to Prevenar when co-administered with DTPw-HBV/Hib and OPV or IPV vaccines, in terms of post-immunization booster reactions with rectal temperature > 39.0°C in children at 12 to 18 months of age.

Criteria for safety:

Non-inferiority will be demonstrated if one can rule out an increase, in terms of percentage of subjects with rectal temperature >39.0°C (10Pn-PD-DiT group as compared to Prevenar group), above 5% + half the incidence in the control group (= the null hypothesis) as shown by a one-sided P-value < 2.5%.

Secondary:

- To assess the safety and reactogenicity of a booster dose of GSK Biologicals 10-valent pneumococcal conjugate vaccine, when co-administered with DTPw-HBV/Hib and OPV or IPV vaccines at 12 to 18 months of age.
- To assess, one month post booster vaccination, the immunogenicity of a booster dose of GSK Biologicals 10-valent pneumococcal conjugate vaccine, when co-administered with DTPw-HBV/Hib and OPV or IPV vaccines at 12 to 18 months of age.
- To assess the antibody persistence, 7-12 months after completion of the 3-dose immunization course with GSK Biologicals. 10-valent pneumococcal conjugate vaccine in study 10PN-PD-DIT-012 (107007).
- To assess the immunogenicity of a booster dose of GSK Biologicals DTPw-HBV/Hib and OPV or IPV vaccines when co-administered with GSK Biologicals 10-valent pneumococcal conjugate vaccine or Prevenar at 12-18 months of age.

- Study design

Phase III, multicentre, multi-country, double-blind (observer-blind), controlled study with 2 parallel groups that received the primary vaccination according to two different schedules (6-10-14 weeks of age schedule or 2-4-6 months of age schedule):

- 10Pn-PD-DiT group received GSK Biologicals 10-valent pneumococcal conjugate vaccine
- Prevenar group received Prevenar

All subjects receiving the 6-10-14 week schedule were recruited in the Philippines, and all subjects receiving the 2-4-6 schedule were recruited in Poland.

- Study population /Sample size

Diagnosis and criteria for inclusion:

- Subjects for whom the investigator believed that their parents/guardians could and would comply with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits).
- Male or female between, and including, 12-18 months of age at the time of the booster vaccination.
- Male or female who previously participated in study 10PN-PD-DIT-012 (107007) and received three doses of pneumococcal conjugate vaccine.
- Written informed consent obtained from the parent or guardian of the subject.
- Free of obvious health problems as established by medical history and clinical examination before entering into the study.

The sample size was contingent on the number of subjects eligible after the primary vaccination course. In the primary study 10PN-PD-DIT-012 (107007), 800 subjects (600 in 10Pn-PD-DiT group and 200 in Prevenar group) were planned to be enrolled. Assuming that approximately 15% of these subjects would not enter the booster study, one could consider approximately 680 subjects (510 in 10Pn-PD-DiT group and 170 in Prevenar group) receiving the booster dose.

- Treatments

The vaccination schedules are summarised below. All subjects received a single booster vaccination of 10-PD-DiT (Synflorix) or Prevenar at 12-18 months of age.

Vaccination schedule	Sub-group	Vaccines	Co-administered vaccines
Philippines			
6-10-14 weeks (EPI schedule) + 12-18 months of age	10PnEPI	10Pn-PD-DiT	DTPw-HBV/Hib + OPV
	PrevEPI	Prevenar	
Poland			
2-4-6 months + 12-18 months of age	10Pn246	10Pn-PD-DiT	DTPw-HBV/Hib + IPV
	Prev246	Prevenar	

- Outcomes/endpoints

Safety /reactogenicity:

- Occurrence of fever with rectal temperature > 39°C within 4 days (days 0 to 3) after booster vaccination.
- Occurrence of solicited local symptoms (any and grade 3) within 4 days (day 0-day 3) after booster vaccination.
- Occurrence of solicited general symptoms (any and grade 3) within 4 days (day 0-day 3) after booster vaccination.
- Occurrence of unsolicited adverse events within 31 days (day 0-day 30) after booster vaccination.
- Occurrence of serious adverse events throughout the active phase of the study (Visit 1 to Visit 2).
- Occurrence of serious adverse events throughout the entire study period starting from Visit 1 up to the end of the extended 6-month safety follow-up (phone contact).

Immunogenicity /efficacy:

- Antibody concentrations against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (22F-inhibition ELISA), prior to and one month post-booster dose.
- Opsonophagocytic activity (OPA) against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F, prior to and one month post-booster dose.
- Antibody concentrations to protein D (ELISA), prior to and one month post-booster dose.
- Antibody concentrations against pneumococcal cross-reactive serotypes 6A and 19A (22F inhibition ELISA), prior to and one month post-booster dose.

- Statistical Methods

Safety-inferential analysis:

- Standardized asymptotic 95% CIs for the difference between groups (10Pn-PD-DiT group minus Prevenar group), in percentage of subjects reporting fever with rectal temperature > 39.0°C after the booster vaccination.

- The one-sided P-value for the null hypothesis that the increase in the percentage of subjects with rectal temperature > 39.0°C (10Pn-PD-DiT group as compared to Prevenar group) was above 5% + half the incidence in the control group. The primary objective was reached if the P-value was below 2.5%.

Safety-descriptive analysis:

- Incidence of solicited and/or unsolicited local and/or general adverse events (AEs) was calculated with exact 95% CI, according to the type of symptom, intensity and relationship to vaccination.
- Incidence of each local and each general solicited symptoms reported during the 4-day (days 0-3) follow-up period after the booster vaccination was calculated with exact 95% CI, according to the type of symptom, intensity and relationship to vaccination.
- The percentages of subjects with at least one unsolicited symptom reported up to 30 days after booster vaccination and classified by the Medical Dictionary for Regulatory Activities (MedDRA) were summarized with exact 95% CI. The same tabulations were performed for unsolicited adverse events classified as grade 3, with causal relationship and with medically attended visit.
- Prevalence of concomitant medication during the 4-day (days 0-3) follow-up period after the booster vaccination was computed with exact 95% CI.
- Serious adverse events, large swelling reactions and withdrawals due to adverse event(s) reported during the active phase of the study (Visit 1 to Visit 2) were described in detail.
- Serious adverse events recorded during the entire study period starting from Visit 1 up to the end of the extended 6 months safety follow-up were described in detail.

Immunogenicity-descriptive analysis:

- Geometric mean antibody concentrations/titres (GMCs/GMTs), seropositivity/seroprotection/booster immune response rates were calculated with their 95% CI for each group, each antigen/serotype and at each applicable blood sampling time point.
- Distribution of antibody concentrations/titres was displayed using tables and/or reverse cumulative curves for each group, each antigen/serotype and at each applicable blood sampling time point.

➢ **Results**

- Recruitment/ Number analysed

Out of the 756 subjects enrolled, 744 subjects completed the active phase of the study and 740 subjects were contacted during the extended safety follow-up. The mean age at booster vaccination was 16.7 months. Overall 46.7% of the subjects were female. All subjects in the 6-10-14 weeks + 12-18 months of age schedule were Asian (Southeast Asian heritage) and all subjects in the 2-4-6 months + 12-18 months of age schedule were White/Caucasian.

- Efficacy results

Persistence of antibodies against pneumococcal antigens and opsonophagocytic activity

A decline in antibody GMCs was observed in all groups in the time period between primary and booster vaccination for each of the vaccine pneumococcal serotypes for which subjects were primed (Tables 35 and 36).

Booster immune response to pneumococcal antigens

For each of the pneumococcal serotypes common to both vaccines, one month after the booster dose robust booster immune responses were observed in both groups for all serotypes (Tables 35 and 36).

Immune responses to co-administered vaccines

Seropositivity/seroprotection/booster vaccine response rates for antibodies against the antigens contained in the co-administered DTPw-HBV/Hib and OPV vaccines were in line with previous observations for these co-administered vaccines (Data not shown in this AR).

Table 35 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, per schedule (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	10PnEPI	PIII(M3)	136	136	100	97.3	100	136	100	97.3	100	3.59	3.13	4.12
		PRE-BOOSTER	136	135	99.3	96.0	100	100	73.5	65.3	80.7	0.35	0.29	0.42
		POST-BOOSTER	136	136	100	97.3	100	136	100	97.3	100	10.80	9.22	12.66
	PrevEPI	PIII(M3)	42	7	16.7	7.0	31.4	0	0.0	0.0	8.4	0.03	0.03	0.03
		PRE-BOOSTER	42	7	16.7	7.0	31.4	2	4.8	0.6	16.2	0.03	0.03	0.04
		POST-BOOSTER	42	11	26.2	13.9	42.0	3	7.1	1.5	19.5	0.04	0.03	0.05
	10Pn246	PIII(M5)	130	130	100	97.2	100	126	96.9	92.3	99.2	0.95	0.81	1.10
		PRE-BOOSTER	128	122	95.3	90.1	98.3	64	50.0	41.0	59.0	0.19	0.16	0.22
		POST-BOOSTER	125	125	100	97.1	100	125	100	97.1	100	2.14	1.80	2.55
	Prev246	PIII(M5)	44	7	15.9	6.6	30.1	0	0.0	0.0	8.0	0.03	0.03	0.03
		PRE-BOOSTER	40	8	20.0	9.1	35.6	2	5.0	0.6	16.9	0.04	0.03	0.05
		POST-BOOSTER	43	9	20.9	10.0	36.0	2	4.7	0.6	15.8	0.04	0.03	0.05
ANTI-4	10PnEPI	PIII(M3)	136	136	100	97.3	100	135	99.3	96.0	100	5.32	4.59	6.17
		PRE-BOOSTER	135	134	99.3	95.9	100	113	83.7	76.4	89.5	0.55	0.45	0.67
		POST-BOOSTER	136	136	100	97.3	100	136	100	97.3	100	13.16	11.43	15.14
	PrevEPI	PIII(M3)	43	43	100	91.8	100	43	100	91.8	100	5.71	4.60	7.09
		PRE-BOOSTER	43	43	100	91.8	100	25	58.1	42.1	73.0	0.34	0.25	0.45
		POST-BOOSTER	43	43	100	91.8	100	43	100	91.8	100	11.84	8.74	16.04
	10Pn246	PIII(M5)	130	130	100	97.2	100	127	97.7	93.4	99.5	1.45	1.25	1.68
		PRE-BOOSTER	130	126	96.9	92.3	99.2	78	60.0	51.0	68.5	0.27	0.22	0.33
		POST-BOOSTER	125	125	100	97.1	100	125	100	97.1	100	4.21	3.61	4.91
	Prev246	PIII(M5)	44	44	100	92.0	100	44	100	92.0	100	2.14	1.80	2.55
		PRE-BOOSTER	42	42	100	91.6	100	23	54.8	38.7	70.2	0.24	0.19	0.30
		POST-BOOSTER	43	43	100	91.8	100	43	100	91.8	100	6.86	5.39	8.73

ANTI-5	10PnEPI	PIII(M3)	136	136	100	97.3	100	136	100	97.3	100	4.95	4.42	5.56
		PRE-BOOSTER	135	135	100	97.3	100	118	87.4	80.6	92.5	0.55	0.47	0.64
		POST-BOOSTER	136	136	100	97.3	100	136	100	97.3	100	14.59	12.53	16.99
	PrevEPI	PIII(M3)	43	11	25.6	13.5	41.2	1	2.3	0.1	12.3	0.03	0.03	0.04
		PRE-BOOSTER	42	18	42.9	27.7	59.0	7	16.7	7.0	31.4	0.06	0.04	0.09
		POST-BOOSTER	43	31	72.1	56.3	84.7	8	18.6	8.4	33.4	0.09	0.06	0.13
	10Pn246	PIII(M5)	130	130	100	97.2	100	128	98.5	94.6	99.8	1.46	1.27	1.68
		PRE-BOOSTER	129	128	99.2	95.8	100	98	76.0	67.7	83.1	0.40	0.34	0.47
		POST-BOOSTER	125	125	100	97.1	100	124	99.2	95.6	100	2.54	2.11	3.06
	Prev246	PIII(M5)	44	5	11.4	3.8	24.6	1	2.3	0.1	12.0	0.03	0.03	0.04
		PRE-BOOSTER	42	13	31.0	17.6	47.1	3	7.1	1.5	19.5	0.04	0.03	0.05
		POST-BOOSTER	43	20	46.5	31.2	62.3	3	7.0	1.5	19.1	0.05	0.04	0.06
ANTI-6B	10PnEPI	PIII(M3)	136	133	97.8	93.7	99.5	123	90.4	84.2	94.8	1.19	0.96	1.48
		PRE-BOOSTER	135	132	97.8	93.6	99.5	113	83.7	76.4	89.5	0.66	0.54	0.80
		POST-BOOSTER	136	135	99.3	96.0	100	134	98.5	94.8	99.8	7.02	5.83	8.45
	PrevEPI	PIII(M3)	43	42	97.7	87.7	99.9	40	93.0	80.9	98.5	1.36	0.94	1.97
		PRE-BOOSTER	43	40	93.0	80.9	98.5	24	55.8	39.9	70.9	0.38	0.22	0.65
		POST-BOOSTER	42	42	100	91.6	100	42	100	91.6	100	9.08	6.50	12.70
	10Pn246	PIII(M5)	130	124	95.4	90.2	98.3	111	85.4	78.1	91.0	0.64	0.52	0.79
		PRE-BOOSTER	129	127	98.4	94.5	99.8	90	69.8	61.1	77.5	0.34	0.28	0.41
		POST-BOOSTER	125	124	99.2	95.6	100	122	97.6	93.1	99.5	2.31	1.93	2.75
	Prev246	PIII(M5)	44	40	90.9	78.3	97.5	40	90.9	78.3	97.5	1.13	0.73	1.73
		PRE-BOOSTER	44	39	88.6	75.4	96.2	27	61.4	45.5	75.6	0.34	0.20	0.59
		POST-BOOSTER	43	42	97.7	87.7	99.9	41	95.3	84.2	99.4	6.28	4.18	9.44
ANTI-7F	10PnEPI	PIII(M3)	136	136	100	97.3	100	136	100	97.3	100	4.61	4.09	5.20
		PRE-BOOSTER	135	135	100	97.3	100	128	94.8	89.6	97.9	0.90	0.77	1.04
		POST-BOOSTER	136	136	100	97.3	100	136	100	97.3	100	12.52	11.09	14.13
	PrevEPI	PIII(M3)	43	19	44.2	29.1	60.1	6	14.0	5.3	27.9	0.05	0.04	0.07
		PRE-BOOSTER	43	13	30.2	17.2	46.1	7	16.3	6.8	30.7	0.05	0.03	0.07
		POST-BOOSTER	43	17	39.5	25.0	55.6	9	20.9	10.0	36.0	0.06	0.04	0.10
	10Pn246	PIII(M5)	130	130	100	97.2	100	130	100	97.2	100	2.15	1.89	2.45
		PRE-BOOSTER	130	130	100	97.2	100	118	90.8	84.4	95.1	0.58	0.51	0.67
		POST-BOOSTER	125	125	100	97.1	100	125	100	97.1	100	4.14	3.61	4.74
	Prev246	PIII(M5)	44	14	31.8	18.6	47.6	5	11.4	3.8	24.6	0.04	0.03	0.06
		PRE-BOOSTER	42	8	19.0	8.6	34.1	1	2.4	0.1	12.6	0.03	0.03	0.04
		POST-BOOSTER	43	11	25.6	13.5	41.2	1	2.3	0.1	12.3	0.03	0.03	0.04
ANTI-9V	10PnEPI	PIII(M3)	136	136	100	97.3	100	136	100	97.3	100	4.43	3.86	5.10
		PRE-BOOSTER	135	135	100	97.3	100	132	97.8	93.6	99.5	1.16	0.98	1.37
		POST-BOOSTER	136	136	100	97.3	100	136	100	97.3	100	14.42	12.44	16.70
	PrevEPI	PIII(M3)	43	43	100	91.8	100	43	100	91.8	100	5.12	4.02	6.51
		PRE-BOOSTER	42	42	100	91.6	100	40	95.2	83.8	99.4	0.77	0.59	0.99
		POST-BOOSTER	43	43	100	91.8	100	43	100	91.8	100	20.31	15.44	26.71
	10Pn246	PIII(M5)	130	130	100	97.2	100	130	100	97.2	100	1.45	1.25	1.68
		PRE-BOOSTER	130	130	100	97.2	100	116	89.2	82.6	94.0	0.59	0.50	0.70
		POST-BOOSTER	125	125	100	97.1	100	125	100	97.1	100	4.63	4.00	5.36
	Prev246	PIII(M5)	44	44	100	92.0	100	44	100	92.0	100	2.71	2.23	3.28
		PRE-BOOSTER	44	44	100	92.0	100	42	95.5	84.5	99.4	0.58	0.47	0.71
		POST-BOOSTER	43	43	100	91.8	100	43	100	91.8	100	13.60	11.12	16.62

ANTI-14	10PnEPI	PIII(M3)	136	136	100	97.3	100	136	100	97.3	100	6.96	5.74	8.45
		PRE-BOOSTER	134	134	100	97.3	100	126	94.0	88.6	97.4	1.32	1.07	1.63
		POST-BOOSTER	136	136	100	97.3	100	135	99.3	96.0	100	17.07	14.12	20.64
	PrevEPI	PIII(M3)	43	43	100	91.8	100	43	100	91.8	100	6.06	4.28	8.57
		PRE-BOOSTER	43	42	97.7	87.7	99.9	42	97.7	87.7	99.9	1.83	1.26	2.66
		POST-BOOSTER	43	43	100	91.8	100	43	100	91.8	100	27.42	20.96	35.86
	10Pn246	PIII(M5)	130	130	100	97.2	100	130	100	97.2	100	2.92	2.51	3.41
		PRE-BOOSTER	130	130	100	97.2	100	111	85.4	78.1	91.0	0.84	0.66	1.07
		POST-BOOSTER	125	125	100	97.1	100	125	100	97.1	100	5.93	4.97	7.09
	Prev246	PIII(M5)	44	44	100	92.0	100	44	100	92.0	100	5.12	3.83	6.84
		PRE-BOOSTER	43	43	100	91.8	100	40	93.0	80.9	98.5	1.04	0.75	1.43
		POST-BOOSTER	43	43	100	91.8	100	43	100	91.8	100	15.51	12.14	19.82
ANTI-18C	10PnEPI	PIII(M3)	136	135	99.3	96.0	100	135	99.3	96.0	100	12.11	10.07	14.57
		PRE-BOOSTER	135	135	100	97.3	100	130	96.3	91.6	98.8	1.43	1.20	1.71
		POST-BOOSTER	136	136	100	97.3	100	136	100	97.3	100	39.59	34.04	46.05
	PrevEPI	PIII(M3)	43	43	100	91.8	100	43	100	91.8	100	3.78	2.93	4.87
		PRE-BOOSTER	43	43	100	91.8	100	36	83.7	69.3	93.2	0.42	0.32	0.55
		POST-BOOSTER	43	43	100	91.8	100	43	100	91.8	100	12.07	9.23	15.79
	10Pn246	PIII(M5)	130	130	100	97.2	100	127	97.7	93.4	99.5	3.25	2.64	4.00
		PRE-BOOSTER	130	129	99.2	95.8	100	111	85.4	78.1	91.0	0.63	0.52	0.77
		POST-BOOSTER	125	125	100	97.1	100	125	100	97.1	100	10.49	8.81	12.49
	Prev246	PIII(M5)	44	43	97.7	88.0	99.9	43	97.7	88.0	99.9	2.43	1.84	3.20
		PRE-BOOSTER	44	44	100	92.0	100	35	79.5	64.7	90.2	0.40	0.30	0.53
		POST-BOOSTER	43	43	100	91.8	100	43	100	91.8	100	9.92	7.74	12.71
ANTI-19F	10PnEPI	PIII(M3)	136	136	100	97.3	100	136	100	97.3	100	10.82	9.18	12.75
		PRE-BOOSTER	135	134	99.3	95.9	100	129	95.6	90.6	98.4	1.33	1.08	1.64
		POST-BOOSTER	136	136	100	97.3	100	136	100	97.3	100	21.25	18.07	24.98
	PrevEPI	PIII(M3)	43	43	100	91.8	100	42	97.7	87.7	99.9	3.94	3.01	5.17
		PRE-BOOSTER	43	37	86.0	72.1	94.7	11	25.6	13.5	41.2	0.16	0.10	0.26
		POST-BOOSTER	43	43	100	91.8	100	43	100	91.8	100	6.61	4.90	8.92
	10Pn246	PIII(M5)	130	130	100	97.2	100	128	98.5	94.6	99.8	4.96	4.20	5.87
		PRE-BOOSTER	130	129	99.2	95.8	100	121	93.1	87.3	96.8	0.99	0.81	1.22
		POST-BOOSTER	125	124	99.2	95.6	100	123	98.4	94.3	99.8	12.23	9.89	15.13
	Prev246	PIII(M5)	44	43	97.7	88.0	99.9	43	97.7	88.0	99.9	2.32	1.77	3.02
		PRE-BOOSTER	44	43	97.7	88.0	99.9	22	50.0	34.6	65.4	0.35	0.20	0.61
		POST-BOOSTER	43	43	100	91.8	100	43	100	91.8	100	6.01	4.75	7.60
ANTI-23F	10PnEPI	PIII(M3)	136	136	100	97.3	100	134	98.5	94.8	99.8	2.46	2.09	2.89
		PRE-BOOSTER	133	132	99.2	95.9	100	123	92.5	86.6	96.3	0.94	0.76	1.16
		POST-BOOSTER	136	136	100	97.3	100	135	99.3	96.0	100	13.47	11.38	15.94
	PrevEPI	PIII(M3)	43	42	97.7	87.7	99.9	41	95.3	84.2	99.4	2.41	1.62	3.58
		PRE-BOOSTER	43	40	93.0	80.9	98.5	32	74.4	58.8	86.5	0.41	0.26	0.64
		POST-BOOSTER	43	42	97.7	87.7	99.9	42	97.7	87.7	99.9	14.78	9.45	23.11
	10Pn246	PIII(M5)	130	125	96.2	91.3	98.7	121	93.1	87.3	96.8	1.08	0.88	1.32
		PRE-BOOSTER	130	125	96.2	91.3	98.7	89	68.5	59.7	76.3	0.33	0.27	0.40
		POST-BOOSTER	125	124	99.2	95.6	100	123	98.4	94.3	99.8	3.16	2.61	3.83
	Prev246	PIII(M5)	44	44	100	92.0	100	44	100	92.0	100	2.48	1.96	3.14
		PRE-BOOSTER	44	43	97.7	88.0	99.9	40	90.9	78.3	97.5	0.62	0.43	0.91
		POST-BOOSTER	43	42	97.7	87.7	99.9	42	97.7	87.7	99.9	10.77	7.19	16.12

10PnEPI = 10Pn-PD-DiT + DTPw-HBV/Hib + OPV (6-10-14 weeks+ 12-18 months of age schedule)
PrevEPI = Prevenar + DTPw-HBV/Hib + OPV (6-10-14 weeks + 12-18 months of age schedule)
10Pn246 = 10Pn-PD-DiT + DTPw-HBV/Hib + IPV (2-4-6 months+ 12-18 months of age schedule)
Prev246 = Prevenar + DTPw-HBV/Hib + IPV (2-4-6 months + 12-18 months of age schedule)

Table 36 **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, per schedule (ATP cohort for immunogenicity)**

				≥ 8				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
OPSONO-1	10PnEPI	PIII(M3)	133	109	82.0	74.4	88.1	91.9	66.0	127.9
		PRE-BOOSTER	134	61	45.5	36.9	54.3	13.2	10.2	16.9
		POST-BOOSTER	134	134	100	97.3	100	1571.6	1210.7	2040.0
	PrevEPI	PIII(M3)	43	1	2.3	0.1	12.3	4.2	3.8	4.6
		PRE-BOOSTER	43	3	7.0	1.5	19.1	4.6	3.9	5.4
		POST-BOOSTER	43	5	11.6	3.9	25.1	4.9	4.1	5.8
	10Pn246	PIII(M5)	130	56	43.1	34.4	52.0	14.4	10.8	19.2
		PRE-BOOSTER	122	45	36.9	28.3	46.1	8.5	7.0	10.5
		POST-BOOSTER	120	114	95.0	89.4	98.1	161.4	120.7	215.9
	Prev246	PIII(M5)	44	0	0.0	0.0	8.0	4.0	4.0	4.0
		PRE-BOOSTER	37	3	8.1	1.7	21.9	4.7	3.8	5.8
		POST-BOOSTER	37	5	13.5	4.5	28.8	5.4	4.0	7.4

OPSONO-4	10PnEPI	PIII(M3)	129	128	99.2	95.8	100	989.7	825.6	1186.3
		PRE-BOOSTER	127	83	65.4	56.4	73.6	40.5	27.6	59.2
		POST-BOOSTER	134	134	100	97.3	100	5035.8	4214.0	6017.8
	PrevEPI	PIII(M3)	40	40	100	91.2	100	1291.7	1018.9	1637.6
		PRE-BOOSTER	42	20	47.6	32.0	63.6	18.5	10.0	34.2
		POST-BOOSTER	43	43	100	91.8	100	4783.5	3432.0	6667.2
	10Pn246	PIII(M5)	130	128	98.5	94.6	99.8	582.6	470.6	721.4
		PRE-BOOSTER	114	39	34.2	25.6	43.7	12.5	8.9	17.4
		POST-BOOSTER	119	119	100	96.9	100	2498.7	2103.3	2968.4
	Prev246	PIII(M5)	44	44	100	92.0	100	528.6	388.0	720.2
		PRE-BOOSTER	33	12	36.4	20.4	54.9	12.4	6.7	22.8
		POST-BOOSTER	35	35	100	90.0	100	4812.5	3167.8	7311.3
OPSONO-5	10PnEPI	PIII(M3)	131	130	99.2	95.8	100	212.5	178.5	253.1
		PRE-BOOSTER	133	94	70.7	62.2	78.2	19.8	16.0	24.7
		POST-BOOSTER	130	130	100	97.2	100	1135.8	928.5	1389.6
	PrevEPI	PIII(M3)	43	0	0.0	0.0	8.2	4.0	4.0	4.0
		PRE-BOOSTER	43	1	2.3	0.1	12.3	4.2	3.8	4.6
		POST-BOOSTER	43	4	9.3	2.6	22.1	4.9	3.9	6.0
	10Pn246	PIII(M5)	129	113	87.6	80.6	92.7	63.2	48.3	82.7
		PRE-BOOSTER	119	56	47.1	37.8	56.4	10.9	8.8	13.6
		POST-BOOSTER	117	114	97.4	92.7	99.5	149.1	115.4	192.5
	Prev246	PIII(M5)	44	0	0.0	0.0	8.0	4.0	4.0	4.0
		PRE-BOOSTER	36	2	5.6	0.7	18.7	4.5	3.7	5.5
		POST-BOOSTER	36	1	2.8	0.1	14.5	4.3	3.8	4.8
OPSONO-6B	10PnEPI	PIII(M3)	133	124	93.2	87.5	96.9	1008.1	748.9	1357.0
		PRE-BOOSTER	132	93	70.5	61.9	78.1	97.8	61.5	155.5
		POST-BOOSTER	136	134	98.5	94.8	99.8	2896.8	2247.5	3733.8
	PrevEPI	PIII(M3)	40	37	92.5	79.6	98.4	1705.8	903.2	3221.8
		PRE-BOOSTER	43	21	48.8	33.3	64.5	56.6	21.3	150.1
		POST-BOOSTER	43	43	100	91.8	100	9302.7	7187.3	12040.8
	10Pn246	PIII(M5)	130	110	84.6	77.2	90.3	373.6	259.2	538.7
		PRE-BOOSTER	124	34	27.4	19.8	36.2	9.9	7.2	13.5
		POST-BOOSTER	120	106	88.3	81.2	93.5	405.3	267.4	614.3
	Prev246	PIII(M5)	44	40	90.9	78.3	97.5	846.3	462.6	1548.4
		PRE-BOOSTER	37	14	37.8	22.5	55.2	23.3	9.1	60.1
		POST-BOOSTER	35	32	91.4	76.9	98.2	3547.1	1500.7	8384.5
OPSONO-7F	10PnEPI	PIII(M3)	128	128	100	97.2	100	5150.2	4275.3	6204.1
		PRE-BOOSTER	135	133	98.5	94.8	99.8	2278.4	1803.1	2879.0
		POST-BOOSTER	136	136	100	97.3	100	12484.0	10750.7	14496.8
	PrevEPI	PIII(M3)	41	10	24.4	12.4	40.3	15.6	7.2	33.8
		PRE-BOOSTER	41	28	68.3	51.9	81.9	378.8	136.9	1048.0
		POST-BOOSTER	40	36	90.0	76.3	97.2	1407.7	694.6	2852.9
	10Pn246	PIII(M5)	129	127	98.4	94.5	99.8	2166.0	1683.8	2786.3
		PRE-BOOSTER	116	109	94.0	88.0	97.5	796.3	582.2	1089.1
		POST-BOOSTER	122	122	100	97.0	100	6436.1	5507.6	7521.0
	Prev246	PIII(M5)	44	3	6.8	1.4	18.7	5.7	3.8	8.7
		PRE-BOOSTER	31	15	48.4	30.2	66.9	63.6	21.3	190.1
		POST-BOOSTER	24	13	54.2	32.8	74.4	90.6	25.2	325.5

OPSONO-9V	10PnEPI	PIII(M3)	121	121	100	97.0	100	1638.6	1342.0	2000.8
		PRE-BOOSTER	136	135	99.3	96.0	100	788.0	655.1	947.8
		POST-BOOSTER	134	134	100	97.3	100	4842.0	4122.7	5686.9
	PrevEPI	PIII(M3)	40	40	100	91.2	100	1614.7	1218.6	2139.5
		PRE-BOOSTER	42	42	100	91.6	100	666.8	482.1	922.2
		POST-BOOSTER	42	42	100	91.6	100	7387.8	5429.2	10052.9
	10Pn246	PIII(M5)	129	129	100	97.2	100	1196.6	975.8	1467.3
		PRE-BOOSTER	122	121	99.2	95.5	100	380.2	313.1	461.7
		POST-BOOSTER	121	121	100	97.0	100	3499.9	2950.8	4151.3
	Prev246	PIII(M5)	44	44	100	92.0	100	1075.0	714.8	1616.8
		PRE-BOOSTER	37	36	97.3	85.8	99.9	247.5	164.9	371.3
		POST-BOOSTER	35	35	100	90.0	100	6881.4	4883.6	9696.4
OPSONO-14	10PnEPI	PIII(M3)	133	129	97.0	92.5	99.2	1624.3	1216.0	2169.7
		PRE-BOOSTER	130	119	91.5	85.4	95.7	298.4	220.1	404.7
		POST-BOOSTER	132	132	100	97.2	100	3579.7	2966.3	4319.9
	PrevEPI	PIII(M3)	43	40	93.0	80.9	98.5	1987.9	1100.5	3590.7
		PRE-BOOSTER	42	39	92.9	80.5	98.5	337.2	207.0	549.2
		POST-BOOSTER	42	42	100	91.6	100	4097.3	3019.2	5560.2
	10Pn246	PIII(M5)	130	127	97.7	93.4	99.5	624.7	498.1	783.3
		PRE-BOOSTER	106	93	87.7	79.9	93.3	179.6	127.4	253.2
		POST-BOOSTER	120	120	100	97.0	100	1961.3	1630.0	2359.8
	Prev246	PIII(M5)	44	43	97.7	88.0	99.9	946.5	630.2	1421.5
		PRE-BOOSTER	31	29	93.5	78.6	99.2	236.6	132.6	422.2
		POST-BOOSTER	36	36	100	90.3	100	2939.5	2022.3	4272.7
OPSONO-18C	10PnEPI	PIII(M3)	130	129	99.2	95.8	100	668.6	564.3	792.2
		PRE-BOOSTER	129	84	65.1	56.2	73.3	19.8	15.2	25.9
		POST-BOOSTER	134	133	99.3	95.9	100	2417.2	1989.9	2936.2
	PrevEPI	PIII(M3)	42	42	100	91.6	100	266.1	194.4	364.1
		PRE-BOOSTER	42	3	7.1	1.5	19.5	4.5	3.9	5.2
		POST-BOOSTER	43	42	97.7	87.7	99.9	966.5	607.1	1538.6
	10Pn246	PIII(M5)	129	122	94.6	89.1	97.8	181.1	139.3	235.5
		PRE-BOOSTER	121	42	34.7	26.3	43.9	7.8	6.5	9.4
		POST-BOOSTER	115	114	99.1	95.3	100	694.0	532.9	903.7
	Prev246	PIII(M5)	44	43	97.7	88.0	99.9	120.3	80.2	180.6
		PRE-BOOSTER	37	4	10.8	3.0	25.4	4.5	4.0	5.2
		POST-BOOSTER	36	36	100	90.3	100	612.1	338.4	1107.0
OPSONO-19F	10PnEPI	PIII(M3)	131	129	98.5	94.6	99.8	1118.5	920.9	1358.4
		PRE-BOOSTER	135	117	86.7	79.7	91.9	58.6	45.2	76.0
		POST-BOOSTER	136	135	99.3	96.0	100	2016.0	1609.0	2526.0
	PrevEPI	PIII(M3)	43	39	90.7	77.9	97.4	77.7	49.4	122.3
		PRE-BOOSTER	43	7	16.3	6.8	30.7	7.3	4.5	11.8
		POST-BOOSTER	42	39	92.9	80.5	98.5	473.2	263.5	849.9
	10Pn246	PIII(M5)	128	126	98.4	94.5	99.8	330.6	250.9	435.6
		PRE-BOOSTER	125	96	76.8	68.4	83.9	33.3	25.7	43.2
		POST-BOOSTER	122	118	96.7	91.8	99.1	1059.8	808.2	1389.7
	Prev246	PIII(M5)	44	40	90.9	78.3	97.5	32.5	23.5	44.9
		PRE-BOOSTER	37	12	32.4	18.0	49.8	11.1	6.0	20.6
		POST-BOOSTER	37	36	97.3	85.8	99.9	471.0	270.0	821.8

OPSONO-23F	10PnEPI	PIII(M3)	132	132	100	97.2	100	2212.7	1860.9	2631.1
		PRE-BOOSTER	136	130	95.6	90.6	98.4	948.9	688.4	1308.2
		POST-BOOSTER	136	136	100	97.3	100	7456.2	6301.9	8822.0
	PrevEPI	PIII(M3)	40	39	97.5	86.8	99.9	3898.8	2397.7	6339.7
		PRE-BOOSTER	43	37	86.0	72.1	94.7	661.9	312.5	1402.0
		POST-BOOSTER	43	42	97.7	87.7	99.9	23177.9	13235.9	40587.7
	10Pn246	PIII(M5)	128	119	93.0	87.1	96.7	933.7	681.4	1279.4
		PRE-BOOSTER	118	99	83.9	76.0	90.0	301.8	198.4	459.0
		POST-BOOSTER	121	120	99.2	95.5	100	3427.3	2727.7	4306.3
	Prev246	PIII(M5)	44	43	97.7	88.0	99.9	3311.9	2119.9	5174.0
		PRE-BOOSTER	36	30	83.3	67.2	93.6	790.6	326.8	1912.6
		POST-BOOSTER	37	37	100	90.5	100	19943.3	13473.1	29520.5

10PnEPI = 10Pn-PD-DiT + DTPw-HBV/Hib + OPV (6-10-14 weeks+ 12-18 months of age schedule)
PrevEPI = Prevenar + DTPw-HBV/Hib + OPV (6-10-14 weeks + 12-18 months of age schedule)
10Pn246 = 10Pn-PD-DiT + DTPw-HBV/Hib + IPV (2-4-6 months+ 12-18 months of age schedule)
Prev246 = Prevenar + DTPw-HBV/Hib + IPV (2-4-6 months + 12-18 months of age schedule)

- Safety results

Confirmatory inferential analysis:

The primary objective of the study was reached as the upper limit of the 95% CI (5.59%) of the difference between groups (10Pn minus Prev) in terms of the percentage of subjects reporting fever with rectal temperature > 39.0°C was below the pre-defined limit of 10.3% (P-value < 0.1%). Thus a booster dose of the 10Pn-PD-DiT vaccine did not induce more fever with rectal temperature > 39.0°C than Prevenar when co-administered with DTPw-HBV/Hib and OPV or IPV vaccines (Table 18).

Table 18 Difference between groups (10Pn minus Prev) in terms of percentage of subjects reporting fever with rectal temperature greater than 39°C during the 4-day (Days 0-3) post-vaccination period (Total vaccinated cohort)

								Difference in percentage (10Pn minus Prev)			
		10Pn			Prev				95% CI		
Symptoms	**Type**	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**	**P-value***
Fever/(Rectally) (°C)	> 39.0°C	558	64	11.5	189	20	10.6	0.89	-4.82	5.59	<0.001

10Pn = 10Pn-PD-DiT + DTPw-HBV/Hib + OPV or IPV (6-10-14 weeks+ 12-18 months and 2-4-6 months + 12-18 months of age schedule)
Prev = Prevenar + DTPw-HBV/Hib + OPV or IPV (6-10-14 weeks+ 12-18 months and 2-4-6 months + 12-18 months of age schedule)

Descriptive analysis:

6-10-14 weeks + 12-18 months of age schedule:

After booster vaccination, 85.7% of the subjects in the 10PnEPI group and 83.9% of the subjects in the PrevEPI group reported at least one adverse event (solicited or unsolicited, local or general).

The most frequently reported solicited local adverse event was pain in both groups and the most frequently reported solicited general adverse event was irritability in both groups (Table 2).

Large swelling reactions were reported by 5 subjects (4 subjects in the 10PnEPI group and 1 subject in the PrevEPI group). Four of these large swelling reactions were reported at the DTPw-HBV/Hib injection site and one at the 10Pn-PD-DiT injection site. All were local or diffuse swelling reactions not involving adjacent joints that resolved without sequelae.

No cases of grade 3 fever (rectal temperature > 40° C) were reported in any of the groups (Table 3).

Low incidences of grade 3 solicited general adverse events, assessed by the investigator to be causally related to vaccination, were reported in both groups (maximum 4.3%).

The observed percentage of subjects reporting at least one unsolicited adverse event within 31 days after booster vaccination was 8.9% in the 10PnEPI group and 9.7% in the PrevEPI group. Up to 0.7% of the subjects reported at least one unsolicited adverse event with grade 3 intensity. None of the

reported unsolicited adverse events were assessed by the investigator to be causally related to vaccination.

2-4-6 months + 12-18 months of age schedule:
After booster vaccination, a higher incidence of adverse events (solicited or unsolicited, local or general) was reported in both groups compared to the incidence reported in the 6-10-14 weeks + 12-18 months schedule. 99.3% of the subjects in the 10Pn246 group and 96.9% of the subjects in the Prev246 group reported at least one adverse event (solicited or unsolicited, local or general).
The most frequently reported solicited local adverse event was pain in both groups with high incidences of solicited local grade 3 pain (up to 42.1%). Higher incidences of grade 3 pain were reported at the DTPw-HBV/Hib injection site (40.4%) compared to the pneumococcal conjugate vaccine injection sites (up to 26.3%) (Table 2).
Large swelling reactions were reported by 14 subjects (12 subjects in the 10Pn246 group and 2 subjects in the Prev246 group). Ten of these large swelling reactions were reported at the DTPw-HBV/Hib injection site, 3 at the 10Pn-PD-DiT injection site and 1 at the IPV injection site. All were local or diffuse swelling reactions not involving adjacent joints that resolved without sequelae.
The most frequently reported solicited general adverse event was irritability in both groups. One case of grade 3 fever (rectal temperature > 40° C), assessed by the investigator to be causally related to vaccination, was reported in the 10Pn246 group. (Table 3)
Low incidences of grade 3 solicited general adverse events, assessed by the investigator to be causally related to vaccination (up to 4.7%), were reported in both groups, except for irritability (up to 14.4%).
The observed percentage of subjects reporting at least one unsolicited adverse event within 31 days after booster vaccination was 37.2% in the 10Pn246 group and 35.7% in the Prev246 group. A low percentage of subjects reported at least one adverse event with intensity grade 3 (up to 6.7%) or an adverse event which was assessed by the investigator to be causally related to vaccination (up to 6.3%).

Table 2: Incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period, per schedule (Total vaccinated cohort)

		10PnEPI					PrevEPI					10Pn246					Prev246				
					95 % CI					95 % CI					95 % CI					95 % CI	
Product	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Pain																					
Total	All	280	203	72.5	66.9	77.6	93	66	71.0	60.6	79.9	278	248	89.2	85.0	92.6	96	77	80.2	70.8	87.6
	Grade 3	280	40	14.3	10.4	18.9	93	20	21.5	13.7	31.2	278	117	42.1	36.2	48.1	96	39	40.6	30.7	51.1
	Med.advice	280	1	0.4	0.0	2.0	93	0	0.0	0.0	3.9	278	10	3.6	1.7	6.5	96	1	1.0	0.0	5.7
10Pn-PD-DiT	All	280	184	65.7	59.8	71.3	-	-	-	-	-	278	210	75.5	70.0	80.5	-	-	-	-	-
	Grade 3	280	23	8.2	5.3	12.1	-	-	-	-	-	278	73	26.3	21.2	31.8	-	-	-	-	-
	Med.advice	280	0	0.0	0.0	1.3	-	-	-	-	-	278	9	3.2	1.5	6.1	-	-	-	-	-
Prevenar	All	-	-	-	-	-	93	55	59.1	48.5	69.2	-	-	-	-	-	96	60	62.5	52.0	72.2
	Grade 3	-	-	-	-	-	93	13	14.0	7.7	22.7	-	-	-	-	-	96	20	20.8	13.2	30.3
	Med.advice	-	-	-	-	-	93	0	0.0	0.0	3.9	-	-	-	-	-	96	1	1.0	0.0	5.7
DTPw-HBV/Hib	All	280	187	66.8	60.9	72.3	93	58	62.4	51.7	72.2	275	237	86.2	81.5	90.0	95	73	76.8	67.1	84.9
	Grade3	280	36	12.9	9.2	17.4	93	15	16.1	9.3	25.2	275	111	40.4	34.5	46.4	95	38	40.0	30.1	50.6
	Med.advice	280	1	0.4	0.0	2.0	93	0	0.0	0.0	3.9	275	8	2.9	1.3	5.7	95	1	1.1	0.0	5.7
IPV	All	-	-	-	-	-	-	-	-	-	-	276	197	71.4	65.7	76.6	95	63	66.3	55.9	75.7
	Grade 3	-	-	-	-	-	-	-	-	-	-	276	87	31.5	26.1	37.4	95	26	27.4	18.7	37.5
	Med.advice	-	-	-	-	-	-	-	-	-	-	276	6	2.2	0.8	4.7	95	1	1.1	0.0	5.7
Redness (mm)																					
Total	All	280	107	38.2	32.5	44.2	93	37	39.8	29.8	50.5	278	197	70.9	65.1	76.1	96	66	68.8	58.5	77.8
	> 20mm	280	11	3.9	2.0	6.9	93	6	6.5	2.4	13.5	278	47	16.9	12.7	21.8	96	16	16.7	9.8	25.6
	> 30mm	280	8	2.9	1.2	5.6	93	3	3.2	0.7	9.1	278	35	12.6	8.9	17.1	96	11	11.5	5.9	19.6
	Med.advice	280	1	0.4	0.0	2.0	93	0	0.0	0.0	3.9	278	4	1.4	0.4	3.6	96	3	3.1	0.6	8.9
10Pn-PD-DiT	All	280	88	31.4	26.0	37.2	-	-	-	-	-	278	139	50.0	44.0	56.0	-	-	-	-	-
	> 20mm	280	7	2.5	1.0	5.1	-	-	-	-	-	278	15	5.4	3.1	8.7	-	-	-	-	-
	> 30mm	280	6	2.1	0.8	4.6	-	-	-	-	-	278	8	2.9	1.3	5.6	-	-	-	-	-
	Med.advice	280	0	0.0	0.0	1.3	-	-	-	-	-	278	3	1.1	0.2	3.1	-	-	-	-	-
Prevenar	All	-	-	-	-	-	93	27	29.0	20.1	39.4	-	-	-	-	-	96	45	46.9	36.6	57.3
	> 20mm	-	-	-	-	-	93	2	2.2	0.3	7.6	-	-	-	-	-	96	4	4.2	1.1	10.3
	> 30mm	-	-	-	-	-	93	0	0.0	0.0	3.9	-	-	-	-	-	96	3	3.1	0.6	8.9
	Med.advice	-	-	-	-	-	93	0	0.0	0.0	3.9	-	-	-	-	-	96	1	1.0	0.0	5.7
DTPw-HBV/Hib	All	280	92	32.9	27.4	38.7	93	32	34.4	24.9	45.0	275	181	65.8	59.9	71.4	95	62	65.3	54.8	74.7
	> 20mm	280	6	2.1	0.8	4.6	93	6	6.5	2.4	13.5	275	42	15.3	11.2	20.1	95	14	14.7	8.3	23.5
	> 30mm	280	3	1.1	0.2	3.1	93	3	3.2	0.7	9.1	275	33	12.0	8.4	16.4	95	10	10.5	5.2	18.5
	Med.advice	280	1	0.4	0.0	2.0	93	0	0.0	0.0	3.9	275	3	1.1	0.2	3.2	95	3	3.2	0.7	9.0
IPV	All	-	-	-	-	-	-	-	-	-	-	276	107	38.8	33.0	44.8	95	36	37.9	28.1	48.4
	> 20mm	-	-	-	-	-	-	-	-	-	-	276	5	1.8	0.6	4.2	95	1	1.1	0.0	5.7
	> 30mm	-	-	-	-	-	-	-	-	-	-	276	4	1.4	0.4	3.7	95	1	1.1	0.0	5.7
	Med.advice	-	-	-	-	-	-	-	-	-	-	276	1	0.4	0.0	2.0	95	1	1.1	0.0	5.7
Swelling (mm)																					
Total	All	280	92	32.9	27.4	38.7	93	32	34.4	24.9	45.0	278	158	56.8	50.8	62.7	96	52	54.2	43.7	64.4
	> 20mm	280	33	11.8	8.3	16.2	93	14	15.1	8.5	24.0	278	58	20.9	16.2	26.1	96	15	15.6	9.0	24.5
	> 30mm	280	21	7.5	4.7	11.2	93	9	9.7	4.5	17.6	278	34	12.2	8.6	16.7	96	8	8.3	3.7	15.8
	Med.advice	280	2	0.7	0.1	2.6	93	0	0.0	0.0	3.9	278	10	3.6	1.7	6.5	96	3	3.1	0.6	8.9
10Pn-PD-DiT	All	280	71	25.4	20.4	30.9	-	-	-	-	-	278	110	39.6	33.8	45.6	-	-	-	-	-
	> 20mm	280	16	5.7	3.3	9.1	-	-	-	-	-	278	19	6.8	4.2	10.5	-	-	-	-	-
	> 30mm	280	9	3.2	1.5	6.0	-	-	-	-	-	278	11	4.0	2.0	7.0	-	-	-	-	-
	Med.advice	280	1	0.4	0.0	2.0	-	-	-	-	-	278	7	2.5	1.0	5.1	-	-	-	-	-
Prevenar	All	-	-	-	-	-	93	24	25.8	17.3	35.9	-	-	-	-	-	96	29	30.2	21.3	40.4
	> 20mm	-	-	-	-	-	93	8	8.6	3.8	16.2	-	-	-	-	-	96	2	2.1	0.3	7.3
	> 30mm	-	-	-	-	-	93	5	5.4	1.8	12.1	-	-	-	-	-	96	1	1.0	0.0	5.7
	Med.advice	-	-	-	-	-	93	0	0.0	0.0	3.9	-	-	-	-	-	96	2	2.1	0.3	7.3
DTPw-HBV/Hib	All	280	82	29.3	24.0	35.0	93	29	31.2	22.0	41.6	275	139	50.5	44.5	56.6	95	47	49.5	39.1	59.9
	> 20mm	280	30	10.7	7.3	14.9	93	11	11.8	6.1	20.2	275	47	17.1	12.8	22.1	95	14	14.7	8.3	23.5
	> 30mm	280	19	6.8	4.1	10.4	93	7	7.5	3.1	14.9	275	28	10.2	6.9	14.4	95	7	7.4	3.0	14.6
	Med.advice	280	2	0.7	0.1	2.6	93	0	0.0	0.0	3.9	275	9	3.3	1.5	6.1	95	3	3.2	0.7	9.0
IPV	All	-	-	-	-	-	-	-	-	-	-	276	83	30.1	24.7	35.9	95	27	28.4	19.6	38.6
	> 20mm	-	-	-	-	-	-	-	-	-	-	276	13	4.7	2.5	7.9	95	2	2.1	0.3	7.4
	> 30mm	-	-	-	-	-	-	-	-	-	-	276	7	2.5	1.0	5.2	95	1	1.1	0.0	5.7
	Med.advice	-	-	-	-	-	-	-	-	-	-	276	4	1.4	0.4	3.7	95	1	1.1	0.0	5.7

10PnEPI = 10Pn-PD-DiT + DTPw-HBV/Hib + OPV (6-10-14 weeks+ 12-18 months of age schedule)
PrevEPI = Prevenar + DTPw-HBV/Hib + OPV (6-10-14 weeks + 12-18 months of age schedule)
10Pn246 = 10Pn-PD-DiT + DTPw-HBV/Hib + IPV (2-4-6 months+ 12-18 months of age schedule)
Prev246 = Prevenar + DTPw-HBV/Hib + IPV (2-4-6 months + 12-18 months of age schedule)
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; Med.advice=medical advice

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

	10PnEPI					PrevEPI					10Pn246					Prev246				
				95 % CI					95 % CI					95 % CI					95 % CI	
Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Drowsiness																				
All	280	90	32.1	26.7	38.0	93	32	34.4	24.9	45.0	278	190	68.3	62.5	73.8	96	66	68.8	58.5	77.8
Grade 3	280	5	1.8	0.6	4.1	93	1	1.1	0.0	5.8	278	7	2.5	1.0	5.1	96	2	2.1	0.3	7.3
Related	280	90	32.1	26.7	38.0	93	32	34.4	24.9	45.0	278	188	67.6	61.8	73.1	96	66	68.8	58.5	77.8
Grade 3 & Related	280	5	1.8	0.6	4.1	93	1	1.1	0.0	5.8	278	7	2.5	1.0	5.1	96	2	2.1	0.3	7.3
Medical advice	280	0	0.0	0.0	1.3	93	0	0.0	0.0	3.9	278	8	2.9	1.3	5.6	96	0	0.0	0.0	3.8
Fever/(Rectally) (°C)																				
All	280	138	49.3	43.3	55.3	93	51	54.8	44.2	65.2	278	215	77.3	72.0	82.1	96	65	67.7	57.4	76.9
> 38.5°C	280	54	19.3	14.8	24.4	93	19	20.4	12.8	30.1	278	128	46.0	40.1	52.1	96	35	36.5	26.9	46.9
> 39.0°C	280	12	4.3	2.2	7.4	93	8	8.6	3.8	16.2	278	52	18.7	14.3	23.8	96	12	12.5	6.6	20.8
> 39.5°C	280	3	1.1	0.2	3.1	93	3	3.2	0.7	9.1	278	21	7.6	4.7	11.3	96	3	3.1	0.6	8.9
> 40.0°C	280	0	0.0	0.0	1.3	93	0	0.0	0.0	3.9	278	1	0.4	0.0	2.0	96	0	0.0	0.0	3.8
Related	280	137	48.9	42.9	54.9	93	51	54.8	44.2	65.2	278	213	76.6	71.2	81.5	96	65	67.7	57.4	76.9
> 40.0°C & Related	280	0	0.0	0.0	1.3	93	0	0.0	0.0	3.9	278	1	0.4	0.0	2.0	96	0	0.0	0.0	3.8
Medical advice	280	1	0.4	0.0	2.0	93	0	0.0	0.0	3.9	278	17	6.1	3.6	9.6	96	3	3.1	0.6	8.9
Irritability																				
All	280	173	61.8	55.8	67.5	93	64	68.8	58.4	78.0	278	243	87.4	82.9	91.1	96	79	82.3	73.2	89.3
Grade 3	280	12	4.3	2.2	7.4	93	3	3.2	0.7	9.1	278	40	14.4	10.5	19.1	96	5	5.2	1.7	11.7
Related	280	172	61.4	55.5	67.2	93	64	68.8	58.4	78.0	278	241	86.7	82.1	90.5	96	78	81.3	72.0	88.5
Grade 3 & Related	280	12	4.3	2.2	7.4	93	3	3.2	0.7	9.1	278	40	14.4	10.5	19.1	96	5	5.2	1.7	11.7
Medical advice	280	0	0.0	0.0	1.3	93	0	0.0	0.0	3.9	278	9	3.2	1.5	6.1	96	1	1.0	0.0	5.7
Loss of appetite																				
All	280	97	34.6	29.1	40.5	93	28	30.1	21.0	40.5	278	184	66.2	60.3	71.7	96	57	59.4	48.9	69.3
Grade 3	280	8	2.9	1.2	5.6	93	1	1.1	0.0	5.8	278	13	4.7	2.5	7.9	96	1	1.0	0.0	5.7
Related	280	96	34.3	28.7	40.2	93	28	30.1	21.0	40.5	278	182	65.5	59.6	71.0	96	57	59.4	48.9	69.3
Grade 3 & Related	280	7	2.5	1.0	5.1	93	1	1.1	0.0	5.8	278	13	4.7	2.5	7.9	96	1	1.0	0.0	5.7
Medical advice	280	0	0.0	0.0	1.3	93	0	0.0	0.0	3.9	278	10	3.6	1.7	6.5	96	1	1.0	0.0	5.7

10PnEPI = 10Pn-PD-DiT + DTPw-HBV/Hib + OPV (6-10-14 weeks+ 12-18 months of age schedule)
PrevEPI = Prevenar + DTPw-HBV/Hib + OPV (6-10-14 weeks + 12-18 months of age schedule)
10Pn246 = 10Pn-PD-DiT + DTPw-HBV/Hib + IPV (2-4-6 months+ 12-18 months of age schedule)
Prev246 = Prevenar + DTPw-HBV/Hib + IPV (2-4-6 months + 12-18 months of age schedule)
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

Serious adverse events:
During the active phase of the study, 9 subjects reported at least one SAE: 2 subjects out of 280 in the 10PnEPI group, 5 subjects out of 285 in the 10Pn246 group and 2 subjects out of 98 in the Prev246 group. No fatal SAEs were reported. One of the reported SAEs in the 10Pn246 group (pharyngitis with febrile condition) was assessed by the investigator to be causally related to vaccination. All SAEs resolved without sequelae.
During the extended safety follow-up of the study, 18 subjects reported at least one SAE: 4 subjects out of 280 in the 10PnEPI, 1 subject out of 93 in the PrevEPI group, 10 subjects out of 272 in the 10Pn246 group and 3 subjects out of 95 in the Prev246 group. One fatal SAE was reported in the PrevEPI group (subject 904 died from acute respiratory distress syndrome) but was not assessed by the investigator to be causally related to vaccination. None of the other reported SAEs were assessed by the investigator to be causally related to vaccination and all resolved without sequelae.

No subjects were withdrawn due to a SAE during the active phase or during the ESFU of the study.

- MAH's conclusions

Immunogenicity

For the 6-10-14 weeks + 12-18 months of age schedule, high persisting antibody concentrations ≥ 0.2 µg/mL were observed prior to booster vaccination especially in the 10PnEPI group. Robust booster immune responses were observed in both groups and were within the same range for all serotypes common to both vaccines. In the 10PnEPI group higher antibody GMCs and OPA GMTs were observed for the common serotypes 18C and 19F compared to the PrevEPI goup.

For the 2-4-6- months + 12-18 months of age schedule persisting immune responses were observed prior to booster vaccination. Post-booster vaccination, the observed percentage of subjects with antibody concentrations ≥ 0.2 µg/mL and the percentage of subjects with opsonophagocytic activity ≥ 8 was within the same range in both groups for each of the pneumococcal serotypes common to both vaccines. The antibody GMCs and OPA GMTs were higher for most of the common serotypes in the Prev246 group compared to the 10Pn246 group except for serotype 19F (higher in the 10Pn246 group) and serotype 18C (within the same range for both groups).

Safety

The primary objective of this study was reached: a booster dose of the 10Pn-PD-DiT vaccine coadministered with DTPw-HBV/Hib and poliovirus vaccines did not induce more fever with rectal temperature > 39° C than a booster dose of Prevenar co-administered with the same vaccines.
High overall incidences of adverse events (solicited and unsolicited, general and local) were reported in the 2-4-6 months + 12-18 months of age schedule with high incidences of grade 3 pain.
Only one case of grade 3 fever was reported in the 2-4-6 months + 12-18 months of age schedule.
Low incidences of unsolicited adverse events were observed in the 6-10-14 weeks + 12-18 months schedule (less than 9.7%).
Large swelling reactions were reported by 19 subjects (5 subjects in the 6-10-14 weeks + 12-18 months schedule and 14 subjects in the 2-4-6 months + 12-18 months of age schedule). Most of these large swelling reactions were reported at the DTPw-HBV/Hib injection site (reported by 14 subjects). All were local or diffuse swelling reactions not involving adjacent joints that resolved without sequelae.
9 subjects reported at least one SAE during the active phase of the study. No fatal SAEs were reported. One of the reported SAEs was assessed by the investigator to be causally related to vaccination. All SAEs resolved without sequelae.
18 subjects reported at least one SAE during the extended safety follow-up. One fatal SAE was reported. None of the reported SAEs were assessed by the investigator to be causally related to vaccination. All SAEs resolved without sequelae.

Assessor's comments: The conclusions of the MAH are endorsed. The relatively large difference in antibody responses (GMCs and GMTs) and reacotgenicity between the EPI schedule and the 2-4-6 months schedule could be explained by the different study populations (Philippines and Poland), and the design of this study does not allow any conclusion on the different priming schedules. The study generally confirms the previously shown results on persistence and booster at 12-18 months of age.

10PN-PD-DIT-029; A phase III, single group, open study to assess the immunogenicity, safety and reactogenicity of GlaxoSmithKline (GSK) Biologicals. 10-valent pneumococcal conjugate vaccine in Mexico when co-administered with GSK Biologicals. Infanrix hexa (DTPa-HBV-IPV/Hib) vaccine as a 3-dose primary immunization course at 2, 4 and 6 months of age and GSK Biologicals. Rotarix vaccine (HRV) as a 2-dose primary immunization course at 2 and 4 months of age.

- **Methods**
  - Objective(s)

Primary:

To compare the immunogenicity of GSK Biologicals. 10-valent pneumococcal conjugate vaccine in Mexico, one month post dose III, when co-administered with GSK Biologicals. Infanrix hexa and GSK Biologicals. Rotarix vaccines, to the immune responses as observed in the pivotal non-inferiority, lot-to-lot consistency study 10PN-PD-DIT-001 in Europe.

Criteria for non-inferiority:

Comparability to the 10PN-PD-DIT-001 study in terms of non-inferiority will be demonstrated if the upper limit of the 2-sided 95% confidence interval (95% CI) on the Geometric Mean antibody

Concentration (antibody GMC) ratio.s (antibody GMCs from study 10PN-PD-DIT-001 over antibody GMCs of the current study) is below a limit of 2 for all of the 10 vaccine pneumococcal serotypes and for protein D.

Secondary:
To asses the safety and reactogenicity of GSK Biologicals. 10-valent pneumococcal conjugate vaccine in Mexico, when co-administered with GSK Biologicals. Infanrix hexa and GSK Biologicals. Rotarix vaccines.

- Study design

This was a phase III, multicentre, single-arm, open study:
- 10Pn-PD-DiT group ("10Pn" in result tables and figures): 10Pn-PD-DiT + DTPa-HBVIPV/ Hib + HRV
Three-dose primary vaccination course starting at 6 to 12 weeks of age with allowable intervals between the primary vaccination doses of 49-83 days.
One blood sample was collected one month post-dose III for the testing of antibodies against pneumococcal serotypes.
Parents/guardians were invited to enroll their child/ward in a separate study to receive a booster vaccination during the child.s/ward.s second year of life.

- Study population /Sample size

Diagnosis and criteria for inclusion:
Male or female, between and including 6-12 weeks (42-90 days) of age at the time of the first vaccination.
Subjects for whom the investigator believes that their parents/guardians could and would comply with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits).
Written informed consent obtained from the parent or guardian 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.

Sample size
Comparability to the 10PN-PD-DIT-001 study in terms of non-inferiority would be demonstrated if the upper limit of the 2-sided 95% confidence interval (95% CI) on the Geometric Mean antibody Concentration (antibody GMC) ratio.s (antibody GMCs from 10PN-PD-DIT-001 study over antibody GMC in the current study) was below a limit of 2 for antibodies against all of the 10 vaccine pneumococcal serotypes and protein D.
When comparing the local immunogenicity data with the immunogenicity data obtained from 10PN-PD-DIT-001 study, 200 evaluable subjects provided at least 98% or 85% power (under equal mean or in case of 1.2-fold decrease in antibody GMC, respectively) to show non-inferiority (limit of 2) 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 antibody GMC ratios for the 10 vaccine pneumococcal serotypes and protein D. Considering that up to 13% of the subjects enrolled would be excluded from the ATP cohort for analysis of immunogenicity, 230 subjects were to be enrolled.

- Treatments

Vaccination schedules:
- 10Pn-PD-DiT: 2-4-6 months of age
- Infanrix hexa (DTPa-HBV-IPV/Hib): 2-4-6 months of age
- Rotarix (oral live attenuated HRV vaccine): 2-4 months of age

- Outcomes/endpoints

Immunogenicity:
One month post-dose III of the 10Pn-PD-DiT vaccine:
Antibody concentrations against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (22F-inhibition ELISA).
Opsonophagocytic activity (OPA) against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.
Antibody concentrations against pneumococcal cross-reactive serotypes 6A and 19A (22F inhibition ELISA).

Opsonophagocytic activity against pneumococcal cross-reactive serotypes 6A and 19A.
Antibody concentrations against protein D

Safety /reactogenicity:
Occurrence of solicited local symptoms (any and grade 3) within 4 days (days 0-3) after each vaccination dose.
Occurrence of solicited general symptoms (any and grade 3) within 4 days (days 0-3) after each vaccination dose.
Occurrence of unsolicited adverse events within 31 days (days 0-30) after each vaccination dose.
Occurrence of serious adverse events following the administration of the first dose of study vaccine throughout the entire study period up to Visit 4.

- Statistical Methods

Immunogenicity:
Confirmatory inferential analysis
95% CIs for the ELISA antibody GMC ratio (antibody GMCs from 10PN-PD-DIT-001 study over antibody GMCs from current study), one month post-dose III, was computed for antibodies against each of the 10 vaccine pneumococcal serotypes and protein D, using an ANOVA model on the logarithm10 transformation of the concentrations (pooled variance).
The primary objective of comparison of immunogenicity data from the current study to the 10PN-PDDIT- 001 study would be reached if the upper limit of the 2-sided 95% confidence interval (95% CI) on the antibody GMC ratios (antibody GMCs from 10PN-PD-DIT-001 study over antibody GMCs in the current study) was below a limit of 2 for all of the 10 vaccine pneumococcal serotypes and protein D.

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

Safety /reactogenicity:
Descriptive analysis:
Incidence of solicited and/or unsolicited local and/or general adverse events during the 31-day (days 0-30) post-vaccination period was calculated with exact 95% CI, after each vaccine dose and overall, according to the type of symptom, intensity and relationship to vaccination.
Incidence of each local and each general solicited symptom reported during the 4-day (days 0-3) post-vaccination period was calculated with exact 95% CI, after each vaccine dose and overall, according to the type of symptom, intensity and relationship to vaccination.
The percentages of subjects with at least one unsolicited symptom classified by the Medical Dictionary for Regulatory Activities (MedDRA) and reported within the 31-day post-vaccination period were summarized with exact 95% CI, after each vaccine dose and overall. The same tabulations were performed for unsolicited adverse events classified as grade 3, with causal relationship and with medically attended visit.
Prevalence of concomitant antipyretic/medication during the 4-day (days 0-3) post-vaccination period was computed with exact 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

	10Pn
Number of subjects vaccinated	230
Number of subjects completed	226
Number of subjects withdrawn	4

- Efficacy results

Confirmatory inferential analysis:

The primary objective of non-inferiority of the immune response of the 10Pn-PD-DiT vaccine in Mexican children compared to the immunogenicity in the pivotal 10PN-PD-DIT-001 study in Europe was reached since the upper limit of the 2-sided 95% CI for ELISA antibody GMC ratios (10Pn group in study 10PN-PD-DIT-001 / 10Pn group in study 10PN-PD-DIT-029) was below the protocol defined limit of 2 for all of the 10 vaccine pneumococcal serotypes and protein D.

ELISA antibody GMCs from the 10Pn group in study 10PN-PD-DIT-029 were statistically significantly higher than for the 10Pn group in study 10PN-PD-DIT-001, for all of the 10 vaccine pneumococcal serotypes and protein D (upper limit of the 95% CIs of the GMC ratios below 1).

Table 1: Ratios of post-dose III antibody GMCs, between 10Pn-001 (10PN-PD-DIT-001) and 10Pn-029 (10PN-PD-DIT-029) groups, with their 95% CIs 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)

							GMC ratio			
									95% CI	
Antibody	Group description	N	GMC	Group description	N	GMC	Ratio order	Value	LL	UL
ANTI-1	10Pn-001	1100	1.05	10Pn-029	219	2.13	10Pn-001 /10Pn-029	0.49	0.44	0.55
ANTI-4	10Pn-001	1106	1.45	10Pn-029	218	3.04	10Pn-001 /10Pn-029	0.48	0.42	0.54
ANTI-5	10Pn-001	1104	1.70	10Pn-029	218	3.24	10Pn-001 /10Pn-029	0.52	0.47	0.59
ANTI-6B	10Pn-001	1100	0.33	10Pn-029	218	1.32	10Pn-001 /10Pn-029	0.25	0.21	0.30
ANTI-7F	10Pn-001	1107	1.72	10Pn-029	218	3.72	10Pn-001 /10Pn-029	0.46	0.41	0.52
ANTI-9V	10Pn-001	1103	1.32	10Pn-029	218	3.71	10Pn-001 /10Pn-029	0.35	0.32	0.40
ANTI-14	10Pn-001	1100	2.90	10Pn-029	218	5.27	10Pn-001 /10Pn-029	0.55	0.48	0.63
ANTI-18C	10Pn-001	1102	1.66	10Pn-029	219	6.05	10Pn-001 /10Pn-029	0.27	0.24	0.32
ANTI-19F	10Pn-001	1104	1.84	10Pn-029	219	5.49	10Pn-001 /10Pn-029	0.34	0.28	0.40
ANTI-23F	10Pn-001	1102	0.53	10Pn-029	218	2.00	10Pn-001 /10Pn-029	0.27	0.22	0.32

10Pn-001 = Pooled 10Pn-PD-DiT lots + DTPa-HBV-IPV/Hib (10PN-PD-DIT-001 study)
10Pn-029 = 10Pn-PD-DiT + DTPa-HBV-IPV/Hib + HRV (2 doses) (10PN-PD-DIT-029 study)
GMC = geometric mean antibody concentration; N = Number of subjects with post-vaccination results available;
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit

Table 2: Ratios of post-dose III antibody GMCs, between 10Pn-001 (10PN-PD-DIT-001) and 10Pn-029 (10PN-PD-DIT-029) groups, with their 95% CIs for ANTI-PD antibodies (ATP cohort for immunogenicity)

						GMC ratio			
								95% CI	
Group description	N	GMC	Group description	N	GMC	Ratio order	Value	LL	UL
10Pn-001	1095	1529.9	10Pn-029	219	2923.2	10Pn-001 /10Pn-029	0.52	0.46	0.60

10Pn-001 = Pooled 10Pn-PD-DiT lots + DTPa-HBV-IPV/Hib (10PN-PD-DIT-001 study)
10Pn-029 = 10Pn-PD-DiT + DTPa-HBV-IPV/Hib + HRV (2 doses) (10PN-PD-DIT-029 study)
GMC = geometric mean antibody concentration; N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit.

- Safety results

The most frequently reported solicited local adverse event was pain. High overall/dose incidence of grade 3 pain was reported which was however within the same range at the 10Pn-PD-DiT and DTPa-HBV-IPV/Hib injection sites (15.0% and 14.5% of doses respectively).

Table 5: Incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period, overall/dose (Total vaccinated cohort)

			10Pn				
						95% CI	
Symptom	**Product**	**Type**	**N**	**n**	**%**	**LL**	**UL**
Pain	Total	All	685	406	59.3	55.5	63.0
		Grade 3	685	112	16.4	13.7	19.3
		Medical advice	685	2	0.3	0.0	1.1
	10Pn-PD-DiT	All	685	383	55.9	52.1	59.7
		Grade 3	685	103	15.0	12.4	17.9
		Medical advice	685	1	0.1	0.0	0.8
	DTPa-HBV-IPV/Hib	All	684	376	55.0	51.2	58.7
		Grade 3	684	99	14.5	11.9	17.3
		Medical advice	684	2	0.3	0.0	1.1
Redness (mm)	Total	All	685	168	24.5	21.3	27.9
		>20.0	685	7	1.0	0.4	2.1
		>30.0	685	0	0.0	0.0	0.5
		Medical advice	685	1	0.1	0.0	0.8
	10Pn-PD-DiT	All	685	149	21.8	18.7	25.0
		>20.0	685	2	0.3	0.0	1.1
		>30.0	685	0	0.0	0.0	0.5
		Medical advice	685	1	0.1	0.0	0.8
	DTPa-HBV-IPV/Hib	All	684	141	20.6	17.6	23.8
		>20.0	684	7	1.0	0.4	2.1
		>30.0	684	0	0.0	0.0	0.5
		Medical advice	684	1	0.1	0.0	0.8
Swelling (mm)	Total	All	685	352	51.4	47.6	55.2
		>20.0	685	34	5.0	3.5	6.9
		>30.0	685	15	2.2	1.2	3.6
		Medical advice	685	2	0.3	0.0	1.1
	10Pn-PD-DiT	All	685	306	44.7	40.9	48.5
		>20.0	685	26	3.8	2.5	5.5
		>30.0	685	10	1.5	0.7	2.7
		Medical advice	685	1	0.1	0.0	0.8
	DTPa-HBV-IPV/Hib	All	684	306	44.7	41.0	48.6
		>20.0	684	26	3.8	2.5	5.5
		>30.0	684	11	1.6	0.8	2.9
		Medical advice	684	2	0.3	0.0	1.1

10Pn = 10Pn-PD-DiT + DTPa-HBV-IPV/Hib + HRV (2 doses); 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. 95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

The most frequently reported solicited general adverse event was irritability. Low incidences of grade 3 solicited general adverse events, were reported (maximum 3.5%) and most of these were considered by the investigator to be causally related to vaccination. No grade 3 fever (axillary temperature > 39.5°C) was reported during the 4-day post-vaccination period.

Table 6: Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period, overall/dose (Total vaccinated cohort)

		10Pn				
					95% CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**
Diarrhoea	All	685	66	9.6	7.5	12.1
	Grade 3	685	5	0.7	0.2	1.7
	Related	685	65	9.5	7.4	11.9
	Grade 3 & Related	685	5	0.7	0.2	1.7
	Medical advice	685	6	0.9	0.3	1.9
Drowsiness	All	685	269	39.3	35.6	43.0
	Grade 3	685	7	1.0	0.4	2.1
	Related	685	263	38.4	34.7	42.2
	Grade 3 & Related	685	7	1.0	0.4	2.1
	Medical advice	685	1	0.1	0.0	0.8
Fever(Axillary) (°C)	All	685	231	33.7	30.2	37.4
	>38.0	685	97	14.2	11.6	17.0
	>38.5	685	23	3.4	2.1	5.0
	>39.0	685	2	0.3	0.0	1.1
	>39.5	685	0	0.0	0.0	0.5
	Related	685	230	33.6	30.0	37.3
	>39.5 & Related	685	0	0.0	0.0	0.5
	Medical advice	685	4	0.6	0.2	1.5
Irritability	All	685	406	59.3	55.5	63.0
	Grade 3	685	24	3.5	2.3	5.2
	Related	685	398	58.1	54.3	61.8
	Grade 3 & Related	685	23	3.4	2.1	5.0
	Medical advice	685	5	0.7	0.2	1.7
Loss of appetite	All	685	155	22.6	19.5	25.9
	Grade 3	685	1	0.1	0.0	0.8
	Related	685	151	22.0	19.0	25.3
	Grade 3 & Related	685	1	0.1	0.0	0.8
	Medical advice	685	4	0.6	0.2	1.5
Vomiting	All	685	80	11.7	9.4	14.3
	Grade 3	685	8	1.2	0.5	2.3
	Related	685	80	11.7	9.4	14.3
	Grade 3 & Related	685	8	1.2	0.5	2.3
	Medical advice	685	2	0.3	0.0	1.1

10Pn = 10Pn-PD-DiT + DTPa-HBV-IPV/Hib + HRV (2 doses). 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

Unsolicited adverse events

48.9% of administered doses were followed by at least one unsolicited AE. The most frequently reported unsolicited AE was nasopharyngitis. Low overall/dose incidences of unsolicited AEs considered by the investigator to be causally related to vaccination (maximum 3.8%) or grade 3 unsolicited AEs (maximum 4.8%) were observed.

Serious adverse events

One subject experienced a fatal SAE (nasopharyngitis and bronchopneumonia) which was not considered by the investigator to be causally related to vaccination.

14 out of 230 vaccinated subjects reported at least one non-fatal SAE during the entire study period. None was considered by the investigator to be causally related to vaccination. One subject reported

one SAE (convulsive disorder) which was still ongoing at the end of the study. The same subject reported 2 other SAEs which both resolved with sequelae.

Withdrawals due to adverse events /serious adverse events:
2 subjects were withdrawn due to a serious adverse event (SAE):
One subject was diagnosed with an infarction of the germinal matrix of the brain on the day of administration of the second dose of study vaccines. The event resolved without sequelae and was not considered by the investigator to be causally related to vaccination.

One subject died 3 days after study vaccination due to nasopharyngitis and bronchopneumonia. An autopsy was not performed. The events were not considered by the investigator to be causally related to vaccination.

Assessor's comment: This study confirms previously reported results. No further action is required based on this study.

10PN-PD-DIT-031; Primary vaccination course in children receiving the pneumococcal vaccine GSK 1024850A, Infanrix hexa and Rotarix.

- **Description**

- **Methods**

- Objective(s)

Primary:

- To evaluate the immunogenicity of GSK Biologicals. 10-valent pneumococcal conjugate vaccine in Taiwan, one month post-dose III, when co-administered with GSK Biologicals. Infanrix hexa and GSK Biologicals. Rotarix vaccines.

Secondary:

- To assess the safety and reactogenicity of GSK Biologicals. 10-valent pneumococcal conjugate vaccine in Taiwan, when co-administered with GSK Biologicals. Infanrix hexa and GSK Biologicals. Rotarix vaccines.
- To assess the immunogenicity of GSK Biologicals. Infanrix hexa and Rotarix vaccines, when coadministered with GSK Biologicals. 10-valent pneumococcal conjugate vaccine.

- Study design

This was a phase III, multicentre, single-arm, open study:

- Study population /Sample size

Diagnosis and criteria for inclusion:
Male or female between, and including 6-8 weeks (42-62 days) of age at the time of 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.

- Treatments

Three-dose primary vaccination course with 10Pn-PD-DiT and DTPa-HBV-IPV/Hib vaccines starting at 6 to 8 weeks (42-62 days) of age with allowable intervals between the primary vaccination doses of 35-63 days between visits 1 and 2, 77 to 110 days between visits 2 and 3 and 30 to 42 days between visits 3 and 4. HRV vaccine was administered as a 2-dose primary vaccination starting at 6 to 8 weeks (42-62 days) of age with allowable intervals between the primary vaccination doses of 35-63 days between visits 1 and 2.
Two blood samples were collected: prior to dose I and one month post-dose III.

- Outcomes/endpoints

Immunogenicity:

Antibody concentrations against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F (22F-inhibition ELISA), prior to dose I and one month post-dose III;
Opsonophagocytic activity (OPA) against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F, one month post-dose III;
Antibody concentrations against protein D, prior to dose I and one month post-dose III;
Antibody concentrations against diphtheria, tetanus, PT, FHA, PRN, HBs and PRP, one month post-dose.
Titres against polio type 1, 2 and 3, one month post-dose III.
Serum rotavirus IgA antibody concentrations, four months post-dose II.

Safety:
Occurrence of solicited local symptoms (any and grade 3) within 4 days (days 0-3) after each vaccination dose.
Occurrence of solicited general symptoms (any and grade 3) within 4 days (days 0-3) after each vaccination dose.
Occurrence of unsolicited adverse events within 31 days (days 0-30) after each vaccination dose.
Occurrence of serious adverse events following the administration of the first dose of study vaccine throughout the entire study period up to Visit 4.

- Statistical Methods

Immunogenicity:
Descriptive analyses:
Geometric mean antibody concentrations/OPA titres (antibody GMCs/GMTs) with 95% CIs were tabulated for each appropriate serotype/antigen at each applicable blood sampling time point.
Seropositivity/seroprotection rates with exact 95% CIs were calculated for each appropriate serotype/antigen at each applicable blood sampling time point.
The distribution of antibody concentrations/titres was displayed by using tables and/or reverse cumulative distribution curves for each appropriate serotype/antigen at each applicable blood sampling time point.

Safety/reactogenicity:
Descriptive analyses:
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

Planned: 230
Enrolled: 230
Completed: 229
Safety Total vaccinated cohort: 222
Immunogenicity ATP cohort: 219

- Efficacy results

Immune response to the pneumococcal vaccine
Descriptive analysis:
One month post-dose III, for each of the vaccine pneumococcal serotypes, at least 95.4% of subjects had antibody concentration ≥ 0.2 µg/mL (Table 1).

One month post-dose III, for each of the vaccine pneumococcal serotypes, at least 96.1% of subjects had an opsonophagocytic activity ≥ 8, except for serotype 6B (87.3%) (Table 2).
One month post-dose III, all subjects, except one, had measurable antibodies against protein D (≥ 100 EL.U/mL).

Table 1: 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)

				≥ 0.2 µg/mL				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
ANTI-1	10Pn	PIII(M5.5)	219	219	100	98.3	100	2.92	2.65	3.22
ANTI-4	10Pn	PIII(M5.5)	219	218	99.5	97.5	100	3.79	3.42	4.19
ANTI-5	10Pn	PIII(M5.5)	219	219	100	98.3	100	4.50	4.11	4.93
ANTI-6B	10Pn	PIII(M5.5)	219	209	95.4	91.8	97.8	1.69	1.47	1.94
ANTI-7F	10Pn	PIII(M5.5)	219	219	100	98.3	100	4.07	3.72	4.46
ANTI-9V	10Pn	PIII(M5.5)	219	219	100	98.3	100	3.90	3.51	4.32
ANTI-14	10Pn	PIII(M5.5)	219	218	99.5	97.5	100	5.69	5.10	6.35
ANTI-18C	10Pn	PIII(M5.5)	219	219	100	98.3	100	7.28	6.43	8.25
ANTI-19F	10Pn	PIII(M5.5)	219	219	100	98.3	100	8.04	7.37	8.78
ANTI-23F	10Pn	PIII(M5.5)	218	212	97.2	94.1	99.0	2.81	2.44	3.22

10Pn = 10Pn-PD-DiT + DTPa-HBV-IPV/Hib + HRV (2 doses). 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(M5.5) = one month after dose III

Table 2: 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(M5.5)	102	98	96.1	90.3	98.9	206.6	158.9	268.6
OPSONO-4	10Pn	PIII(M5.5)	103	103	100	96.5	100	1227.4	1054.7	1428.4
OPSONO-5	10Pn	PIII(M5.5)	102	101	99.0	94.7	100	233.8	189.6	288.3
OPSONO-6B	10Pn	PIII(M5.5)	102	89	87.3	79.2	93.0	685.2	439.8	1067.7
OPSONO-7F	10Pn	PIII(M5.5)	103	103	100	96.5	100	5053.9	4279.2	5968.8
OPSONO-9V	10Pn	PIII(M5.5)	98	98	100	96.3	100	2052.9	1691.4	2491.7
OPSONO-14	10Pn	PIII(M5.5)	102	101	99.0	94.7	100	1259.7	1004.8	1579.1
OPSONO-18C	10Pn	PIII(M5.5)	101	99	98.0	93.0	99.8	319.5	239.8	425.6
OPSONO-19F	10Pn	PIII(M5.5)	103	101	98.1	93.2	99.8	567.3	450.7	713.9
OPSONO-23F	10Pn	PIII(M5.5)	102	98	96.1	90.3	98.9	2542.5	1832.0	3528.6

10Pn = 10Pn-PD-DiT + DTPa-HBV-IPV/Hib + HRV (2 doses)
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(M5.5) = one month after dose III

Immune response to the co-administered DTPa-HBV-IPV/Hib and HRV vaccines
All subjects were seroprotected/seropositive for antibodies against diphtheria, tetanus, each of the pertussis antigens (PT, FHA and PRN) and the hepatitis B surface (HBs) antigens one month post dose III. All subjects were seroprotected against poliovirus types 1, 2 and 3 (titres ≥ 8). All subjects had seropositive anti-PRP antibody levels (≥ 0.15 µg/mL), whereas 96.6% of subjects had seroprotective anti-PRP antibody levels (≥ 1 µg/mL).
Four months post-dose II, 86.3% of subjects had a seropositive anti-HRV level (≥20 U/mL). Antibody GMC calculated for seropositive subjects at visit 4 was 273 U/mL.

- Safety results

Solicited adverse events:
The most frequently reported solicited local AE was redness. Low overall/dose incidence of grade 3 solicited local AEs was reported whatever the injection site (from 0.7% for redness to 4.2% for pain).

Table 5: Incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period, overall/dose (Total vaccinated cohort)

			10Pn				
						95% CI	
Symptom	Product	Type	N	n	%	LL	UL
Pain	Total	All	686	272	39.7	36.0	43.4
		Grade 3	686	29	4.2	2.8	6.0
		Medical advice	686	0	0.0	0.0	0.5
	10Pn-PD-DiT	All	686	253	36.9	33.3	40.6
		Grade 3	686	26	3.8	2.5	5.5
		Medical advice	686	0	0.0	0.0	0.5
	DTPa-HBV-IPV/Hib	All	685	253	36.9	33.3	40.7
		Grade 3	685	24	3.5	2.3	5.2
		Medical advice	685	0	0.0	0.0	0.5
Redness (mm)	Total	All	686	297	43.3	39.5	47.1
		>20.0	686	11	1.6	0.8	2.9
		>30.0	686	5	0.7	0.2	1.7
		Medical advice	686	0	0.0	0.0	0.5
	10Pn-PD-DiT	All	686	260	37.9	34.3	41.6
		>20.0	686	6	0.9	0.3	1.9
		>30.0	686	2	0.3	0.0	1.0
		Medical advice	686	0	0.0	0.0	0.5
	DTPa-HBV-IPV/Hib	All	685	266	38.8	35.2	42.6
		>20.0	685	9	1.3	0.6	2.5
		>30.0	685	4	0.6	0.2	1.5
		Medical advice	685	0	0.0	0.0	0.5
Swelling (mm)	Total	All	686	263	38.3	34.7	42.1
		>20.0	686	14	2.0	1.1	3.4
		>30.0	686	6	0.9	0.3	1.9
		Medical advice	686	0	0.0	0.0	0.5
	10Pn-PD-DiT	All	686	207	30.2	26.8	33.8
		>20.0	686	6	0.9	0.3	1.9
		>30.0	686	2	0.3	0.0	1.0
		Medical advice	686	0	0.0	0.0	0.5
	DTPa-HBV-IPV/Hib	All	685	242	35.3	31.7	39.0
		>20.0	685	11	1.6	0.8	2.9
		>30.0	685	5	0.7	0.2	1.7
		Medical advice	685	0	0.0	0.0	0.5

10Pn = 10Pn-PD-DiT + DTPa-HBV-IPV/Hib + HRV (2 doses)
N= number of documented doses
n/%= number/percentage of doses followed by at least one type of symptom
Total: n/%= number/percentage of doses with at least one local symptom whatever the number of injections.
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

The most frequently reported solicited general AE was irritability. The overall/dose incidence of grade 3 solicited general AEs ranged from 0.0% (fever and diarrhoea) to 6.3% (irritability). Most of the grade 3 solicited general AEs were considered by the investigator to be causally related to vaccination.

Table 6: Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period, overall/dose (Total vaccinated cohort)

		10Pn				
					95% CI	
Symptom	Type	N	n	%	LL	UL
Diarrhoea*	All	686	7	1.0	0.4	2.1
	Grade 3	686	0	0.0	0.0	0.5
	Related	686	4	0.6	0.2	1.5
	Grade 3 & Related	686	0	0.0	0.0	0.5
	Medical advice	686	1	0.1	0.0	0.8
Drowsiness	All	686	384	56.0	52.2	59.7
	Grade 3	686	8	1.2	0.5	2.3
	Related	686	335	48.8	45.0	52.6
	Grade 3 & Related	686	7	1.0	0.4	2.1
	Medical advice	686	1	0.1	0.0	0.8
Fever/(Rectally) (°C)	All	686	256	37.3	33.7	41.1
	>38.5	686	82	12.0	9.6	14.6
	>39.0	686	24	3.5	2.3	5.2
	>39.5	686	5	0.7	0.2	1.7
	>40.0	686	0	0.0	0.0	0.5
	Related	686	234	34.1	30.6	37.8
	>40.0 & Related	686	0	0.0	0.0	0.5
	Medical advice	686	3	0.4	0.1	1.3
Irritability	All	686	423	61.7	57.9	65.3
	Grade 3	686	43	6.3	4.6	8.4
	Related	686	362	52.8	49.0	56.6
	Grade 3 & Related	686	34	5.0	3.5	6.9
	Medical advice	686	0	0.0	0.0	0.5
Loss of appetite	All	686	281	41.0	37.3	44.7
	Grade 3	686	5	0.7	0.2	1.7
	Related	686	235	34.3	30.7	37.9
	Grade 3 & Related	686	3	0.4	0.1	1.3
	Medical advice	686	2	0.3	0.0	1.0
Vomiting (occurrences)	All	686	73	10.6	8.4	13.2
	≥3	686	7	1.0	0.4	2.1
	Related	686	47	6.9	5.1	9.0
	≥3 & Related	686	4	0.6	0.2	1.5
	Medical advice	686	1	0.1	0.0	0.8

10Pn = 10Pn-PD-DiT + DTPa-HBV-IPV/Hib + HRV (2 doses)
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
*Grade 3 for diarrhoea: ≥6 looser than normal stools/day

Unsolicited adverse events:
18.0% of administered doses were followed by at least one unsolicited AE. The most frequently reported unsolicited AE was upper respiratory tract infection (9.0% of overall doses).
A low overall/dose incidence of unsolicited AEs considered by the investigator to be causally related to vaccination (maximum 0.3% of overall doses) or grade 3 unsolicited adverse events (maximum 0.4% of overall doses) were observed.

Serious adverse events:

15 out of 230 vaccinated subjects reported at least one SAE during the entire study period. No fatal SAE was reported during the entire study period.
None of the reported SAEs was considered by the investigator to be causally related to vaccination.
Subject number 103 had one SAE (dermatitis atopic) which was still ongoing at the end of the study.
There was no withdrawal due to adverse events /serious adverse events.

Assessor's comment: This study confirms the previously reported results for Synflorix, and does not change the benefit risk balance. No further regulatory action is required following this study.

10PN-PD-DIT-032; A phase III, randomized, open, controlled study to assess the immunogenicity, safety and reactogenicity of GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine as a 3-dose primary immunization course at 6, 10 and 14 weeks of age in Sub-Saharan Africa, coadministered with GSK Biologicals' DTPw-HBV/Hib and OPV vaccines.

- **Description**

A phase III, randomized, open, controlled study to assess the immunogenicity, safety and reactogenicity of GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine as a 3-dose primary immunization course at 6, 10 and 14 weeks of age in Sub-Saharan Africa, co-administered with GSK Biologicals' DTPw-HBV/Hib and HPV vaccines.

- **Methods**

- Objective(s)

Primary:
To evaluate the immunogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine in infants in Sub-Saharan Africa, one month post dose 3.
Secondary:
o assess the safety and reactogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine in infants in Sub-Saharan Africa.
To evaluate the immunogenicity of GSK Biologicals' Zilbrix Hib vaccine, co-administered with GSK Biologicals' 10-valent pneumococcal conjugate vaccine.

- Study design

This was a multi-center, open, randomized, controlled study with two parallel groups:

- 10Pn-PD-DiT group (referred as '10Pn' in results tables and figures): subjects primed with three doses of the 10Pn-PD-DiT vaccine co-administered with DTPw-HBV/Hib and OPV vaccines.
- Zilbrix Hib group (referred as 'Zilbrix' in results tables and figures): subjects primed with three doses of DTPw-HBV/Hib and OPV vaccines.

Treatment allocation 2:1
Three-dose primary vaccination course at 6, 10 and 14 weeks of age.
Blood samples were collected prior to vaccination and one month post dose 3.

- Study population /Sample size

Diagnosis and criteria for inclusion:
Male or female between, and including 6-10 weeks (42-76 days) of age at the time of the first vaccination.
Written or oral, signed or thumb-printed informed consent obtained from the parent(s) or guardian(s) of the subject. Where parent(s)/guardian(s) were illiterate, the consent form was to be countersigned by a witness.
Free of any known or suspected health problems, as established by medical history and clinical examination before entering into the study, that would contraindicate the initiation of routine immunizations outside a clinical trial context.

The target sample size was 345 enrolled subjects (230 in the 10Pn-PD-DiT group and 115 in the Zilbrix Hib group).

- Treatments

Vaccination schedule /site: The 10Pn-PD-DiT and DTPw-HBV/Hib vaccines were administered intramuscularly in the right and left thigh, respectively. The OPV vaccine was given orally. All vaccines were given at 6, 10 and 14 weeks of age.

- Outcomes/endpoints

Immunogenicity:
Prior to any vaccination and one month after dose 3:
Antibody concentrations against pneumococcal serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (22F-inhibition ELISA).
Antibody concentrations against protein D.
Opsonophagocytic activity (OPA) against pneumococcal serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.
Antibody concentrations against diphtheria, tetanus, B. pertussis, HBs and PRP.

Safety /reactogenicity:
Occurrence of fever (oral/axillary/tympanic temperature > 38.5°C or rectal temperature > 39.0°C) within 4 days (days 0 to 3) after at least one vaccination.
Occurrence of solicited local symptoms (any and grade 3) within 4 days (days 0-3) after each vaccination.
Occurrence of solicited general symptoms (any and grade 3) within 4 days (days 0-3) after each vaccination.
Occurrence of unsolicited adverse events within 31 days (days 0-30) after each vaccination.
Occurrence of serious adverse events following the administration of the first dose of the study vaccines throughout the entire study period up to Visit 4.

- Statistical Methods

Immunogenicity:
Descriptive analyses:
Geometric mean concentrations/titers (GMCs/GMTs) with 95% CIs were tabulated for each appropriate serotype/antigen at each applicable blood sampling time point.
Seropositivity/seroprotection rates with exact 95% CIs were calculated for each appropriate serotype/antigen at each applicable blood sampling time point.
The distribution of antibody concentrations/titers was displayed by using tables and/or reverse cumulative distribution curves for each appropriate serotype/antigen at each applicable blood sampling time point.
Geometric mean of ratios of opsonophagocytic titers/ELISA antibody concentrations with 95% CIs was tabulated for each appropriate pneumococcal serotype at each applicable blood sampling time point.

Safety/reactogenicity:
Descriptive analyses:
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 (SAEs) reported during the entire study period were described in detail.

➢ **Results**

- Recruitment/ Number analysed

357 subjects (239 subjects in the 10Pn group and 118 subjects in the Zilbrix group) out of 365 enrolled subjects were vaccinated. 347 subjects (231 subjects in the 10Pn group and 116 subjects in the Zilbrix group) completed the study.

- Efficacy results

Immune response to the pneumococcal vaccine:
One month post-dose III, for each of the vaccine pneumococcal serotypes, at least 97.2% of subjects in the 10Pn group had antibody concentrations ≥0.2 µg/mL, except for serotypes 6B (82.0%) and 23F (87.6%). (Table 1). Although higher antibody GMCs were observed for serotypes 6B, 9V, 14, 18C and

23F in Nigeria (no overlap of 95% CIs), the percentages of subjects with antibody concentrations ≥0.2 µg/mL were in the same ranges for both countries.

Table 1: 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	PRE	204	126	61.8	54.7	68.5	40	19.6	14.4	25.7	0.07	0.06	0.09
		PIII(M3)	217	217	100	98.3	100	217	100	98.3	100	2.69	2.42	2.99
	Zilbrix	PRE	110	65	59.1	49.3	68.4	20	18.2	11.5	26.7	0.07	0.06	0.09
		PIII(M3)	108	14	13.0	7.3	20.8	2	1.9	0.2	6.5	0.03	0.03	0.03
ANTI-4	10Pn	PRE	209	116	55.5	48.5	62.4	31	14.8	10.3	20.4	0.07	0.06	0.08
		PIII(M3)	217	217	100	98.3	100	217	100	98.3	100	3.44	3.06	3.87
	Zilbrix	PRE	112	61	54.5	44.8	63.9	18	16.1	9.8	24.2	0.07	0.06	0.08
		PIII(M3)	112	12	10.7	5.7	18.0	3	2.7	0.6	7.6	0.03	0.03	0.03
ANTI-5	10Pn	PRE	210	120	57.1	50.2	63.9	37	17.6	12.7	23.5	0.07	0.06	0.08
		PIII(M3)	217	217	100	98.3	100	217	100	98.3	100	4.17	3.75	4.63
	Zilbrix	PRE	111	58	52.3	42.6	61.8	22	19.8	12.9	28.5	0.07	0.05	0.08
		PIII(M3)	109	18	16.5	10.1	24.8	4	3.7	1.0	9.1	0.03	0.03	0.04
ANTI-6B	10Pn	PRE	205	137	66.8	59.9	73.2	43	21.0	15.6	27.2	0.09	0.07	0.10
		PIII(M3)	217	196	90.3	85.6	93.9	178	82.0	76.3	86.9	0.95	0.76	1.20
	Zilbrix	PRE	111	75	67.6	58.0	76.1	35	31.5	23.0	41.0	0.10	0.08	0.12
		PIII(M3)	112	15	13.4	7.7	21.1	2	1.8	0.2	6.3	0.03	0.03	0.03
ANTI-7F	10Pn	PRE	207	137	66.2	59.3	72.6	56	27.1	21.1	33.6	0.09	0.08	0.11
		PIII(M3)	217	217	100	98.3	100	216	99.5	97.5	100	3.33	2.99	3.71
	Zilbrix	PRE	111	76	68.5	59.0	77.0	26	23.4	15.9	32.4	0.08	0.07	0.10
		PIII(M3)	110	19	17.3	10.7	25.7	2	1.8	0.2	6.4	0.03	0.03	0.04
ANTI-9V	10Pn	PRE	208	159	76.4	70.1	82.0	80	38.5	31.8	45.4	0.13	0.11	0.16
		PIII(M3)	217	213	98.2	95.3	99.5	211	97.2	94.1	99.0	2.39	2.06	2.76
	Zilbrix	PRE	110	86	78.2	69.3	85.5	43	39.1	29.9	48.9	0.15	0.11	0.19
		PIII(M3)	112	31	27.7	19.6	36.9	11	9.8	5.0	16.9	0.04	0.03	0.05
ANTI-14	10Pn	PRE	206	200	97.1	93.8	98.9	181	87.9	82.6	92.0	0.75	0.64	0.89
		PIII(M3)	217	217	100	98.3	100	215	99.1	96.7	99.9	3.80	3.24	4.46
	Zilbrix	PRE	110	109	99.1	95.0	100	93	84.5	76.4	90.7	0.76	0.60	0.97
		PIII(M3)	112	91	81.3	72.8	88.0	40	35.7	26.9	45.3	0.14	0.11	0.17
ANTI-18C	10Pn	PRE	204	151	74.0	67.4	79.9	74	36.3	29.7	43.3	0.12	0.10	0.15
		PIII(M3)	217	216	99.5	97.5	100	216	99.5	97.5	100	10.01	8.49	11.80
	Zilbrix	PRE	110	80	72.7	63.4	80.8	38	34.5	25.7	44.2	0.12	0.09	0.15
		PIII(M3)	112	23	20.5	13.5	29.2	4	3.6	1.0	8.9	0.03	0.03	0.04
ANTI-19F	10Pn	PRE	208	191	91.8	87.2	95.2	142	68.3	61.5	74.5	0.33	0.28	0.40
		PIII(M3)	217	217	100	98.3	100	214	98.6	96.0	99.7	7.65	6.55	8.93
	Zilbrix	PRE	111	111	100	96.7	100	76	68.5	59.0	77.0	0.36	0.29	0.45
		PIII(M3)	111	73	65.8	56.2	74.5	25	22.5	15.1	31.4	0.08	0.07	0.10
ANTI-23F	10Pn	PRE	202	114	56.4	49.3	63.4	59	29.2	23.0	36.0	0.08	0.07	0.10
		PIII(M3)	217	207	95.4	91.7	97.8	190	87.6	82.4	91.6	1.10	0.91	1.33
	Zilbrix	PRE	108	67	62.0	52.2	71.2	34	31.5	22.9	41.1	0.10	0.07	0.12
		PIII(M3)	112	23	20.5	13.5	29.2	3	2.7	0.6	7.6	0.03	0.03	0.04

10Pn = 10Pn-PD-DiT + DTPw-HBV/Hib + OPV
Zilbrix = DTPw-HBV/Hib + OPV
GMC = geometric mean 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
PRE = before first dose
PIII(M3) = one month after dose III

One month post-dose III, for each of the vaccine pneumococcal serotypes, at least 93.3% of subjects in the 10Pn group had opsonophagocytic activity ≥8, except for serotypes 1 (87.6%) and 6B (85.4%) (Table 2).

Table 2: 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 antibodies (ATP cohort for immunogenicity)

				≥ 8				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
OPSONO-1	10Pn	PIII(M3)	105	92	87.6	79.8	93.2	83.0	61.7	111.7
	Zilbrix	PIII(M3)	56	3	5.4	1.1	14.9	5.0	3.8	6.4
OPSONO-4	10Pn	PIII(M3)	105	105	100	96.5	100	892.5	759.4	1049.0
	Zilbrix	PIII(M3)	55	3	5.5	1.1	15.1	4.6	3.9	5.5
OPSONO-5	10Pn	PIII(M3)	105	100	95.2	89.2	98.4	82.7	65.4	104.4
	Zilbrix	PIII(M3)	56	2	3.6	0.4	12.3	4.5	3.8	5.2
OPSONO-6B	10Pn	PIII(M3)	103	88	85.4	77.1	91.6	538.6	346.0	838.3
	Zilbrix	PIII(M3)	54	5	9.3	3.1	20.3	5.7	4.1	7.9
OPSONO-7F	10Pn	PIII(M3)	105	105	100	96.5	100	2733.0	2188.3	3413.3
	Zilbrix	PIII(M3)	49	21	42.9	28.8	57.8	31.5	15.5	64.0
OPSONO-9V	10Pn	PIII(M3)	105	103	98.1	93.3	99.8	1023.7	784.8	1335.2
	Zilbrix	PIII(M3)	54	13	24.1	13.5	37.6	8.4	5.8	12.4
OPSONO-14	10Pn	PIII(M3)	104	100	96.2	90.4	98.9	1079.2	776.0	1500.9
	Zilbrix	PIII(M3)	53	13	24.5	13.8	38.3	8.9	5.7	14.1
OPSONO-18C	10Pn	PIII(M3)	105	103	98.1	93.3	99.8	617.6	495.3	770.0
	Zilbrix	PIII(M3)	56	2	3.6	0.4	12.3	4.4	3.8	5.2
OPSONO-19F	10Pn	PIII(M3)	105	101	96.2	90.5	99.0	358.3	269.9	475.5
	Zilbrix	PIII(M3)	56	2	3.6	0.4	12.3	4.6	3.8	5.7
OPSONO-23F	10Pn	PIII(M3)	104	97	93.3	86.6	97.3	881.8	615.0	1264.4
	Zilbrix	PIII(M3)	53	5	9.4	3.1	20.7	6.6	4.2	10.3

10Pn = 10Pn-PD-DiT + DTPw-HBV/Hib + OPV
Zilbrix = DTPw-HBV/Hib + OPV
GMT = geometric mean titer
N = number of subjects with available results
n/% = number/percentage of subjects with titer within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3) = one month after dose III

One month post-dose III, all subjects in the 10Pn group had measurable antibodies against protein D (≥100 EL.U/mL). A higher anti-protein D GMC was observed in the 10Pn group in Mali than in Nigeria (no overlap of 95% CIs).

Immune response to the co-administered DTPw-HBV/Hib vaccine:
One month post-dose III, all subjects of the 10Pn group and all subjects except one in the Zilbrix group had anti-PRP antibody concentrations ≥ 0.15 µg/mL. 97.3% and 91.1% of subjects in the 10Pn group and Zilbrix group, respectively, had anti-PRP antibody concentrations ≥1.0 µg/mL. All subjects were seroprotected/seropositive for antibodies against the other antigens in the DTPw- HBV/Hib vaccine except two subjects in the 10Pn group who were not seroprotected for HBs. Antitetanus and anti-PRP antibody GMCs were higher in the 10Pn group than in the Zilbrix group (no overlap of 95% CIs).

- Safety results

Similar incidences of solicited local and general adverse events were observed in each group during the 4- day (days 0-3) post-vaccination period.

Solicited local adverse events:
Pain was the most frequently reported solicited local adverse event in each group.
Swelling was the most frequently reported grade 3 solicited local adverse event in each group (following 3.1% of doses). In the 10Pn group, higher incidences of pain, swelling and grade 3 swelling were reported at the DTPw-HBV/Hib injection site than at the 10Pn-PD-DiT injection site (no overlap of 95% CIs).
In general, there was no increase in the incidence of each solicited local adverse event with successive doses during the primary vaccination course.

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

			10Pn					Zilbrix				
						95 % CI					95 % CI	
Symptom	Product	Type	N	n	%	LL	UL	N	n	%	LL	UL
Pain	Total	All	707	571	80.8	77.7	83.6	351	257	73.2	68.3	77.8
		Grade 3	707	8	1.1	0.5	2.2	351	3	0.9	0.2	2.5
	10Pn-PD-DiT	All	704	440	62.5	58.8	66.1	-	-	-	-	-
		Grade 3	704	3	0.4	0.1	1.2	-	-	-	-	-
	DTPw-HBV/Hib	All	706	554	78.5	75.3	81.4	351	257	73.2	68.3	77.8
		Grade 3	706	8	1.1	0.5	2.2	351	3	0.9	0.2	2.5
Redness (mm)	Total	All	707	77	10.9	8.7	13.4	351	36	10.3	7.3	13.9
		>20mm	707	8	1.1	0.5	2.2	351	2	0.6	0.1	2.0
		>30mm	707	0	0.0	0.0	0.5	351	0	0.0	0.0	1.0
	10Pn-PD-DiT	All	704	43	6.1	4.5	8.1	-	-	-	-	-
		>20mm	704	2	0.3	0.0	1.0	-	-	-	-	-
		>30mm	704	0	0.0	0.0	0.5	-	-	-	-	-
	DTPw-HBV/Hib	All	706	52	7.4	5.5	9.5	351	36	10.3	7.3	13.9
		>20mm	706	6	0.8	0.3	1.8	351	2	0.6	0.1	2.0
		>30mm	706	0	0.0	0.0	0.5	351	0	0.0	0.0	1.0
Swelling (mm)	Total	All	707	462	65.3	61.7	68.9	351	225	64.1	58.8	69.1
		>20mm	707	128	18.1	15.3	21.1	351	64	18.2	14.3	22.7
		>30mm	707	22	3.1	2.0	4.7	351	11	3.1	1.6	5.5
	10Pn-PD-DiT	All	704	309	43.9	40.2	47.6	-	-	-	-	-
		>20mm	704	17	2.4	1.4	3.8	-	-	-	-	-
		>30mm	704	1	0.1	0.0	0.8	-	-	-	-	-
	DTPw-HBV/Hib	All	706	449	63.6	59.9	67.2	351	225	64.1	58.8	69.1
		>20mm	706	122	17.3	14.6	20.3	351	64	18.2	14.3	22.7
		>30mm	706	21	3.0	1.9	4.5	351	11	3.1	1.6	5.5

10Pn = 10Pn-PD-DiT + DTPw-HBV/Hib + OPV
Zilbrix = DTPw-HBV/Hib + OPV
N= number of documented doses
n/%= number/percentage of doses followed by at least one type of symptom
Total: n/%= number/percentage of doses 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:
Fever was the most frequently reported solicited general adverse event in each group. The overall/dose incidence of fever >39.0°C (rectal temperature) was within the same range in each group (maximum 6.2%). One subject in the 10Pn group reported grade 3 fever (rectal temperature >40.0°C).

Low overall/dose incidences of grade 3 solicited general adverse events were reported (ranging from 0% to 0.8%). All of these were considered by the investigator to be causally related to vaccination.
In general, there was no increase in the incidence of each solicited general adverse event with successive doses during the primary vaccination course.

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

		10Pn					Zilbrix				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Drowsiness	All	707	27	3.8	2.5	5.5	351	13	3.7	2.0	6.3
	Grade 3	707	0	0.0	0.0	0.5	351	0	0.0	0.0	1.0
	Related	707	27	3.8	2.5	5.5	351	12	3.4	1.8	5.9
	Grade 3 & Related	707	0	0.0	0.0	0.5	351	0	0.0	0.0	1.0
Fever (Rectally) (°C)	All	707	388	54.9	51.1	58.6	351	200	57.0	51.6	62.2
	>38.5°C	707	145	20.5	17.6	23.7	351	70	19.9	15.9	24.5
	>39.0°C	707	44	6.2	4.6	8.3	351	16	4.6	2.6	7.3
	>39.5°C	707	7	1.0	0.4	2.0	351	5	1.4	0.5	3.3
	>40.0°C	707	1	0.1	0.0	0.8	351	0	0.0	0.0	1.0
	Related	707	373	52.8	49.0	56.5	351	197	56.1	50.8	61.4
	>40.0°C & Related	707	1	0.1	0.0	0.8	351	0	0.0	0.0	1.0
Irritability	All	707	339	47.9	44.2	51.7	351	151	43.0	37.8	48.4
	Grade 3	707	6	0.8	0.3	1.8	351	2	0.6	0.1	2.0
	Related	707	330	46.7	42.9	50.4	351	148	42.2	36.9	47.5
	Grade 3 & Related	707	6	0.8	0.3	1.8	351	2	0.6	0.1	2.0
Loss of appetite	All	707	39	5.5	4.0	7.5	351	17	4.8	2.8	7.6
	Grade 3	707	1	0.1	0.0	0.8	351	0	0.0	0.0	1.0
	Related	707	37	5.2	3.7	7.1	351	16	4.6	2.6	7.3
	Grade 3 & Related	707	1	0.1	0.0	0.8	351	0	0.0	0.0	1.0

10Pn = 10Pn-PD-DiT + DTPw-HBV/Hib + OPV
Zilbrix = DTPw-HBV/Hib + OPV
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

Unsolicited adverse events:
The percentage of administered doses followed by at least one unsolicited adverse event was 53.0% in the 10Pn group and 57.3% in the Zilbrix group. The most frequently reported unsolicited adverse events in each group were rhinitis and allergic bronchitis (both reported only in Mali). 5.7% and 9.7% of administered doses in the 10Pn group and Zilbrix group, respectively, were followed by at least one unsolicited adverse event assessed by the investigator to be causally related to vaccination.
A low percentage of doses was followed by at least one grade 3 unsolicited adverse event (1.1% in each group) with no differences observed between countries. None of these were assessed by the investigator to be causally related to vaccination.
Serious adverse events:
Five subjects of the 10Pn group reported at least one serious adverse event. None of these serious adverse events were assessed by the investigator to be causally related to vaccination and all resolved without sequelae.
No fatal events have been reported in this study.
No subjects were withdrawn due to a non-serious adverse event. One subject (subject number 528 in the 10Pn group) was withdrawn due to a serious adverse event (bronchopneumonia).

Assessor's comment: The overall incidence of fever was very high in this study, but the incidence was similar in both groups and in most cases <38.5°C. The incidence of high fever was not unusually high.

Otherwise, the results of this study were in line with previously reported studies, and no further action is required.

10PN-PD-DIT-037; A phase III, randomized, single-blind, controlled study to assess the immunogenicity, safety and reactogenicity of GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine as a 3-dose primary immunization course at 6, 10 and 14 weeks of age in India, co-administered with GSK Biologicals' Tritanrix-HepB/Hib (DTPw-HBV/Hib) vaccine.

- **Description**

A phase III, randomized, single-blind, controlled study to assess the immunogenicity, safety and reactogenicity of GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine as a 3-dose primary immunization course at 6, 10 and 14 weeks of age in India, co-administered with GSK Biologicals' Tritanrix-HepB/Hib (DTPw-HBV/Hib) vaccine.

- **Methods**

- Objective(s)

Primary:
To evaluate the immunogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine in India, one month post dose 3.

Secondary:
To assess the safety and reactogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine in India.
To evaluate the immunogenicity of GSK Biologicals' DTPw-HBV/Hib vaccine, co-administered with GSK Biologicals' 10-valent pneumococcal conjugate vaccine.

- Study design

This was a phase III, multi-centre, single-blind, randomized, controlled study with two parallel groups:
- 10Pn-PD-DiT group ('10Pn' in results tables and figures): receiving 10Pn-PD-DiT + DTPw-HepB/Hib
- Hiberix group ('Hiberix' in results tables and figures): receiving Hiberix + DTPw-HepB

Treatment allocation: (2:1)
Vaccination schedule: 6-10-14 weeks of age (vaccination according to the Expanded Program on Immunization (EPI) schedule)
Three-dose primary vaccination course starting at 6 to 10 weeks (42-76 days) of age with allowable intervals of 28-42 days between the primary vaccination doses
Blood sample were collected before vaccination and one month post-dose 3
Control: Hiberix + DTPw-HepB (Tritanrix-HepB)
Parent(s)/guardian(s) were invited to enrol their child/ward in a separate follow-up study

- 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, 6-10 weeks (42-76 days) of age at the time of the first vaccination.
Written or oral, signed or thumb-printed informed consent obtained from the parent(s) / guardian(s) of the child/ward. Where parent(s)/guardian(s) were illiterate, the consent form was countersigned by a witness.
Free of obvious health problems as established by medical history and clinical examination before entering into the study that contraindicated the initiation of routine immunizations outside a clinical trial context.

The target enrolment in this multi-centre study was 360 subjects (240 subjects in the 10Pn-PD-DiT group and 120 in the Hiberix group).

- Treatments

Three dose primary vaccination course starting at 6 to 10 weeks (42-76 days) of age with allowable intervals of 28-42 days between the primary vaccination doses.

Group	Visit	Vaccination	Dose	Vaccine	Route	Site	Side
10Pn-PD-DiT	1, 2, 3	10Pn-PD-DiT	1, 2, 3	10Pn-PD-DiT	IM[1]	Thigh	Right
	1, 2, 3	DTPw-HBV/Hib	1, 2, 3	Tritanrix-HepB/Hib	IM[1]	Thigh	Left
Hiberix	1, 2, 3	Hib	1, 2, 3	Hiberix	IM[1]	Thigh	Right
	1, 2, 3	DTPw-HBV	1, 2, 3	Tritanrix-HepB	IM[1]	Thigh	Left

[1] Intramuscular (IM)

- Outcomes/endpoints

Immunogenicity (one month post-dose III):
Antibody concentrations against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.
Opsonophagocytic activity (OPA) against pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.
Antibody concentration against protein D.
Antibody concentration against diphtheria, tetanus, PRP, B. pertussis and HBs.

Safety /reactogenicity:
Occurrence of fever (oral/axillary/tympanic temperature > 38.5°C or rectal temperature > 39.0°C) within 4 days (days 0 to 3) after at least one vaccination.
Occurrence of solicited local and general AEs (any and grade 3) within 4 days (days 0 to 3) after each vaccination dose.
Occurrence of unsolicited AEs within 31 days (days 0 to 30) after each vaccination dose.
Occurrence of serious adverse events following the administration of the first dose of study vaccines throughout the entire study period up to Visit 4.

- Statistical Methods

Immunogenicity:
Descriptive analysis:
Geometric mean concentrations/titres (GMCs/GMTs), seropositivity/seroprotection rates were calculated with their 95% CI for each group, each antigen/serotype, at each applicable blood sampling time point.
Distribution of antibody concentrations/titres was displayed using tables and/or reverse cumulative curves for each group, each antigen/serotype, at each applicable blood sampling time point.

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 exact 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 exact 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 exact 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 exact 95% CI, after each vaccine dose and overall.
Serious adverse events and withdrawal due to adverse event(s) were described in detail.

➢ **Results**

- Recruitment/ Number analysed

Number of subjects	Total	10Pn	Hiberix
Planned:	360	240	120
Enrolled:	360	240	120
Completed:	349	232	117
Total vaccinated cohort	360	240	120
ATP cohort for immunogenicity	345	229	116

- Efficacy results

One month post-dose III, for each of the 10 vaccine pneumococcal serotypes, at least 98.3% subjects in the 10Pn group had antibody concentrations ≥0.2 µg/mL, except serotypes 23F (89.5%) and 6B (77.7%).
Robust increases in antibody GMCs were observed for each of the 10 vaccine pneumococcal serotypes in the 10Pn group, one month post-dose 3 compared to pre-vaccination levels (3.6 to 69.2-fold increases in 10Pn group).

Synopsis table 1: 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)

				≥0.2 µg/mL				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
ANTI-1	10Pn	PRE	228	40	17.5	12.8	23.1	0.07	0.07	0.09
		PIII(M3)	229	228	99.6	97.6	100	3.27	2.91	3.67
	Hiberix	PRE	116	20	17.2	10.9	25.4	0.07	0.06	0.09
		PIII(M3)	116	2	1.7	0.2	6.1	0.03	0.03	0.04
ANTI-4	10Pn	PRE	228	53	23.2	17.9	29.3	0.08	0.07	0.10
		PIII(M3)	229	225	98.3	95.6	99.5	3.80	3.33	4.33
	Hiberix	PRE	116	32	27.6	19.7	36.7	0.09	0.07	0.12
		PIII(M3)	116	10	8.6	4.2	15.3	0.04	0.03	0.05
ANTI-5	10Pn	PRE	229	73	31.9	25.9	38.3	0.12	0.10	0.14
		PIII(M3)	229	226	98.7	96.2	99.7	4.17	3.72	4.67
	Hiberix	PRE	116	39	33.6	25.1	43.0	0.13	0.11	0.16
		PIII(M3)	116	10	8.6	4.2	15.3	0.05	0.04	0.05
ANTI-6B	10Pn	PRE	229	92	40.2	33.8	46.8	0.15	0.13	0.18
		PIII(M3)	229	178	77.7	71.8	82.9	0.71	0.59	0.86
	Hiberix	PRE	116	52	44.8	35.6	54.3	0.16	0.12	0.21
		PIII(M3)	116	9	7.8	3.6	14.2	0.05	0.04	0.06
ANTI-7F	10Pn	PRE	229	92	40.2	33.8	46.8	0.13	0.12	0.16
		PIII(M3)	229	228	99.6	97.6	100	3.87	3.47	4.31
	Hiberix	PRE	116	54	46.6	37.2	56.0	0.18	0.14	0.23
		PIII(M3)	116	16	13.8	8.1	21.4	0.06	0.05	0.07
ANTI-9V	10Pn	PRE	229	107	46.7	40.1	53.4	0.17	0.14	0.20
		PIII(M3)	229	227	99.1	96.9	99.9	4.21	3.71	4.78
	Hiberix	PRE	116	62	53.4	44.0	62.8	0.20	0.16	0.26
		PIII(M3)	116	21	18.1	11.6	26.3	0.06	0.05	0.08
ANTI-14	10Pn	PRE	229	208	90.8	86.3	94.2	1.43	1.20	1.70
		PIII(M3)	229	229	100	98.4	100	5.21	4.51	6.01
	Hiberix	PRE	116	106	91.4	84.7	95.8	1.65	1.28	2.11
		PIII(M3)	116	66	56.9	47.4	66.1	0.26	0.20	0.34
ANTI-18C	10Pn	PRE	229	124	54.1	47.5	60.7	0.22	0.19	0.26
		PIII(M3)	229	227	99.1	96.9	99.9	15.23	12.96	17.90
	Hiberix	PRE	116	64	55.2	45.7	64.4	0.23	0.18	0.30
		PIII(M3)	116	20	17.2	10.9	25.4	0.07	0.05	0.08
ANTI-19F	10Pn	PRE	228	169	74.1	67.9	79.7	0.46	0.38	0.55
		PIII(M3)	229	227	99.1	96.9	99.9	11.78	10.26	13.53
	Hiberix	PRE	116	83	71.6	62.4	79.5	0.49	0.38	0.63
		PIII(M3)	116	40	34.5	25.9	43.9	0.12	0.10	0.16
ANTI-23F	10Pn	PRE	229	81	35.4	29.2	41.9	0.11	0.09	0.13
		PIII(M3)	229	205	89.5	84.8	93.2	1.18	0.98	1.42
	Hiberix	PRE	116	39	33.6	25.1	43.0	0.12	0.09	0.15
		PIII(M3)	116	12	10.3	5.5	17.4	0.05	0.04	0.05

10Pn = 10Pn-PD-DiT+DTPw-HBV/Hib
Hiberix = Hib + DTPw-HBV
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
PRE = prior to first dose
PIII(M3) = one month after dose III

One month post-dose III, for each of the 10 pneumococcal serotypes, at least 95.7% of subjects in the 10Pn group had OPA titres ≥ 8, except for serotypes 1 (90.5%) and 6B (84.5%).

Synopsis table 2: 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(M3)	116	105	90.5	83.7	95.2	151.4	114.1	201.0
	Hiberix	PIII(M3)	57	3	5.3	1.1	14.6	4.8	3.8	6.0
OPSONO-4	10Pn	PIII(M3)	116	114	98.3	93.9	99.8	805.1	621.6	1042.7
	Hiberix	PIII(M3)	55	24	43.6	30.3	57.7	17.1	10.5	27.9
OPSONO-5	10Pn	PIII(M3)	116	111	95.7	90.2	98.6	95.6	75.7	120.7
	Hiberix	PIII(M3)	56	2	3.6	0.4	12.3	4.4	3.7	5.2
OPSONO-6B	10Pn	PIII(M3)	116	98	84.5	76.6	90.5	427.4	279.1	654.6
	Hiberix	PIII(M3)	54	5	9.3	3.1	20.3	5.5	4.0	7.6
OPSONO-7F	10Pn	PIII(M3)	116	116	100	96.9	100	1591.9	1312.2	1931.3
	Hiberix	PIII(M3)	53	35	66.0	51.7	78.5	66.1	35.8	122.4
OPSONO-9V	10Pn	PIII(M3)	115	113	98.3	93.9	99.8	1384.7	1090.2	1758.8
	Hiberix	PIII(M3)	56	9	16.1	7.6	28.3	7.9	5.0	12.3
OPSONO-14	10Pn	PIII(M3)	115	110	95.7	90.1	98.6	876.7	628.3	1223.3
	Hiberix	PIII(M3)	56	14	25.0	14.4	38.4	7.7	5.4	11.0
OPSONO-18C	10Pn	PIII(M3)	115	113	98.3	93.9	99.8	920.2	735.1	1151.9
	Hiberix	PIII(M3)	55	2	3.6	0.4	12.5	4.9	3.7	6.5
OPSONO-19F	10Pn	PIII(M3)	116	114	98.3	93.9	99.8	848.5	669.8	1075.0
	Hiberix	PIII(M3)	56	7	12.5	5.2	24.1	5.7	4.2	7.7
OPSONO-23F	10Pn	PIII(M3)	116	113	97.4	92.6	99.5	1613.3	1220.0	2133.4
	Hiberix	PIII(M3)	54	9	16.7	7.9	29.3	9.2	5.5	15.4

10Pn = 10Pn-PD-DiT+DTPw-HBV/Hib
Hiberix = Hib + DTPw-HBV
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(M3) = one month after dose III

One month post-dose III, all subjects except one (99.6%) in the 10Pn group were seropositive for antibodies against protein D (≥100 EL.U/mL).
One month post-dose III, all subjects in both groups were seroprotected/seropositive for antibodies against diphtheria, tetanus, B. pertussis, PRP and the hepatitis B surface (HBs) antigens (except one subject in the Hiberix group for PRP).

- Safety results

Overall incidence of adverse events
During the 31-day post-vaccination period, 83.1% and 84.2% of documented doses in the 10Pn and Hiberix groups respectively were followed by at least one AE (solicited and unsolicited). Local AEs were more frequently reported than general AEs in both groups.
No increase in the incidences of any AEs (solicited and unsolicited) was observed with successive doses during the primary vaccination course.

Solicited local adverse events
Pain was the most frequently reported solicited local adverse event in both groups.

Observed overall/dose incidences of any solicited local AEs were within the same ranges in both groups.
High overall/dose incidences of pain (any and grade 3) were reported in both groups which were however in the same range in both groups (i.e. 71.0% and 70.6% of doses in the 10Pn and Hiberix groups respectively for any pain and 27.7% and 24.9% of doses in the 10Pn and Hiberix groups respectively for grade 3 pain). These rates of overall/dose incidences of pain (any and grade 3) are in line with those observed in other studies where 10Pn-PD-DiT was co-administered with DTPw combined vaccine (e.g. Poland, The Philippines).
The overall/dose incidences of grade 3 solicited local AEs ranged from 1.3% (for redness) to 27.7% (for pain) in the 10Pn group and between 0.8% (for redness) to 24.9% (for pain) in the Hiberix group, whatever the injection site.
There was no increase in the incidence of solicited local adverse events with successive doses during the primary vaccination course.

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

			10Pn					Hiberix				
						95% CI					95% CI	
Symptom	Vaccine	Type	N	n	%	LL	UL	N	n	%	LL	UL
Pain	Total	All	708	503	71.0	67.6	74.4	354	250	70.6	65.6	75.3
		Grade 3	708	196	27.7	24.4	31.1	354	88	24.9	20.4	29.7
	10Pn-PD-DiT	All	708	419	59.2	55.5	62.8	-	-	-	-	-
		Grade 3	708	113	16.0	13.3	18.9	-	-	-	-	-
	Hiberix	All	-	-	-	-	-	354	211	59.6	54.3	64.8
		Grade 3	-	-	-	-	-	354	48	13.6	10.2	17.6
	DTPw- HBV/Hib	All	708	471	66.5	62.9	70.0	-	-	-	-	-
		Grade 3	708	179	25.3	22.1	28.7	-	-	-	-	-
	DTPw-HBV	All	-	-	-	-	-	354	237	66.9	61.8	71.8
		Grade 3	-	-	-	-	-	354	79	22.3	18.1	27.0
Redness (mm)	Total	All	708	232	32.8	29.3	36.4	354	129	36.4	31.4	41.7
		>20mm	708	26	3.7	2.4	5.3	354	5	1.4	0.5	3.3
		>30mm	708	9	1.3	0.6	2.4	354	3	0.8	0.2	2.5
	10Pn-PD-DiT	All	708	172	24.3	21.2	27.6	-	-	-	-	-
		>20mm	708	16	2.3	1.3	3.6	-	-	-	-	-
		>30mm	708	4	0.6	0.2	1.4	-	-	-	-	-
	Hiberix	All	-	-	-	-	-	354	82	23.2	18.9	27.9
		>20mm	-	-	-	-	-	354	2	0.6	0.1	2.0
		>30mm	-	-	-	-	-	354	2	0.6	0.1	2.0
	DTPw-HBV/Hib	All	708	206	29.1	25.8	32.6	-	-	-	-	-
		>20mm	708	23	3.2	2.1	4.8	-	-	-	-	-
		>30mm	708	9	1.3	0.6	2.4	-	-	-	-	-
	DTPw-HBV	All	-	-	-	-	-	354	117	33.1	28.2	38.2
		>20mm	-	-	-	-	-	354	4	1.1	0.3	2.9
		>30mm	-	-	-	-	-	354	1	0.3	0.0	1.6
Swelling (mm)	Total	All	708	336	47.5	43.7	51.2	354	169	47.7	42.4	53.1
		>20mm	708	107	15.1	12.6	18.0	354	49	13.8	10.4	17.9
		>30mm	708	60	8.5	6.5	10.8	354	31	8.8	6.0	12.2
	10Pn-PD-DiT	All	708	244	34.5	31.0	38.1	-	-	-	-	-
		>20mm	708	56	7.9	6.0	10.1	-	-	-	-	-
		>30mm	708	28	4.0	2.6	5.7	-	-	-	-	-
	Hiberix	All	-	-	-	-	-	354	114	32.2	27.4	37.3
		>20mm	-	-	-	-	-	354	26	7.3	4.9	10.6
		>30mm	-	-	-	-	-	354	15	4.2	2.4	6.9
	DTPw-HBV/Hib	All	708	300	42.4	38.7	46.1	-	-	-	-	-
		>20mm	708	96	13.6	11.1	16.3	-	-	-	-	-
		>30mm	708	48	6.8	5.0	8.9	-	-	-	-	-
	DTPw-HBV	All	-	-	-	-	-	354	159	44.9	39.7	50.3
		>20mm	-	-	-	-	-	354	40	11.3	8.2	15.1
		>30mm	-	-	-	-	-	354	23	6.5	4.2	9.6

10Pn = 10Pn-PD-DiT+DTPw-HBV/Hib
Hiberix = Hib + DTPw-HBV
N= number of documented dose
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.
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 (52.8% and 49.2% of doses in the 10Pn and Hiberix groups, respectively).
Except for any fever, the overall/dose incidences of any solicited general AEs were within the same ranges in both groups. Although any fever seemed to be reported more frequently in the 10Pn group than in the Hiberix group (no overlap of 95% CI), the incidences of grade 3 fever (rectal temperature >40°C) were within the same range in both groups. Fever >39°C (rectal temperature) was reported following 3.7% of doses in the 10Pn group and 1.4% of doses in the Hiberix group.
The overall/dose incidences of grade 3 solicited general AEs ranged from 0.0% (for fever) to 8.3% (for irritability), whatever the group. Except for drowsiness, most of the grade 3 solicited general AEs were considered by the investigator to be causally related to vaccination.
There was no increase in the incidence of solicited general AEs with successive doses during the primary vaccination course.

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

		10Pn					Hiberix				
					95% CI					95% CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Drowsiness	All	708	132	18.6	15.8	21.7	354	63	17.8	14.0	22.2
	Grade 3	708	23	3.2	2.1	4.8	354	9	2.5	1.2	4.8
	Rel	708	61	8.6	6.7	10.9	354	26	7.3	4.9	10.6
	Grade 3 & Rel	708	12	1.7	0.9	2.9	354	2	0.6	0.1	2.0
Fever (Rectally) (°C)	All	708	344	48.6	44.8	52.3	354	137	38.7	33.6	44.0
	>38.5°C	708	84	11.9	9.6	14.5	354	27	7.6	5.1	10.9
	>39.0°C	708	26	3.7	2.4	5.3	354	5	1.4	0.5	3.3
	>39.5°C	708	5	0.7	0.2	1.6	354	1	0.3	0.0	1.6
	>40.0°C	708	3	0.4	0.1	1.2	354	0	0.0	0.0	1.0
	Rel	708	332	46.9	43.2	50.6	354	127	35.9	30.9	41.1
	>40.0°C & Rel	708	3	0.4	0.1	1.2	354	0	0.0	0.0	1.0
Irritability	All	708	374	52.8	49.1	56.6	354	174	49.2	43.8	54.5
	Grade 3	708	59	8.3	6.4	10.6	354	15	4.2	2.4	6.9
	Rel	708	263	37.1	33.6	40.8	354	117	33.1	28.2	38.2
	Grade 3 & Rel	708	43	6.1	4.4	8.1	354	9	2.5	1.2	4.8
Loss of appetite	All	708	169	23.9	20.8	27.2	354	78	22.0	17.8	26.7
	Grade 3	708	9	1.3	0.6	2.4	354	2	0.6	0.1	2.0
	Rel	708	106	15.0	12.4	17.8	354	44	12.4	9.2	16.3
	Grade 3 & Rel	708	9	1.3	0.6	2.4	354	2	0.6	0.1	2.0

10Pn = 10Pn-PD-DiT+DTPw-HBV/Hib
Hiberix = Hib + DTPw-HBV
Rel = related
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

Unsolicited adverse events
6.0% and 4.8% of administered doses in the 10Pn and Hiberix groups, respectively were followed by at least one unsolicited AE, classified by MedDRA Primary System Organ Class and Preferred Term. The most frequently reported unsolicited AE was rhinitis and cough in the 10Pn group and rhinitis in the Hiberix group.
Low overall/dose incidences of grade 3 unsolicited AEs were observed in both groups (0.3% and 0.0% of doses in the 10Pn and Hiberix groups, respectively). None of the grade 3 unsolicited AEs was considered by the investigator to be causally related to the vaccination.

Serious adverse events:
One subject in the 10Pn group (subject number 680) died 14 days after the third dose of 10Pn-PDDiT vaccine co-administered with DTPw-HBV/Hib vaccine. The medical diagnosis for the cause of death was

aspiration pneumonia. An autopsy was not performed. The event was not considered by the investigator to be causally related to vaccination.
Four subjects out of 240 vaccinated subjects in the 10Pn group (1.7%) and 1 subject out of 120 vaccinated subjects in the Hiberix group (1%) reported at least one non-fatal SAE during the entire study period. None of the non-fatal SAEs was considered by the investigator to be causally related to vaccination and all resolved without sequelae.
One subject was withdrawn due to a SAE (subject number 680 in the 10Pn group) as described above.

Assessor's comment: The results of this study were in line with previously reported studies and no further regulatory action is required.

10PN-PD-DIT-048; A phase III, multi-centre, double-blind, randomised study to assess the noninferiority of a commercial lot of GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate (10Pn-PD-DiT) vaccine compared to a clinical phase III vaccine lot, when given as a threedose primary immunization course.

- **Description**

- **Methods**

- Objective(s)

Primary:
To compare the immunogenicity of the commercial lot to the phase III clinical lot of GSK Biologicals' 10-valent pneumococcal conjugate vaccine (10Pn-PD-DiT), one month following a 3-dose primary vaccination course.

Secondary:
To assess the safety and reactogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine (clinical and commercial lots) and of GSK Biologicals' DTPa-combined and HRV vaccines.
To evaluate the immunogenicity of GSK Biologicals' DTPa-combined vaccines, one month following a 3-dose primary vaccination course.
To evaluate the immunogenicity of GSK Biologicals' HRV vaccine, three months following a 2-dose primary vaccination course.

- Study design

A phase III, multi-centre, randomised, controlled, double-blind primary vaccination study with two arallel groups:
Clin group: received the phase III clinical lot of 10Pn-PD-DiT co-administered with DTPa- HBV-IPV/Hib or DTPa-IPV/Hib and HRV.
Com group: received the commercial lot of 10Pn-PD-DiT co-administered with DTPa-HBVIPV/ Hib or DTPa-IPV/Hib and HRV.

One blood sample was collected one month post vaccination (Visit 4).

- 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 (e.g. completion of the diary cards, return for followup visits).
A male or female between, and including, 6 and 12 weeks (42-90 days) of age at the time of the first vaccination.
Written informed consent obtained from the parent(s)/guardian(s) of the subject.
Free of obvious health problems as established by medical history and clinical examination before entering into the study that would contraindicate the initiation of routine immunizations outside a clinical trial context.
Born after a gestation period of ≥36 to ≤42 weeks.

Comparability between the commercial lot and the phase III clinical lot in terms of noninferiority was demonstrated if the upper limit of the two-sided 95% 95% CIs on the adjusted GMC ratios [GMC of the phase III clinical lot over the GMC of the commercial lot] was below a limit of 2-fold for antibodies against all vaccine pneumococcal serotypes and protein D as measured by ELISA.

When comparing both lots, 200 evaluable subjects per group would provide at least 98% or 85% power (under equal mean or in case of 1.2-fold decrease in GMCs, respectively) to show non-inferiority (limit of 2-fold) of the 10Pn-PD-DiT commercial lot compared to the 10Pn-PD-DiT phase III clinical lot with respect to adjusted ELISA GMC ratios for the 10 vaccine pneumococcal serotypes and for protein D.
Considering that up to 13% of the subjects enrolled could have been excluded from the ATP cohort for analysis of immunogenicity, 230 subjects were planned to be enrolled in each group.

- Treatments

Vaccine	Vaccination schedule	Administration
10Pn-PD-DiT	2-3-5 months of age	intramuscular injection in the right thigh
DTPa-HBV-IPV/Hib	2-3-5 months of age in Malaysia	intramuscular injection in the left thigh
	2-5 months of age in Singapore	
DTPa-IPV/Hib	3 months of age in Singapore	
HRV	2-3 months of age	oral

- Outcomes/endpoints

Immunogenicity /efficacy:
Antibody concentrations and opsonophagocytic activity (OPA) against vaccine pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F and cross-reactive serotypes 6A and 19A one month after the primary immunization course.
Antibody concentrations against protein D one month after the primary immunization course.
Antibody concentrations against diphtheria and tetanus toxoids, polyribosyl-ribitol phosphate (PRP), pertussis toxoid (PT), filamentous haemagglutinin (FHA), pertactin (PRN), Hepatitis B surface antigens (HBs), and antibody titres against poliovirus types 1, 2, and 3 titres one month after the primary immunization course.
Antibody concentrations against HRV three months after the 2-dose immunization course with HRV vaccine.

Safety /reactogenicity:
Occurrence of solicited local (any and grade 3) and general (any and grade 3) adverse events (AEs) within 4 days (Day 0 to Day 3) after each vaccination.
Occurrence of unsolicited AEs within 31 days (Day 0 to Day 30) after each vaccination.
Occurrence of serious adverse events (SAEs) during the entire study period.

- Statistical Methods

Immunogenicity
Confirmatory analysis:
95% CIs for the enzyme-linked immunosorbent assay (ELISA) adjusted GMCs ratio (GMCs of the phase III clinical lot over the GMCs of the commercial lot), one month after administration of the third vaccine dose, were computed for each of the 10 vaccine pneumococcal serotypes and for protein D, using an analysis of variance (ANOVA) model on the logarithm 10 transformation of the concentrations (pooled variance). The ANOVA model included the group and the country as fixed effects.
The primary objective was reached if the upper limit of the two-sided 95% CIs on the adjusted GMC ratios [GMCs of the phase III clinical lot over the GMCs of the commercial lot] was below a limit of 2-fold for antibodies against all vaccine pneumococcal serotypes and protein D as measured by ELISA.

Descriptive analysis:
GMCs/GMTs with 95% CIs were tabulated for each serotype/antigen overall and by country.
Seropositivity/seroprotection rates with exact 95% CIs were calculated for each appropriate serotype/antigen overall and by country.
The distribution of antibody concentrations/titres for each serotype/antigen was displayed using tables and/or reverse cumulative distribution curves.

Safety / Reactogenicity:
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) follow-up

period was tabulated with exact 95% CI after each vaccine dose and overall. The percentage of doses followed by at least one local AE (solicited and unsolicited), by at least one general AE (solicited and unsolicited) and by any AE was tabulated, over the whole vaccination course, with exact 95% CI. The same calculations were performed for symptoms rated as grade 3.
The percentage of subjects reporting each individual solicited local and general AE during the 4-day (Day 0-Day 3) follow-up period were tabulated after each vaccine dose and overall, with exact 95% CI. The percentage of doses followed by each individual solicited local and general AE were tabulated, over the whole vaccination course, with exact 95% CI.
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.
The proportion of subjects/doses with at least one report of unsolicited AE classified by the Medical Dictionary for Regulatory Activities and reported up to 30 days after 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 or other medication at least once during the 4-day (Day 0-Day 3) solicited follow-up period were tabulated after each vaccine dose and overall, with exact 95% CI. The number and percentage of doses for which the subjects took concomitant antipyretic or other medication at least once during the 4-day (Day 0- Day 3) solicited follow-up period were tabulated over the full vaccination course, with exact 95% CI.
SAEs and withdrawal due to AE(s) were described in detail.

➢ **Results**

- Recruitment/ Number analysed

Of the 466 enrolled and vaccinated subjects, 464 subjects completed the study.
The mean age of subjects in the ATP cohort for immunogenicity at the time of the first vaccination was 7.3 weeks.
In the ATP cohort for immunogenicity, 46.5% of subjects were female and 99.3% of subjects were Asian (South East Asian heritage).

- Efficacy results

Pneumococcal vaccine - Confirmatory inferential analysis results:
The primary objective was reached because the upper limits of the two-sided 95% CIs of the adjusted GMC ratios (GMCs of the phase III clinical lot over the GMCs of the commercial lot) were below a limit of 2-fold for antibodies against each of the 10 vaccine pneumococcal serotypes (≤ 1.45) and protein D (1.58) as measured by ELISA.

Table 1 Ratios of adjusted post-dose III GMCs, between Clin and Com groups with their 95% CIs for ANTI-1, ANTI-4, ANTI-5, ANTI-6B, ANTI-7F, ANTI-9V, ANTI-14, ANTI-18C, ANTI-19F, ANTI-23F and ANTI-PD antibody concentrations (ATP cohort for immunogenicity)

					Ratio of adjusted GMCs (Clin / Com)		
	Clin		Com			95% CI	
Anti body	N	Adjusted GMC	N	Adjusted GMC	Value	LL	UL
ANTI-1	219	2.68	218	2.47	1.09	0.96	1.23
ANTI-4	219	3.94	218	3.14	1.26	1.09	1.45
ANTI-5	219	4.31	218	3.57	1.21	1.06	1.37
ANTI-6B	219	1.30	218	1.22	1.07	0.88	1.28
ANTI-7F	218	3.06	217	3.16	0.97	0.85	1.10
ANTI-9V	219	3.32	218	3.12	1.06	0.92	1.23
ANTI-14	219	4.99	218	4.63	1.08	0.91	1.27
ANTI-18C	219	5.03	218	5.17	0.97	0.80	1.18
ANTI-19F	219	6.69	218	6.95	0.96	0.83	1.11
ANTI-23F	219	1.98	218	1.68	1.18	0.99	1.40
ANTI-PD	219	2591.82	218	1901.14	1.36	1.18	1.58

Clin = 10Pn-PD-DiT (phase III clinical lot) + DTPa-(HBV-)IPV/Hib + HRV
Com = 10Pn-PD-DiT (commercial lot) + DTPa-(HBV-)IPV/Hib + HRV
Adjusted GMC = geometric mean antibody concentration adjusted for country
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMC ratio (ANOVA model: adjustment for country - pooled variance); LL = lower limit, UL = upper limit

Pneumococcal vaccine - Descriptive analysis results:
One month post-dose III, at least 96.3% of all subjects in the Clin group and 93.6% in the Com group had antibody concentrations ≥0.2 µg/mL for each of the 10 vaccine pneumococcal serotypes.

At least 88.5% of all subjects in the Clin group and 90.0% in the Com group had opsonophagocytic titres ≥8 for each of the 10 vaccine pneumococcal serotypes one month post-dose III.
All subjects, except one in the Com group, had measurable antibodies against protein D (≥ 100 EL.U/mL).

Table 2: 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	Clin	PIII(M4)	219	219	100	98.3	100	219	100	98.3	100	2.67	2.46	2.91
	Com	PIII(M4)	218	218	100	98.3	100	218	100	98.3	100	2.46	2.25	2.69
ANTI-4	Clin	PIII(M4)	219	219	100	98.3	100	219	100	98.3	100	3.95	3.59	4.36
	Com	PIII(M4)	218	218	100	98.3	100	218	100	98.3	100	3.14	2.84	3.47
ANTI-5	Clin	PIII(M4)	219	219	100	98.3	100	218	99.5	97.5	100	4.34	3.95	4.76
	Com	PIII(M4)	218	218	100	98.3	100	218	100	98.3	100	3.59	3.29	3.92
ANTI-6B	Clin	PIII(M4)	219	217	99.1	96.7	99.9	211	96.3	92.9	98.4	1.31	1.16	1.48
	Com	PIII(M4)	218	214	98.2	95.4	99.5	204	93.6	89.5	96.4	1.23	1.07	1.41
ANTI-7F	Clin	PIII(M4)	218	218	100	98.3	100	218	100	98.3	100	3.10	2.83	3.39
	Com	PIII(M4)	217	217	100	98.3	100	217	100	98.3	100	3.20	2.92	3.51
ANTI-9V	Clin	PIII(M4)	219	219	100	98.3	100	219	100	98.3	100	3.34	3.03	3.69
	Com	PIII(M4)	218	218	100	98.3	100	218	100	98.3	100	3.14	2.83	3.49
ANTI-14	Clin	PIII(M4)	219	219	100	98.3	100	218	99.5	97.5	100	5.13	4.54	5.79
	Com	PIII(M4)	218	218	100	98.3	100	218	100	98.3	100	4.74	4.23	5.32
ANTI-18C	Clin	PIII(M4)	219	219	100	98.3	100	219	100	98.3	100	5.00	4.40	5.69
	Com	PIII(M4)	218	217	99.5	97.5	100	217	99.5	97.5	100	5.15	4.43	5.97
ANTI-19F	Clin	PIII(M4)	219	219	100	98.3	100	218	99.5	97.5	100	6.69	6.04	7.41
	Com	PIII(M4)	218	218	100	98.3	100	217	99.5	97.5	100	6.96	6.26	7.73
ANTI-23F	Clin	PIII(M4)	219	219	100	98.3	100	215	98.2	95.4	99.5	1.98	1.76	2.23
	Com	PIII(M4)	218	217	99.5	97.5	100	212	97.2	94.1	99.0	1.68	1.49	1.90

Clin = 10Pn-PD-DiT (phase III clinical lot) + DTPa-(HBV-)IPV/Hib + HRV
Com = 10Pn-PD-DiT (commercial lot) + DTPa-(HBV-)IPV/Hib + HRV
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(M4) = one month after dose III

Table 3: 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	Clin	PIII(M4)	209	185	88.5	83.4	92.5	128.9	102.7	161.7
	Com	PIII(M4)	210	189	90.0	85.1	93.7	122.1	98.3	151.7
OPSONO-4	Clin	PIII(M4)	207	207	100	98.2	100	698.3	619.6	786.9
	Com	PIII(M4)	207	203	98.1	95.1	99.5	609.3	519.6	714.3
OPSONO-5	Clin	PIII(M4)	207	204	98.6	95.8	99.7	127.9	109.0	149.9
	Com	PIII(M4)	210	203	96.7	93.3	98.6	98.6	83.0	117.1
OPSONO-6B	Clin	PIII(M4)	205	196	95.6	91.8	98.0	870.7	710.2	1067.6
	Com	PIII(M4)	206	191	92.7	88.3	95.9	619.2	483.4	793.2
OPSONO-7F	Clin	PIII(M4)	206	206	100	98.2	100	3905.8	3420.2	4460.4
	Com	PIII(M4)	208	208	100	98.2	100	3585.7	3119.8	4121.2
OPSONO-9V	Clin	PIII(M4)	207	207	100	98.2	100	1800.0	1596.6	2029.3
	Com	PIII(M4)	208	208	100	98.2	100	1851.3	1612.3	2125.8
OPSONO-14	Clin	PIII(M4)	209	208	99.5	97.4	100	1521.0	1313.3	1761.6
	Com	PIII(M4)	208	207	99.5	97.4	100	1485.8	1280.5	1724.0
OPSONO-18C	Clin	PIII(M4)	204	202	99.0	96.5	99.9	533.5	461.8	616.4
	Com	PIII(M4)	206	199	96.6	93.1	98.6	383.9	319.3	461.5
OPSONO-19F	Clin	PIII(M4)	206	202	98.1	95.1	99.5	689.6	581.1	818.2
	Com	PIII(M4)	206	200	97.1	93.8	98.9	573.5	477.2	689.3
OPSONO-23F	Clin	PIII(M4)	209	207	99.0	96.6	99.9	2716.7	2316.3	3186.3
	Com	PIII(M4)	207	206	99.5	97.3	100	2379.5	2043.4	2770.7

Clin = 10Pn-PD-DiT (phase III clinical lot) + DTPa-(HBV-)IPV/Hib + HRV
Com = 10Pn-PD-DiT (commercial lot) + DTPa-(HBV-)IPV/Hib + HRV
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(M4) = one month after dose III

Co-administered DTPa-combined and HRV vaccines - Descriptive analysis results
All subjects were seroprotected/seropositive for antibodies against diphtheria, tetanus, each of the pertussis antigens (PT, FHA and PRN), the hepatitis B surface (HBs) antigen (except one subject in the Clin group), poliovirus types 1, 2 and 3 and PRP one month post-dose III.
Three months after the second dose of HRV vaccine, at least 81.9% of subjects in each group had seropositive anti-HRV levels (≥20 U/mL).

- Safety results

Solicited local adverse events:
Within the 4-day post-vaccination period, pain was the most frequently reported solicited local AE in each group (48.7% and 48.4% of overall doses in the Clin group and in the Com group, respectively).
The observed overall/dose incidences for each of the solicited local AE were in the same ranges across the groups.
The overall/dose incidence of grade 3 solicited local AEs ranged from 0.4% to 5.7%, for any injection site and group.

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

			Clin					Com				
						95 % CI					95 % CI	
Symptom	Product	Type	N	n	%	LL	UL	N	n	%	LL	UL
Pain	Total	All	698	340	48.7	44.9	52.5	698	338	48.4	44.7	52.2
		Grade 3	698	20	2.9	1.8	4.4	698	40	5.7	4.1	7.7
		Medical advice	698	0	0.0	0.0	0.5	698	0	0.0	0.0	0.5
	10Pn-PD-DiT	All	698	324	46.4	42.7	50.2	698	327	46.8	43.1	50.6
		Grade 3	698	19	2.7	1.6	4.2	698	39	5.6	4.0	7.6
		Medical advice	698	0	0.0	0.0	0.5	698	0	0.0	0.0	0.5
	DTPa-HBV-IPV/Hib	All	549	249	45.4	41.1	49.6	549	269	49.0	44.7	53.3
		Grade 3	549	14	2.6	1.4	4.2	549	30	5.5	3.7	7.7
		Medical advice	549	0	0.0	0.0	0.7	549	0	0.0	0.0	0.7
	DTPa-IPV/Hib	All	149	67	45.0	36.8	53.3	149	59	39.6	31.7	47.9
		Grade 3	149	2	1.3	0.2	4.8	149	7	4.7	1.9	9.4
		Medical advice	149	0	0.0	0.0	2.4	149	0	0.0	0.0	2.4
Redness (mm)	Total	All	698	301	43.1	39.4	46.9	698	296	42.4	38.7	46.2
		>20.0mm	698	11	1.6	0.8	2.8	698	12	1.7	0.9	3.0
		>30.0mm	698	3	0.4	0.1	1.3	698	4	0.6	0.2	1.5
		Medical advice	698	0	0.0	0.0	0.5	698	0	0.0	0.0	0.5
	10Pn-PD-DiT	All	698	281	40.3	36.6	44.0	698	278	39.8	36.2	43.6
		>20.0mm	698	9	1.3	0.6	2.4	698	9	1.3	0.6	2.4
		>30.0mm	698	3	0.4	0.1	1.3	698	4	0.6	0.2	1.5
		Medical advice	698	0	0.0	0.0	0.5	698	0	0.0	0.0	0.5
	DTPa-HBV-IPV/Hib	All	549	211	38.4	34.3	42.6	549	199	36.2	32.2	40.4
		>20.0mm	549	9	1.6	0.8	3.1	549	6	1.1	0.4	2.4
		>30.0mm	549	2	0.4	0.0	1.3	549	0	0.0	0.0	0.7
		Medical advice	549	0	0.0	0.0	0.7	549	0	0.0	0.0	0.7
	DTPa-IPV/Hib	All	149	72	48.3	40.1	56.6	149	57	38.3	30.4	46.6
		>20.0mm	149	0	0.0	0.0	2.4	149	1	0.7	0.0	3.7
		>30.0mm	149	0	0.0	0.0	2.4	149	0	0.0	0.0	2.4
		Medical advice	149	0	0.0	0.0	2.4	149	0	0.0	0.0	2.4
Swelling (mm)	Total	All	698	260	37.2	33.7	41.0	698	238	34.1	30.6	37.7
		>20.0mm	698	15	2.1	1.2	3.5	698	16	2.3	1.3	3.7
		>30.0mm	698	5	0.7	0.2	1.7	698	4	0.6	0.2	1.5
		Medical advice	698	0	0.0	0.0	0.5	698	0	0.0	0.0	0.5
	10Pn-PD-DiT	All	698	235	33.7	30.2	37.3	698	218	31.2	27.8	34.8
		>20.0mm	698	10	1.4	0.7	2.6	698	12	1.7	0.9	3.0
		>30.0mm	698	2	0.3	0.0	1.0	698	4	0.6	0.2	1.5
		Medical advice	698	0	0.0	0.0	0.5	698	0	0.0	0.0	0.5
	DTPa-HBV-IPV/Hib	All	549	187	34.1	30.1	38.2	549	176	32.1	28.2	36.1
		>20.0mm	549	11	2.0	1.0	3.6	549	8	1.5	0.6	2.9
		>30.0mm	549	4	0.7	0.2	1.9	549	1	0.2	0.0	1.0
		Medical advice	549	0	0.0	0.0	0.7	549	0	0.0	0.0	0.7
	DTPa-IPV/Hib	All	149	53	35.6	27.9	43.8	149	42	28.2	21.1	36.1
		>20.0mm	149	0	0.0	0.0	2.4	149	1	0.7	0.0	3.7
		>30.0mm	149	0	0.0	0.0	2.4	149	1	0.7	0.0	3.7
		Medical advice	149	0	0.0	0.0	2.4	149	0	0.0	0.0	2.4

Clin = 10Pn-PD-DiT (phase III clinical lot) + DTPa-(HBV-)IPV/Hib + HRV
Com = 10Pn-PD-DiT (commercial lot) + DTPa-(HBV-)IPV/Hib + HRV
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.
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Solicited general adverse events:

The most frequently reported solicited general AE during the 4-day post-vaccination period in each group was irritability (49.6% and 49.7% of overall doses in the Clin and Com groups, respectively).

The incidence of grade 3 solicited general AEs was at most 3.3% (diarrhoea in the Com group). No cases of grade 3 fever (defined as rectal temperature > 40°C) were reported.

Table 5: Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period, overall/dose (Total vaccinated cohort)

		Clin					Com				
					95% CI					95% CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Drowsiness	All	698	271	38.8	35.2	42.6	698	255	36.5	33.0	40.2
	Grade 3	698	1	0.1	0.0	0.8	698	6	0.9	0.3	1.9
	Related	698	262	37.5	33.9	41.2	698	248	35.5	32.0	39.2
	Grade 3 & Related	698	1	0.1	0.0	0.8	698	6	0.9	0.3	1.9
	Medical advice	698	0	0.0	0.0	0.5	698	0	0.0	0.0	0.5
Fever (Rectal) (°C)	All	698	320	45.8	42.1	49.6	698	305	43.7	40.0	47.5
	>38.5°C	698	85	12.2	9.8	14.8	698	77	11.0	8.8	13.6
	>39.0°C	698	19	2.7	1.6	4.2	698	17	2.4	1.4	3.9
	>39.5°C	698	3	0.4	0.1	1.3	698	1	0.1	0.0	0.8
	>40.0 °C	698	0	0.0	0.0	0.5	698	0	0.0	0.0	0.5
	Related	698	308	44.1	40.4	47.9	698	294	42.1	38.4	45.9
	>40.0 °C & Related	698	0	0.0	0.0	0.5	698	0	0.0	0.0	0.5
	Medical advice	698	8	1.1	0.5	2.2	698	3	0.4	0.1	1.3
Irritability	All	698	346	49.6	45.8	53.3	698	347	49.7	45.9	53.5
	Grade 3	698	12	1.7	0.9	3.0	698	19	2.7	1.6	4.2
	Related	698	336	48.1	44.4	51.9	698	341	48.9	45.1	52.6
	Grade 3 & Related	698	12	1.7	0.9	3.0	698	18	2.6	1.5	4.0
	Medical advice	698	0	0.0	0.0	0.5	698	0	0.0	0.0	0.5
Loss of appetite	All	698	208	29.8	26.4	33.3	698	215	30.8	27.4	34.4
	Grade 3	698	1	0.1	0.0	0.8	698	0	0.0	0.0	0.5
	Related	698	201	28.8	25.5	32.3	698	211	30.2	26.8	33.8
	Grade 3 & Related	698	1	0.1	0.0	0.8	698	0	0.0	0.0	0.5
	Medical advice	698	1	0.1	0.0	0.8	698	0	0.0	0.0	0.5
Diarrhoea^	All	698	71	10.2	8.0	12.7	698	79	11.3	9.1	13.9
	Grade 3	698	15	2.1	1.2	3.5	698	23	3.3	2.1	4.9
	Related	698	68	9.7	7.6	12.2	698	75	10.7	8.5	13.3
	Grade 3 & Related	698	15	2.1	1.2	3.5	698	22	3.2	2.0	4.7
	Medical advice	698	1	0.1	0.0	0.8	698	1	0.1	0.0	0.8
Vomiting^	All	698	65	9.3	7.3	11.7	698	63	9.0	7.0	11.4
	Grade 3	698	5	0.7	0.2	1.7	698	4	0.6	0.2	1.5
	Related	698	56	8.0	6.1	10.3	698	61	8.7	6.8	11.1
	Grade 3 & Related	698	5	0.7	0.2	1.7	698	4	0.6	0.2	1.5
	Medical advice	698	1	0.1	0.0	0.8	698	1	0.1	0.0	0.8

Clin = 10Pn-PD-DiT (phase III clinical lot) + DTPa-(HBV-)IPV/Hib + HRV
Com = 10Pn-PD-DiT (commercial lot) + DTPa-(HBV-)IPV/Hib + HRV
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
^ Diarrhoea and vomiting were solicited due to co-administered HRV vaccine

Unsolicited adverse events:

The percentage of doses followed by at least one unsolicited symptom in the 31-day postvaccination period was 16.2% in the Clin group and 17.0% in the Com group. The most frequently reported unsolicited AE in each group was upper respiratory tract infection (5.0% in the Clin group and 6.0% in the Com group).

The percentage of doses followed by at least one unsolicited symptom considered by the investigator to be causally related to vaccination and the percentage of doses with grade 3 unsolicited AEs in the 31-day post-vaccination period was at most 1.0% in both groups.
No grade 3 unsolicited AEs were considered by the investigator to be causally related to vaccination.

Serious adverse events:
No fatal SAEs were reported in this study. A total of 36 non-fatal SAEs were reported for 25 (5.4%) out of 466 vaccinated subjects: 18 subjects (7.7%) in the Clin group and 7 subjects (3.0%) in the Com group. No SAEs were considered by the investigator to be causally related to vaccination. One SAE did not resolve (spinal muscular atrophy) and one SAE (tuberculous meningitis) was still ongoing at the end of this study.
No subjects were withdrawn due to an AE or SAE during this study.

Assessor's comment: The results of this study confirm the previously reported results for Synflorix. No further regulatory action is required based on this study.

3. Discussion on clinical aspects
The majority of the above described studies do not provide new results that change the overall benefit risk of Synflorix, or require any further regulatory action. Study 009 cause some concern regarding the relatively low responses to some serotypes following the catch-up vaccinations in children 12-23 months of age. However, as the MAH already has a commitment to study booster vaccination after the catch-up schedule, no further action is currently needed.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

- **Recommendation**

☒ **Fulfilled –**

No further action required

☐ **Not fulfilled:**

IV. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable