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Committee for Medicinal Products for Human Use (CHMP)

Synflorix

(Pneumococcal polysaccharide conjugate vaccine, adsorbed)

Procedure No. EMEA/H/C/000973

P46 017

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 June 7, 2012 the MAH submitted a completed paediatric study for Synflorix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

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

This study report is also part of a follow-up measure for Synflorix, with the aim to evaluate the boostability of the immune response following the 2-dose catch-up vaccinatin in children 12-23 months of age. The study was performed in accordance with an agreed paediatric investigation plan (EMEA-000673-PIP01-09).

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the study

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

II.2 Clinical aspects

1. Introduction

The MAH submitted a final report for:

- 10PN-PD-DIT-062; Booster vaccination with pneumococcal vaccine GSK1024850A in primed children and catch-up vaccination in unprimed children.

2. Clinical study

10PN-PD-DIT-062; Booster vaccination with pneumococcal vaccine GSK1024850A in primed children and catch-up vaccination in unprimed children.

➢ **Description**

A phase III, open study in children previously enrolled in study 10PN-PD-DIT-037 (111188) to assess the immunogenicity, safety and reactogenicity of GlaxoSmithKline (GSK) Biologicals' 10-valent pneumococcal conjugate vaccine when administered as a booster dose at either 9-18 or 15-18 months of age in primed children or when administered as a catch-up vaccination (2+1 schedule) in unprimed children during the second year of life.

➢ **Methods**

- Objective(s)

Primary:

- To assess the immune responses following vaccination with a booster dose of the 10Pn-PD-DiT vaccine administered at either 9-12 or 15-18 months of age in children previously vaccinated with the 10Pn-PD-DiT vaccine in study 10PN-PD-DIT-037 (111188) according to a 3-dose primary vaccination at 6, 10 and 14 weeks of age.

Note: In the Pn-Pn9 group, following protocol amendment 1, the age range for receiving booster dose was changed from 9-12 to 9-18 months of age. Therefore, for analysis purposes, the group was divided in two sub-groups [Pn-Pn9 (9-12) and Pn-Pn9 (13-18)] in order to allow evaluation of the early booster subset (9-12 months of age) for the primary objective.

Assessor's comment: It is unfortunate that the design of the study was not in accordance with the primary objective. The consequence of the protocol amendment was that there were fewer children with an early booster.

Secondary:

- To assess, prior to booster vaccination, the antibody persistence following primary vaccination with the 10Pn-PD-DiT vaccine.
- To assess the immunogenicity of the 10Pn-PD-DiT vaccine following a 2-dose primary vaccination administered as a catch-up immunization according to a 2+1 vaccination schedule in unprimed children during the second year of life.
- To assess the immunogenicity of the 10Pn-PD-DiT vaccine following booster vaccination administered as a catch-up immunization according to a 2+1 vaccination schedule in unprimed children during the second year of life.
- To assess the safety and reactogenicity of the 10Pn-PD-DiT vaccine when administered as a catchup immunization according to a 2+1 vaccination schedule in unprimed children during the second year of life.
- To assess the safety and reactogenicity of a booster dose of the 10Pn-PD-DiT vaccine when administered at either 9-18 or 15-18 months of age in children primed with the 10Pn-PD-DiT vaccine in study 10PN-PD-DIT-037 (111188) according to a 3-dose primary vaccination at 6, 10 and 14 weeks of age.
- To assess the antibody persistence following booster vaccination with the 10Pn-PD-DiT vaccine up to approximately 24 months of age in the primed groups.

- Study design

This was a phase III, partially randomized, open study with 3 parallel groups (as described above). Randomization of subjects primed in study 10PN-PD-DIT-037 (111188) into two groups; Pn-Pn9 and Pn-Pn15, in a 1:1 ratio was done at 9-18 months of age (Randomisation visit or Visit 1).

Blood samples:
Pn-Pn9 and Pn-Pn15 groups: prior to vaccination, one month post-vaccination, and at approximately 24 months of age.
Hib-Pn group: prior to dose 1, one month post-dose 2, prior to and one month post-booster vaccination.

- Study population /Sample size

Healthy male or female for whom the investigator believes that their parents/ guardian(s) could and would comply with the requirements of the protocol. Written, signed or thumb-printed informed consent obtained from the parent(s)/guardian(s) of the child/ward. Where parent(s)/guardian(s) are illiterate, the consent form was countersigned by a witness.

For primed subjects:

- Completion of the full vaccination course in study 10PN-PD-DIT-037 (111188).
- 9-18 months at the time of randomization.
- 9-18 months of age at the time of booster vaccination for the Pn-Pn9 group.
- 15-18 months of age at the time of booster vaccination for the Pn-Pn15 group

For unprimed subjects:

- Enrolled in study 10PN-PD-DIT-037 (111188).
- 12-18 months of age at the time of first vaccination in the present study.

The sample size was contingent on the number of subjects who received a 3-dose primary vaccination course with the 10Pn-PD-DiT vaccine for primed subjects or who were enrolled in study 10PN-PD-DIT-037 (111188) for the unprimed group. (*Assessors' note: 240 subjects received priming vaccination in study 10PN-PD-DIT-037 and 120 subjects were included in the control group*).
Assuming that around 20% of these subjects did not enter this study, it could be considered that approximately 96 subjects per group received a booster vaccine dose or catch-up vaccine dose(s) in the current study.

Considering that 96 subjects per group (288 subjects in total) were to be enrolled and included in the Total vaccinated cohort, and up to 10% of the subjects might have been excluded from the ATP cohort for analysis of immunogenicity, there would be 86 evaluable subjects per group (258 subjects in total) in the current study.

- Treatments

The study groups were as follows:

- Pn-Pn9 group: 50% of subjects (randomly selected) previously primed with the 10Pn-PDDiT vaccine in study 10PN-PD-DIT-037 (111188) and receiving a booster dose of 10Pn-PDDiT at 9-18 months of age.
- Pn-Pn15 group: 50% of subjects (randomly selected) previously primed with the 10Pn-PDDiT vaccine in study 10PN-PD-DIT-037 (111188) and receiving a booster dose of 10Pn-PDDiT at 15-18 months of age.
- Hib-Pn group: unprimed subjects previously vaccinated with DTPw-HBV and Hib vaccines in the control group of study 10PN-PD-DIT-037 (111188) and receiving a catch-up vaccination with 10Pn-PD-DiT (2+1 schedule) during the second year of life. Dose 1 was given at 12-18 months of age, dose 2 at 14-20 months and dose 3 at 18-24 months of age.

Notes:

1. *During the study subjects might have been vaccinated with a measles-containing vaccine and with the Infanrix/Hiberix (DTPa/Hib) vaccine according to the national recommended vaccination program. These vaccines were not considered as study vaccines and could be administered either at any "protocol defined study visit" or at any time during the study except in the period 30 days before and 30 days after the administration of the study vaccine (10Pn-PD-DiT).*
2. *In the Pn-Pn9 group, following protocol amendment 1, the age range for receiving booster dose was changed from 9-12 to 9-18 months of age. Therefore, for analysis purposes, the group was divided in two sub-groups [Pn-Pn9 (9-12) and Pn-Pn9 (13-18)] in order to allow evaluation of the early booster subset (9-12 months of age) for the primary objective.*

- Outcomes/endpoints

Primary outcome
Immunogenicity:
Pn-Pn9 and Pn-Pn15 groups:
Evaluation of immune responses to components of the investigational vaccine, one month after booster vaccination:
Concentrations of antibodies against vaccine pneumococcal serotypes.

Secondary Outcomes:
Immunogenicity:
Pn-Pn9 and Pn-Pn15 groups:

- Evaluation of immune responses to components of the investigational vaccine, prior to booster vaccination and at approximately 24 months of age:
    - Concentrations of antibodies against vaccine pneumococcal serotypes.
- Evaluation of immune responses to components of the investigational vaccine, prior to booster vaccination, one month after booster vaccination and at approximately 24 months of age:
    - Opsonophagocytic activity against vaccine pneumococcal serotypes
    - Concentrations of antibodies against cross-reactive pneumococcal serotypes 6A and 19A
    - Opsonophagocytic activity against cross-reactive pneumococcal serotypes 6A and 19A
    - Concentrations of antibodies against protein D

Hib-Pn group:

- Evaluation of immune responses to components of the investigational vaccine prior to vaccination, one month post-dose 2, prior to and one month after the third (booster) vaccine dose:
    - Concentrations of antibodies against vaccine pneumococcal serotypes

- Opsonophagocytic activity against vaccine pneumococcal serotypes
- Concentrations of antibodies against cross-reactive pneumococcal serotypes 6A and 19A
- Opsonophagocytic activity against cross-reactive pneumococcal serotypes 6A and 19A
- Concentrations of antibodies against protein D

Safety and reactogenicity:

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

- Statistical Methods

Demography:

- Demographic characteristics (age in months, gender and race) were tabulated for each study cohort as a whole and per group.
- The mean age in months (plus range and standard deviation) of the enrolled subjects at the time of booster or first vaccination with 10Pn-PD-DiT, as a whole, and per group, was calculated. The mean age in months (plus range and standard deviation) at the time of randomization (screening visit) was also calculated for the primed Pn-Pn15 group.
- The distribution of subjects enrolled among the study centres was tabulated as a whole and per group.
- A summary of the tracking log-sheet that documented outcomes of the contacts made with subjects for enrolment in this study was provided.

Analysis of immunogenicity:

The primary analysis was based on the ATP cohort for persistence or on the ATP cohort for immunogenicity according to the objective. As, in at least one group, the percentage of vaccinated subjects with serological data excluded from this ATP cohort was more than 5%, a second analysis based on the Total vaccinated cohort was performed to complement the ATP analysis.

Descriptive analysis:

- Geometric mean concentrations/titres (GMCs/GMTs), seropositivity rates were calculated with their 95% confidence interval (CI) for each group and each pneumococcal serotype and protein D, at each timepoint that a blood sample result was available.
- Distribution of antibody concentrations/titres was displayed using tables and/or reverse cumulative curves for each group and each pneumococcal serotype and protein D, at each timepoint that a blood sample result was available.

Exploratory Inferential analysis:

- 95% CIs for the ELISA GMCs ratio (GMCs Pn-Pn15 group over GMCs Pn-Pn9 group), one month after booster dose, was computed for each of the pneumococcal serotypes, for the cross-reactive pneumococcal serotypes 6A and 19A and for protein D, using an ANOVA model on the logarithm10 transformation of the concentrations (pooled variance).
- 95% CIs for the OPA GMTs ratio (GMTs Pn-Pn15 group over GMTs Pn-Pn9 group), one month after booster dose, was computed for each of the pneumococcal serotypes and for the cross-reactive pneumococcal serotypes 6A and 19A, using an ANOVA model on the logarithm10 transformation of the titres (pooled variance).

- 95% CIs for the ELISA GMCs ratio [GMCs Pn-Pn15 group over GMCs Pn-Pn9 (9-12) group], one month after booster dose, was computed for each of the vaccine pneumococcal serotypes, for the cross-reactive pneumococcal serotypes 6A and 19A and for protein D using an ANOVA model on the logarithm10 transformation of the concentrations (pooled variance).
- 95% CIs for the OPA GMTs ratio [GMTs Pn-Pn15 group over GMTs Pn-Pn9 (9-12) group], one month after booster dose, was computed for each of the vaccine pneumococcal serotypes and for the cross-reactive pneumococcal serotypes 6A and

19A, using an ANOVA model on the logarithm10 transformation of the titres (pooled variance).

Analysis of safety:

- The primary analysis was based on the Total vaccinated cohort. As, in at least one group, the percentage of vaccinated subjects excluded from the ATP cohort for analysis of safety was more than 5%, a second analysis based on the ATP cohort for safety was performed to complement the primary analysis.

Descriptive analyses:

- Incidence of solicited and/or unsolicited local and/or general AEs during the 31-day postvaccination 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 postvaccination 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/doses with unsolicited symptoms reported within the 31-days postvaccination period were summarized according to the Medical Dictionary for Regulatory Activities (MedDRA), with exact 95% CI, according to the intensity and relationship to vaccination. The same tabulation was done for unsolicited symptoms resulting in a medically attended visit.
- The number and percentage of subjects who took concomitant antipyretic/medication at least once during the 4-day post-vaccination period was computed with exact 95% CI after each vaccine dose and overall. The number and percentage of doses for which the subjects took concomitant antipyretic/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.
- Serious adverse events (SAEs), large swelling reactions and withdrawal(s) due to AE(s) reported during the entire study period were described in detail.

➢ Results

- Recruitment/ Number analysed

Number of subjects	**Pn-Pn9 (9-12)**	**Pn-Pn9 (13-15)**	**Pn-Pn9**	**Pn-Pn15**	**Hib-Pn**
Planned, N	-	-	120	120	120
Randomised, N (Total Vaccinated Cohort)	74	26	100	95	87
Completed, n (%)	47(63.5)	22(84.6)	69(69.0)	71(74.7)	61(70.1)
Demographics	**Pn-Pn9 (9-12)**	**Pn-Pn9 (13-15)**	**Pn-Pn9**	**Pn-Pn15**	**Hib-Pn**
N (Total Vaccinated Cohort)	74	26	100	95	87
Females: Males	30:44	9:17	39:61	50:45	48:39
Mean Age*, months (SD)	10.9 (0.37)	17.0 (0.82)	12.5 (2.74)	15.6 (1.27)	16.1 (1.18)
Asian – Central/South Asian heritage, n (%)	74 (100)	26 (100)	100 (100)	94 (98.9)	87 (100)

Pn-Pn9 (9-12) = Primed group receiving booster dose of 10Pn-PD-DiT at 9-12 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Pn-Pn9 (13-18) = Primed group receiving booster dose of 10Pn-PD-DiT at 13-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Pn-Pn9 = Primed group receiving booster dose of 10Pn-PD-DiT at 9-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study (pooled Pn-Pn9 (9-12) and Pn-Pn9 (13-18) groups)
Pn-Pn15 = Primed group receiving booster dose of 10Pn-PD-DiT at 15-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Hib-Pn = Unprimed group receiving 2+1 catch up vaccination with 10Pn-PD-DiT in the second year of life
*Mean age at first vaccination

Assessor's comment: It is assumed that the Table head for the second group (i.e. Pn-Pn9 (13-15) is a typographical error as it is not in accordance with the explanation below the table (Pn-Pn9 (13-18), and the age limits given in the methods section.

Summary of tracking documents for all subjects initially enrolled in the primary study 10PN-PD-DIT-037 (111188) (Primary Total vaccinated cohort)

	10Pn N = 240		Hiberix N = 120		Total N = 360	
	n	%	n	%	n	%
Not participating to study 10PN-PD-DIT-062 BST:037 (112909)	40	16.7	33	27.5	73	20.3
Not eligible	1	0.4	0	0.0	1	0.3
Lost to follow-up	18	7.5	22	18.3	40	11.1
Not willing to participate due to AE or SAE	0	0.0	0	0.0	0	0.0
Not willing to participate due to other reason	21	8.8	11	9.2	32	8.9
Died	0	0.0	0	0.0	0	0.0
Enrolled in study 10PN-PD-DIT-062 BST:037 (112909)	200	83.3	87	72.5	287	79.7

10Pn = 10Pn-PD-DiT+DTPw-HBV/Hib (Primary study group)
Hiberix = Hib + DTPw-HBV (Primary study group)
N = number of enrolled subjects in the primary study 10PN-PD-DIT-037 (111188)
n/% = number/percentage of subjects in a given category

- Efficacy results

Persistence of immune response to pneumococcal serotype specific polysaccharides prior to booster vaccination

22F Inhibition ELISA
For each of the vaccine pneumococcal serotypes:
At least 94.3% of subjects in the Pn-Pn9 and Pn-Pn15 groups had antibody concentrations ≥ 0.05 µg/mL (Table 27).
At least 80.7% of subjects in the Pn-Pn9 group and 78.9% of subjects in the Pn-Pn15 group had antibody concentrations ≥0.2 µg/mL except for serotype 1 (65.9% in the Pn-Pn9 group and 64.4% in the Pn-Pn15 group) (Table 27).

For cross-reactive serotypes:
The observed percentage of subjects with antibody concentrations ≥0.05 µg/mL was 78.7% for 6A and 79.5% for 19A in the Pn-Pn9 group and 86.2% for 6A and 89.9% for 19A in the Pn-Pn15 group (Table 29).
The observed percentage of subjects with antibody concentrations ≥0.2 µg/mL was 46.1% for 6A and 62.5% for 19A in the Pn-Pn9 group and 52.9% for 6A and 69.7% for 19A in the Pn-Pn15 group (Table 29).

Opsonophagocytic activity
For each of the vaccine pneumococcal serotypes, at least 64.4% of subjects in the Pn-Pn9 group and 60.5% of subjects in the Pn-Pn15 group, respectively, had OPA titres ≥8 except for serotypes 1 (41.4% in the Pn-Pn9 group and 40.5% in the Pn-Pn15 group) and 5 (48.3% in the Pn-Pn9 group and 44.4% in the Pn-Pn15 group) (Table 31).
For cross-reactive serotypes, the observed percentage of subjects with OPA titres ≥8 was 40.7% for 6A and 25.6% for 19A in the Pn-Pn9 group and 47.6% for 6A and 23.2% for 19A in the Pn-Pn15 group (Table 33).

Assessor's comment: The antibody titres decline for most serotypes prior to booster vaccination, which is in agreement with other studies and as expected.

Table 27 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 persistence)

				≥0.05 µg/mL				≥0.2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
ANTI-1	Pn-Pn9 (9-12)	PIII(M3)	66	66	100	94.6	100	66	100	94.6	100	3.38	2.73	4.18
		PRE-BOOSTER	65	65	100	94.5	100	48	73.8	61.5	84.0	0.45	0.34	0.60
	Pn-Pn9 (13-18)	PIII(M3)	23	23	100	85.2	100	23	100	85.2	100	3.22	2.30	4.50
		PRE-BOOSTER	23	21	91.3	72.0	98.9	10	43.5	23.2	65.5	0.21	0.12	0.37
	Pn-Pn9	PIII(M3)	89	89	100	95.9	100	89	100	95.9	100	3.34	2.79	3.98
		PRE-BOOSTER	88	86	97.7	92.0	99.7	58	65.9	55.0	75.7	0.37	0.29	0.48
	Pn-Pn15	PIII(M3)	90	89	98.9	94.0	100	89	98.9	94.0	100	3.60	2.93	4.44
		PRE-BOOSTER	87	82	94.3	87.1	98.1	56	64.4	53.4	74.4	0.30	0.24	0.39
	Hib-Pn	PIII(M3)	84	14	16.7	9.4	26.4	2	2.4	0.3	8.3	0.03	0.03	0.04
		PRE-VACC	84	19	22.6	14.2	33.0	3	3.6	0.7	10.1	0.04	0.03	0.04
ANTI-4	Pn-Pn9 (9-12)	PIII(M3)	66	66	100	94.6	100	63	95.5	87.3	99.1	3.60	2.74	4.74
		PRE-BOOSTER	65	65	100	94.5	100	59	90.8	81.0	96.5	1.03	0.79	1.34
	Pn-Pn9 (13-18)	PIII(M3)	23	23	100	85.2	100	23	100	85.2	100	3.66	2.58	5.21
		PRE-BOOSTER	23	21	91.3	72.0	98.9	14	60.9	38.5	80.3	0.33	0.18	0.62
	Pn-Pn9	PIII(M3)	89	89	100	95.9	100	86	96.6	90.5	99.3	3.62	2.91	4.50
		PRE-BOOSTER	88	86	97.7	92.0	99.7	73	83.0	73.4	90.1	0.76	0.58	1.00
	Pn-Pn15	PIII(M3)	90	89	98.9	94.0	100	89	98.9	94.0	100	4.13	3.32	5.13
		PRE-BOOSTER	85	84	98.8	93.6	100	70	82.4	72.6	89.8	0.57	0.45	0.72
	Hib-Pn	PIII(M3)	84	19	22.6	14.2	33.0	7	8.3	3.4	16.4	0.04	0.03	0.05
		PRE-VACC	83	21	25.3	16.4	36.0	7	8.4	3.5	16.6	0.04	0.03	0.05
ANTI-5	Pn-Pn9 (9-12)	PIII(M3)	66	66	100	94.6	100	65	98.5	91.8	100	4.42	3.56	5.48
		PRE-BOOSTER	65	65	100	94.5	100	58	89.2	79.1	95.6	0.60	0.47	0.77
	Pn-Pn9 (13-18)	PIII(M3)	23	23	100	85.2	100	23	100	85.2	100	4.41	3.33	5.83
		PRE-BOOSTER	23	22	95.7	78.1	99.9	13	56.5	34.5	76.8	0.29	0.18	0.49
	Pn-Pn9	PIII(M3)	89	89	100	95.9	100	88	98.9	93.9	100	4.42	3.71	5.25
		PRE-BOOSTER	88	87	98.9	93.8	100	71	80.7	70.9	88.3	0.50	0.40	0.63
	Pn-Pn15	PIII(M3)	90	90	100	96.0	100	88	97.8	92.2	99.7	4.13	3.39	5.04
		PRE-BOOSTER	87	85	97.7	91.9	99.7	70	80.5	70.6	88.2	0.38	0.31	0.47
	Hib-Pn	PIII(M3)	84	37	44.0	33.2	55.3	9	10.7	5.0	19.4	0.05	0.04	0.06
		PRE-VACC	83	36	43.4	32.5	54.7	10	12.0	5.9	21.0	0.05	0.04	0.06
ANTI-6B	Pn-Pn9 (9-12)	PIII(M3)	66	62	93.9	85.2	98.3	51	77.3	65.3	86.7	0.75	0.51	1.10
		PRE-BOOSTER	66	65	98.5	91.8	100	58	87.9	77.5	94.6	0.64	0.49	0.84
	Pn-Pn9 (13-18)	PIII(M3)	23	23	100	85.2	100	17	73.9	51.6	89.8	0.68	0.38	1.20
		PRE-BOOSTER	22	22	100	84.6	100	17	77.3	54.6	92.2	0.67	0.33	1.37
	Pn-Pn9	PIII(M3)	89	85	95.5	88.9	98.8	68	76.4	66.2	84.8	0.73	0.53	1.00
		PRE-BOOSTER	88	87	98.9	93.8	100	75	85.2	76.1	91.9	0.65	0.50	0.85
	Pn-Pn15	PIII(M3)	90	82	91.1	83.2	96.1	70	77.8	67.8	85.9	0.67	0.49	0.93
		PRE-BOOSTER	90	88	97.8	92.2	99.7	71	78.9	69.0	86.8	0.51	0.40	0.65
	Hib-Pn	PIII(M3)	84	32	38.1	27.7	49.3	8	9.5	4.2	17.9	0.05	0.04	0.07
		PRE-VACC	83	14	16.9	9.5	26.7	3	3.6	0.8	10.2	0.03	0.03	0.04

				≥0.05 µg/mL				≥0.2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
ANTI-7F	Pn-Pn9 (9-12)	PIII(M3)	66	66	100	94.6	100	66	100	94.6	100	3.61	2.95	4.42
		PRE-BOOSTER	65	65	100	94.5	100	63	96.9	89.3	99.6	1.30	1.02	1.65
	Pn-Pn9 (13-18)	PIII(M3)	23	23	100	85.2	100	23	100	85.2	100	4.23	3.15	5.70
		PRE-BOOSTER	23	23	100	85.2	100	23	100	85.2	100	0.74	0.53	1.05
	Pn-Pn9	PIII(M3)	89	89	100	95.9	100	89	100	95.9	100	3.76	3.19	4.44
		PRE-BOOSTER	88	88	100	95.9	100	86	97.7	92.0	99.7	1.12	0.92	1.38
	Pn-Pn15	PIII(M3)	90	90	100	96.0	100	89	98.9	94.0	100	3.69	3.04	4.49
		PRE-BOOSTER	89	89	100	95.9	100	87	97.8	92.1	99.7	0.98	0.79	1.23
	Hib-Pn	PIII(M3)	84	38	45.2	34.3	56.5	12	14.3	7.6	23.6	0.06	0.04	0.08
		PRE-VACC	84	34	40.5	29.9	51.7	16	19.0	11.3	29.1	0.06	0.04	0.08
ANTI-9V	Pn-Pn9 (9-12)	PIII(M3)	66	66	100	94.6	100	66	100	94.6	100	4.36	3.49	5.44
		PRE-BOOSTER	65	65	100	94.5	100	63	96.9	89.3	99.6	1.32	1.04	1.68
	Pn-Pn9 (13-18)	PIII(M3)	23	23	100	85.2	100	22	95.7	78.1	99.9	3.34	2.02	5.53
		PRE-BOOSTER	23	23	100	85.2	100	21	91.3	72.0	98.9	0.90	0.47	1.70
	Pn-Pn9	PIII(M3)	89	89	100	95.9	100	88	98.9	93.9	100	4.07	3.31	5.00
		PRE-BOOSTER	88	88	100	95.9	100	84	95.5	88.8	98.7	1.20	0.94	1.52
	Pn-Pn15	PIII(M3)	90	89	98.9	94.0	100	89	98.9	94.0	100	4.31	3.48	5.35
		PRE-BOOSTER	90	90	100	96.0	100	85	94.4	87.5	98.2	0.98	0.78	1.23
	Hib-Pn	PIII(M3)	84	38	45.2	34.3	56.5	16	19.0	11.3	29.1	0.07	0.05	0.09
		PRE-VACC	83	20	24.1	15.4	34.7	7	8.4	3.5	16.6	0.04	0.03	0.05
ANTI-14	Pn-Pn9 (9-12)	PIII(M3)	66	66	100	94.6	100	66	100	94.6	100	5.22	3.99	6.83
		PRE-BOOSTER	66	64	97.0	89.5	99.6	57	86.4	75.7	93.6	2.09	1.33	3.30
	Pn-Pn9 (13-18)	PIII(M3)	23	23	100	85.2	100	23	100	85.2	100	4.43	2.57	7.66
		PRE-BOOSTER	23	23	100	85.2	100	22	95.7	78.1	99.9	1.06	0.61	1.83
	Pn-Pn9	PIII(M3)	89	89	100	95.9	100	89	100	95.9	100	5.01	3.94	6.36
		PRE-BOOSTER	89	87	97.8	92.1	99.7	79	88.8	80.3	94.5	1.76	1.22	2.53
	Pn-Pn15	PIII(M3)	90	90	100	96.0	100	90	100	96.0	100	5.10	4.04	6.44
		PRE-BOOSTER	89	88	98.9	93.9	100	79	88.8	80.3	94.5	1.37	1.00	1.87
	Hib-Pn	PIII(M3)	84	72	85.7	76.4	92.4	48	57.1	45.9	67.9	0.26	0.19	0.36
		PRE-VACC	83	49	59.0	47.7	69.7	11	13.3	6.8	22.5	0.06	0.05	0.08
ANTI-18C	Pn-Pn9 (9-12)	PIII(M3)	66	66	100	94.6	100	66	100	94.6	100	15.37	11.96	19.75
		PRE-BOOSTER	66	66	100	94.6	100	66	100	94.6	100	3.09	2.35	4.07
	Pn-Pn9 (13-18)	PIII(M3)	23	23	100	85.2	100	23	100	85.2	100	15.03	8.46	26.70
		PRE-BOOSTER	23	23	100	85.2	100	21	91.3	72.0	98.9	1.37	0.78	2.39
	Pn-Pn9	PIII(M3)	89	89	100	95.9	100	89	100	95.9	100	15.28	12.12	19.27
		PRE-BOOSTER	89	89	100	95.9	100	87	97.8	92.1	99.7	2.51	1.94	3.23
	Pn-Pn15	PIII(M3)	90	89	98.9	94.0	100	89	98.9	94.0	100	13.80	10.46	18.20
		PRE-BOOSTER	90	89	98.9	94.0	100	87	96.7	90.6	99.3	1.61	1.26	2.05
	Hib-Pn	PIII(M3)	84	44	52.4	41.2	63.4	19	22.6	14.2	33.0	0.08	0.06	0.11
		PRE-VACC	83	17	20.5	12.4	30.8	7	8.4	3.5	16.6	0.04	0.03	0.05
ANTI-19F	Pn-Pn9 (9-12)	PIII(M3)	66	66	100	94.6	100	66	100	94.6	100	11.85	9.08	15.45
		PRE-BOOSTER	66	66	100	94.6	100	64	97.0	89.5	99.6	2.19	1.60	3.01
	Pn-Pn9 (13-18)	PIII(M3)	23	23	100	85.2	100	23	100	85.2	100	10.62	7.00	16.09
		PRE-BOOSTER	23	23	100	85.2	100	19	82.6	61.2	95.0	0.97	0.55	1.72
	Pn-Pn9	PIII(M3)	89	89	100	95.9	100	89	100	95.9	100	11.52	9.24	14.36
		PRE-BOOSTER	89	89	100	95.9	100	83	93.3	85.9	97.5	1.78	1.34	2.36
	Pn-Pn15	PIII(M3)	90	90	100	96.0	100	88	97.8	92.2	99.7	10.52	8.14	13.60
		PRE-BOOSTER	88	88	100	95.9	100	85	96.6	90.4	99.3	1.36	1.10	1.68
	Hib-Pn	PIII(M3)	84	64	76.2	65.7	84.8	31	36.9	26.6	48.1	0.13	0.10	0.18
		PRE-VACC	83	30	36.1	25.9	47.4	17	20.5	12.4	30.8	0.07	0.05	0.09

				≥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-23F	Pn-Pn9 (9-12)	PIII(M3)	66	63	95.5	87.3	99.1	58	87.9	77.5	94.6	1.25	0.86	1.81
		PRE-BOOSTER	66	65	98.5	91.8	100	55	83.3	72.1	91.4	0.85	0.61	1.19
	Pn-Pn9 (13-18)	PIII(M3)	23	23	100	85.2	100	22	95.7	78.1	99.9	1.26	0.78	2.02
		PRE-BOOSTER	22	21	95.5	77.2	99.9	17	77.3	54.6	92.2	0.46	0.26	0.81
	Pn-Pn9	PIII(M3)	89	86	96.6	90.5	99.3	80	89.9	81.7	95.3	1.25	0.93	1.69
		PRE-BOOSTER	88	86	97.7	92.0	99.7	72	81.8	72.2	89.2	0.73	0.55	0.97
	Pn-Pn15	PIII(M3)	90	86	95.6	89.0	98.8	77	85.6	76.6	92.1	1.03	0.75	1.41
		PRE-BOOSTER	88	86	97.7	92.0	99.7	70	79.5	69.6	87.4	0.64	0.49	0.85
	Hib-Pn	PIII(M3)	84	26	31.0	21.3	42.0	11	13.1	6.7	22.2	0.05	0.04	0.06
		PRE-VACC	83	20	24.1	15.4	34.7	8	9.6	4.3	18.1	0.04	0.03	0.05

Pn-Pn9 (9-12) = Primed group receiving booster dose of 10Pn-PD-DiT at 9-12 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Pn-Pn9 (13-18) = Primed group receiving booster dose of 10Pn-PD-DiT at 13-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Pn-Pn9 = Primed group receiving booster dose of 10Pn-PD-DiT at 9-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study (pooled Pn-Pn9 (9-12) and Pn-Pn9 (13-18) groups)
Pn-Pn15 = Primed group receiving booster dose of 10Pn-PD-DiT at 15-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Hib-Pn= Unprimed group receiving 2+1 catch up vaccination with 10Pn-PD-DiT in the second year of life
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(M3) = one month after dose III of 10Pn-PD-DiT (for Pn-Pn groups) and Hiberix (for Hib-Pn group)
PRE-BOOSTER = prior to booster dose
PRE-VACC = prior to catch-up vaccination

Table 29 Seropositivity rates and GMCs for ANTI-6A and ANTI-19A antibodies (ATP cohort for persistence)

				≥0.05 µg/mL				≥0.2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
ANTI-6A	Pn-Pn9 (9-12)	PIII(M3)	66	55	83.3	72.1	91.4	29	43.9	31.7	56.7	0.16	0.12	0.22
		PRE-BOOSTER	66	51	77.3	65.3	86.7	31	47.0	34.6	59.7	0.18	0.13	0.26
	Pn-Pn9 (13-18)	PIII(M3)	23	17	73.9	51.6	89.8	5	21.7	7.5	43.7	0.11	0.06	0.19
		PRE-BOOSTER	23	19	82.6	61.2	95.0	10	43.5	23.2	65.5	0.21	0.10	0.42
	Pn-Pn9	PIII(M3)	89	72	80.9	71.2	88.5	34	38.2	28.1	49.1	0.14	0.11	0.19
		PRE-BOOSTER	89	70	78.7	68.7	86.6	41	46.1	35.4	57.0	0.19	0.14	0.26
	Pn-Pn15	PIII(M3)	90	77	85.6	76.6	92.1	40	44.4	34.0	55.3	0.16	0.12	0.20
		PRE-BOOSTER	87	75	86.2	77.1	92.7	46	52.9	41.9	63.7	0.22	0.16	0.29
	Hib-Pn	PIII(M3)	84	44	52.4	41.2	63.4	10	11.9	5.9	20.8	0.06	0.05	0.08
		PRE-VACC	83	12	14.5	7.7	23.9	3	3.6	0.8	10.2	0.03	0.03	0.04
ANTI-19A	Pn-Pn9 (9-12)	PIII(M3)	66	60	90.9	81.3	96.6	44	66.7	54.0	77.8	0.32	0.23	0.46
		PRE-BOOSTER	65	52	80.0	68.2	88.9	39	60.0	47.1	72.0	0.32	0.20	0.50
	Pn-Pn9 (13-18)	PIII(M3)	23	20	87.0	66.4	97.2	16	69.6	47.1	86.8	0.37	0.19	0.73
		PRE-BOOSTER	23	18	78.3	56.3	92.5	16	69.6	47.1	86.8	0.28	0.14	0.55
	Pn-Pn9	PIII(M3)	89	80	89.9	81.7	95.3	60	67.4	56.7	77.0	0.34	0.25	0.46
		PRE-BOOSTER	88	70	79.5	69.6	87.4	55	62.5	51.5	72.6	0.31	0.21	0.45
	Pn-Pn15	PIII(M3)	90	80	88.9	80.5	94.5	51	56.7	45.8	67.1	0.27	0.20	0.36
		PRE-BOOSTER	89	80	89.9	81.7	95.3	62	69.7	59.0	79.0	0.33	0.25	0.45
	Hib-Pn	PIII(M3)	84	50	59.5	48.3	70.1	16	19.0	11.3	29.1	0.08	0.06	0.10
		PRE-VACC	84	30	35.7	25.6	46.9	14	16.7	9.4	26.4	0.06	0.04	0.08

Pn-Pn9 (9-12) = Primed group receiving booster dose of 10Pn-PD-DiT at 9-12 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Pn-Pn9 (13-18) = Primed group receiving booster dose of 10Pn-PD-DiT at 13-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Pn-Pn9 = Primed group receiving booster dose of 10Pn-PD-DiT at 9-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study (pooled Pn-Pn9 (9-12) and Pn-Pn9 (13-18) groups)
Pn-Pn15 = Primed group receiving booster dose of 10Pn-PD-DiT at 15-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Hib-Pn= Unprimed group receiving 2+1 catch up vaccination with 10Pn-PD-DiT in the second year of life
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(M3) = one month after dose III of 10Pn-PD-DiT (for Pn-Pn groups) and Hiberix (for Hib-Pn group)
PRE-BOOSTER = prior to booster dose
PRE-VACC = prior to catch-up vaccination

Table 31 Seropositivity rates and GMTs for OPSONO-1, OPSONO-4, OPSONO- 5, OPSONO-6B, OPSONO-7F, OPSONO-9V, OPSONO-14, OPSONO- 18C, OPSONO-19F and OPSONO-23F titres (ATP cohort for persistence)

				≥8				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
OPSONO-1	Pn-Pn9 (9-12)	PIII(M3)	36	33	91.7	77.5	98.2	171.6	102.5	287.3
		PRE-BOOSTER	66	29	43.9	31.7	56.7	18.1	11.5	28.6
	Pn-Pn9 (13-18)	PIII(M3)	13	11	84.6	54.6	98.1	111.7	37.1	336.3
		PRE-BOOSTER	21	7	33.3	14.6	57.0	12.3	5.6	27.1
	Pn-Pn9	PIII(M3)	49	44	89.8	77.8	96.6	153.1	96.7	242.5
		PRE-BOOSTER	87	36	41.4	30.9	52.4	16.5	11.2	24.3
	Pn-Pn15	PIII(M3)	49	43	87.8	75.2	95.4	137.8	85.6	221.6
		PRE-BOOSTER	84	34	40.5	29.9	51.7	15.6	10.5	23.0
	Hib-Pn	PIII(M3)	41	3	7.3	1.5	19.9	5.1	3.8	7.0
		PRE-VACC	77	3	3.9	0.8	11.0	4.4	3.9	5.0
OPSONO-4	Pn-Pn9 (9-12)	PIII(M3)	36	36	100	90.3	100	738.8	462.3	1180.7
		PRE-BOOSTER	65	52	80.0	68.2	88.9	80.5	48.4	133.7
	Pn-Pn9 (13-18)	PIII(M3)	13	13	100	75.3	100	945.8	469.8	1903.9
		PRE-BOOSTER	20	11	55.0	31.5	76.9	45.2	13.6	150.8
	Pn-Pn9	PIII(M3)	49	49	100	92.7	100	788.8	539.7	1153.1
		PRE-BOOSTER	85	63	74.1	63.5	83.0	70.3	43.9	112.5
	Pn-Pn15	PIII(M3)	49	47	95.9	86.0	99.5	747.6	465.5	1200.6
		PRE-BOOSTER	81	66	81.5	71.3	89.2	102.8	66.4	159.1
	Hib-Pn	PIII(M3)	40	17	42.5	27.0	59.1	15.8	9.0	27.5
		PRE-VACC	67	5	7.5	2.5	16.6	6.2	4.2	9.3
OPSONO-5	Pn-Pn9 (9-12)	PIII(M3)	36	35	97.2	85.5	99.9	106.3	69.0	164.0
		PRE-BOOSTER	66	36	54.5	41.8	66.9	13.7	9.7	19.3
	Pn-Pn9 (13-18)	PIII(M3)	13	13	100	75.3	100	73.8	35.4	153.8
		PRE-BOOSTER	21	6	28.6	11.3	52.2	7.6	4.4	13.2
	Pn-Pn9	PIII(M3)	49	48	98.0	89.1	99.9	96.5	67.2	138.6
		PRE-BOOSTER	87	42	48.3	37.4	59.2	11.9	8.9	15.9
	Pn-Pn15	PIII(M3)	49	46	93.9	83.1	98.7	90.3	61.6	132.3
		PRE-BOOSTER	81	36	44.4	33.4	55.9	10.4	7.8	13.7
	Hib-Pn	PIII(M3)	41	2	4.9	0.6	16.5	4.6	3.6	5.8
		PRE-VACC	78	1	1.3	0.0	6.9	4.2	3.8	4.7
OPSONO-6B	Pn-Pn9 (9-12)	PIII(M3)	36	30	83.3	67.2	93.6	364.0	159.1	833.0
		PRE-BOOSTER	66	42	63.6	50.9	75.1	48.1	27.5	83.9
	Pn-Pn9 (13-18)	PIII(M3)	13	12	92.3	64.0	99.8	669.8	202.9	2211.1
		PRE-BOOSTER	21	14	66.7	43.0	85.4	57.6	18.6	178.1
	Pn-Pn9	PIII(M3)	49	42	85.7	72.8	94.1	428.0	219.3	835.0
		PRE-BOOSTER	87	56	64.4	53.4	74.4	50.2	30.7	82.1
	Pn-Pn15	PIII(M3)	49	40	81.6	68.0	91.2	352.5	177.6	699.4
		PRE-BOOSTER	82	56	68.3	57.1	78.1	62.0	36.5	105.5
	Hib-Pn	PIII(M3)	39	5	12.8	4.3	27.4	6.3	4.0	9.8
		PRE-VACC	71	4	5.6	1.6	13.8	5.3	3.9	7.0

						≥8		GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
OPSONO-7F	Pn-Pn9 (9-12)	PIII(M3)	36	36	100	90.3	100	1690.5	1259.0	2269.9
		PRE-BOOSTER	66	66	100	94.6	100	1050.0	796.1	1385.0
	Pn-Pn9 (13-18)	PIII(M3)	13	13	100	75.3	100	1719.0	1080.1	2735.7
		PRE-BOOSTER	21	21	100	83.9	100	1600.4	932.1	2747.8
	Pn-Pn9	PIII(M3)	49	49	100	92.7	100	1698.0	1335.1	2159.7
		PRE-BOOSTER	87	87	100	95.8	100	1162.5	910.0	1485.0
	Pn-Pn15	PIII(M3)	49	49	100	92.7	100	1427.0	1003.4	2029.4
		PRE-BOOSTER	84	84	100	95.7	100	1551.1	1269.4	1895.3
	Hib-Pn	PIII(M3)	38	25	65.8	48.6	80.4	69.2	33.2	144.3
		PRE-VACC	65	54	83.1	71.7	91.2	1186.4	588.8	2390.7
OPSONO-9V	Pn-Pn9 (9-12)	PIII(M3)	36	35	97.2	85.5	99.9	1398.6	886.3	2207.1
		PRE-BOOSTER	63	60	95.2	86.7	99.0	373.3	261.3	533.4
	Pn-Pn9 (13-18)	PIII(M3)	12	12	100	73.5	100	1844.9	1095.2	3107.6
		PRE-BOOSTER	20	20	100	83.2	100	673.7	308.8	1469.7
	Pn-Pn9	PIII(M3)	48	47	97.9	88.9	99.9	1498.9	1047.1	2145.6
		PRE-BOOSTER	83	80	96.4	89.8	99.2	430.4	310.7	596.1
	Pn-Pn15	PIII(M3)	49	48	98.0	89.1	99.9	1187.3	778.2	1811.4
		PRE-BOOSTER	82	81	98.8	93.4	100	617.6	477.6	798.6
	Hib-Pn	PIII(M3)	40	6	15.0	5.7	29.8	7.8	4.5	13.3
		PRE-VACC	60	41	68.3	55.0	79.7	192.6	93.6	396.5
OPSONO-14	Pn-Pn9 (9-12)	PIII(M3)	36	33	91.7	77.5	98.2	800.3	400.3	1600.1
		PRE-BOOSTER	64	54	84.4	73.1	92.2	196.6	115.7	334.2
	Pn-Pn9 (13-18)	PIII(M3)	12	11	91.7	61.5	99.8	602.4	155.4	2334.7
		PRE-BOOSTER	21	21	100	83.9	100	239.2	116.3	491.8
	Pn-Pn9	PIII(M3)	48	44	91.7	80.0	97.7	745.4	411.1	1351.8
		PRE-BOOSTER	85	75	88.2	79.4	94.2	206.4	134.2	317.5
	Pn-Pn15	PIII(M3)	49	48	98.0	89.1	99.9	1001.8	605.4	1657.8
		PRE-BOOSTER	79	67	84.8	75.0	91.9	166.3	105.7	261.6
	Hib-Pn	PIII(M3)	40	11	27.5	14.6	43.9	8.2	5.3	12.6
		PRE-VACC	69	16	23.2	13.9	34.9	13.5	7.8	23.5
OPSONO-18C	Pn-Pn9 (9-12)	PIII(M3)	36	36	100	90.3	100	1023.7	762.5	1374.4
		PRE-BOOSTER	65	48	73.8	61.5	84.0	37.9	25.4	56.5
	Pn-Pn9 (13-18)	PIII(M3)	12	12	100	73.5	100	1106.5	514.2	2381.2
		PRE-BOOSTER	20	7	35.0	15.4	59.2	14.8	5.4	40.4
	Pn-Pn9	PIII(M3)	48	48	100	92.6	100	1043.8	791.7	1376.1
		PRE-BOOSTER	85	55	64.7	53.6	74.8	30.4	20.7	44.6
	Pn-Pn15	PIII(M3)	49	47	95.9	86.0	99.5	748.5	484.7	1155.9
		PRE-BOOSTER	81	49	60.5	49.0	71.2	23.0	15.6	34.0
	Hib-Pn	PIII(M3)	39	2	5.1	0.6	17.3	5.3	3.5	7.9
		PRE-VACC	74	3	4.1	0.8	11.4	4.8	3.8	6.0
OPSONO-19F	Pn-Pn9 (9-12)	PIII(M3)	36	36	100	90.3	100	890.2	600.1	1320.4
		PRE-BOOSTER	65	54	83.1	71.7	91.2	50.2	33.2	75.9
	Pn-Pn9 (13-18)	PIII(M3)	13	13	100	75.3	100	1057.7	469.5	2382.8
		PRE-BOOSTER	21	15	71.4	47.8	88.7	26.6	12.3	57.6
	Pn-Pn9	PIII(M3)	49	49	100	92.7	100	931.8	659.6	1316.5
		PRE-BOOSTER	86	69	80.2	70.2	88.0	43.0	29.9	61.7
	Pn-Pn15	PIII(M3)	49	47	95.9	86.0	99.5	693.6	448.4	1072.8
		PRE-BOOSTER	82	66	80.5	70.3	88.4	42.4	29.5	60.8
	Hib-Pn	PIII(M3)	40	6	15.0	5.7	29.8	6.3	4.2	9.5
		PRE-VACC	76	2	2.6	0.3	9.2	4.2	3.9	4.6

				≥8				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
OPSONO-23F	Pn-Pn9 (9-12)	PIII(M3)	36	35	97.2	85.5	99.9	1611.5	965.1	2691.0
		PRE-BOOSTER	66	46	69.7	57.1	80.4	193.2	96.0	388.6
	Pn-Pn9 (13-18)	PIII(M3)	13	13	100	75.3	100	2351.3	1185.8	4662.3
		PRE-BOOSTER	20	10	50.0	27.2	72.8	79.3	16.9	372.6
	Pn-Pn9	PIII(M3)	49	48	98.0	89.1	99.9	1781.4	1183.9	2680.5
		PRE-BOOSTER	86	56	65.1	54.1	75.1	157.0	83.2	296.3
	Pn-Pn15	PIII(M3)	49	47	95.9	86.0	99.5	1104.7	680.6	1793.0
		PRE-BOOSTER	80	63	78.8	68.2	87.1	531.1	280.3	1006.4
	Hib-Pn	PIII(M3)	39	6	15.4	5.9	30.5	9.0	4.8	16.9
		PRE-VACC	72	24	33.3	22.7	45.4	41.9	18.8	93.2

Pn-Pn9 (9-12) = Primed group receiving booster dose of 10Pn-PD-DiT at 9-12 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Pn-Pn9 (13-18) = Primed group receiving booster dose of 10Pn-PD-DiT at 13-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Pn-Pn9 = Primed group receiving booster dose of 10Pn-PD-DiT at 9-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study (pooled Pn-Pn9 (9-12) and Pn-Pn9 (13-18) groups)
Pn-Pn15 = Primed group receiving booster dose of 10Pn-PD-DiT at 15-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Hib-Pn = Unprimed group receiving 2+1 catch up vaccination with 10Pn-PD-DiT in the second year of life
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 of 10Pn-PD-DiT (for Pn-Pn groups) and Hiberix (for Hib-Pn group)
PRE-BOOSTER = prior to booster dose
PRE-VACC = prior to catch-up vaccination

Table 33 Seropositivity rates and GMTs for OPSONO-6A and OPSONO-19A titres (ATP cohort for persistence)

				≥8				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
OPSONO-6A	Pn-Pn9 (9-12)	PIII(M3)	32	16	50.0	31.9	68.1	24.7	12.0	50.8
		PRE-BOOSTER	65	28	43.1	30.8	56.0	22.1	13.1	37.0
	Pn-Pn9 (13-18)	PIII(M3)	12	6	50.0	21.1	78.9	29.0	7.6	110.9
		PRE-BOOSTER	21	7	33.3	14.6	57.0	18.3	5.9	56.1
	Pn-Pn9	PIII(M3)	44	22	50.0	34.6	65.4	25.8	14.0	47.5
		PRE-BOOSTER	86	35	40.7	30.2	51.8	21.1	13.2	33.6
	Pn-Pn15	PIII(M3)	48	21	43.8	29.5	58.8	19.5	11.0	34.6
		PRE-BOOSTER	82	39	47.6	36.4	58.9	30.1	18.4	49.3
	Hib-Pn	PIII(M3)	41	5	12.2	4.1	26.2	5.6	4.1	7.6
		PRE-VACC	72	13	18.1	10.0	28.9	10.3	6.3	17.0
OPSONO-19A	Pn-Pn9 (9-12)	PIII(M3)	36	9	25.0	12.1	42.2	10.6	5.8	19.4
		PRE-BOOSTER	66	14	21.2	12.1	33.0	8.9	6.0	13.3
	Pn-Pn9 (13-18)	PIII(M3)	12	5	41.7	15.2	72.3	21.2	5.0	89.6
		PRE-BOOSTER	20	8	40.0	19.1	63.9	12.8	6.0	27.1
	Pn-Pn9	PIII(M3)	48	14	29.2	17.0	44.1	12.6	7.2	22.0
		PRE-BOOSTER	86	22	25.6	16.8	36.1	9.7	6.8	13.7
	Pn-Pn15	PIII(M3)	45	13	28.9	16.4	44.3	11.7	6.8	20.2
		PRE-BOOSTER	82	19	23.2	14.6	33.8	7.4	5.7	9.7
	Hib-Pn	PIII(M3)	41	0	0.0	0.0	8.6	4.0	4.0	4.0
		PRE-VACC	78	5	6.4	2.1	14.3	4.8	4.0	5.7

Pn-Pn9 (9-12) = Primed group receiving booster dose of 10Pn-PD-DiT at 9-12 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Pn-Pn9 (13-18) = Primed group receiving booster dose of 10Pn-PD-DiT at 13-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Pn-Pn9 = Primed group receiving booster dose of 10Pn-PD-DiT at 9-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study (pooled Pn-Pn9 (9-12) and Pn-Pn9 (13-18) groups)
Pn-Pn15 = Primed group receiving booster dose of 10Pn-PD-DiT at 15-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Hib-Pn = Unprimed group receiving 2+1 catch up vaccination with 10Pn-PD-DiT in the second year of life
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 of 10Pn-PD-DiT (for Pn-Pn groups) and Hiberix (for Hib-Pn group)
PRE-BOOSTER = prior to booster dose
PRE-VACC = prior to catch-up vaccination

Immune response to booster vaccination in the primed Pn-Pn9 (9-12), Pn-Pn9 and Pn-Pn15 groups (22-inhibition ELISA):

One month after booster vaccination:

For each of the vaccine pneumococcal serotypes, at least 95.2% of subjects in the Pn-Pn9 (9-12) group and 93.8% of subjects in the Pn-Pn15 group had antibody concentrations ≥0.2 µg/mL.
For each of the vaccine pneumococcal serotypes, at least 96.3% of subjects in the Pn-Pn9 group (i.e. pooled Pn-Pn9 (9-12) and Pn-Pn9 (13-18) groups) and at least 93.8% of subjects in the Pn-Pn15 group had antibody concentrations ≥0.2 µg/mL (Table 36).

For cross-reactive serotypes, the observed percentage of subjects with antibody concentrations ≥0.2 µg/mL was 82.7% for 6A and 19A in the Pn-Pn9 group and 82.3% for 6A and 87.5% for 19A in the Pn-Pn15 group.

Persistence of antibodies at age of 24 months (i.e. approximately 9 to 15 months after booster vaccination with 10Pn-PD-DiT)
Approximately 9 to 15 months after booster vaccination:
For each of the vaccine pneumococcal serotypes:
At least 96.6% of subjects in the Pn-Pn9 group and 96.4% of subjects in the Pn- Pn15 group had antibody concentrations ≥0.05 μg/mL.
At least 89.8% of subjects in the Pn-Pn9 group and 90.9% of subjects in the Pn-Pn15 group had antibody concentrations ≥0.2 μg/mL except for serotype 6B in the Pn-Pn9 group (83.1%).

For cross-reactive serotypes,
The observed percentage of subjects with antibody concentrations ≥0.05 μg/mL was 89.8% for 6A and 91.5% for 19A in the Pn-Pn9 group and 89.1% for 6A and 96.4% for 19A in the Pn-Pn15 group.
The observed percentage of subjects with antibody concentrations ≥0.2 μg/mL was 62.7% for 6A and 74.6% for 19A in the Pn-Pn9 group and 58.2% for 6A and 92.7% for 19A in the Pn-Pn15 group.

Immune response to catch-up (2+1 schedule) vaccination in the unprimed Hib-Pn group (22-inhibition ELISA):
One month after dose 2 of catch-up vaccination:
For each of the vaccine pneumococcal serotypes, at least 94.4% of subjects had antibody concentrations ≥0.2 μg/mL except for serotypes 6B (88.6%) and 23F (90.1%).
For cross-reactive serotypes, the observed percentage of subjects with antibody concentrations ≥0.2 μg/mL was 65.7% for 6A and 94.4% for 19A.

Four months after dose 2 of catch-up vaccination:
For each of the vaccine pneumococcal serotypes, at least 93.8% of subjects had antibody concentrations ≥0.2 μg/mL except for serotype 6B (87.7%).
For cross-reactive serotypes, the observed percentage of subjects with antibody concentrations ≥0.2 μg/mL was 60.0% for 6A and 95.4% for 19A.

One month after dose 3 of catch-up vaccination:
For each of the vaccine pneumococcal serotypes, at least 96.3% of subjects had antibody concentrations ≥0.2 μg/mL.
For cross-reactive serotypes, the observed percentage of subjects with antibody concentrations ≥0.2 μg/mL was 87.0% for 6A and 100.0% for 19A.

Assessor's comment: The study was not powered to detect any differences between an early or late booster dose. The ELISA results do not indicate any major differences between the groups, while the OPA GMTs were numerically higher in the late booster group compared to the early booster group for several serotypes. The titres had generally declined to a lower level in the late booster group, which favours an early booster dose in order to decrease the risk of breakthrough cases due to waning immunity before the booster dose.

The responses after the third dose in the catch-up group (i.e. PIII(M7) in the HibPn group) were similar to the responses to the booster response in the children primed with the EPI schedule in terms of number of subjects achieving ELISA antibody levels ≥0.2 μg/mL. In some cases, e.g. serotype 1 and 6B the GMCs and the OPA GMTs were lower in the catch-up group and for serotypes 18C and 19F they were higher in the catch-up group. The ELISA GMCs and the OPA GMTs for all serotypes following the third dose in the catch-up schedule were consistently numerically higher compared to the second dose. Taken together these results indicate that a third dose given during the second year of life after the 2-dose catch-up schedule induces a booster response. However, from this relatively small study in Indian children it is not possible to draw conclusions on when or if a booster dose should be given to children who received a 2-dose catch-up vaccination during the second year of life. In addition, the relevance to an EU population is unclear.

Table 36 Seropositivity rates and GMCs for ANTI-1, ANTI-4, ANTI-5, ANTI-6B, ANTI-7F, ANTI-9V, ANTI-14, ANTI-18C, ANTI-19F and ANTI-23F antibodies (ATP cohort for immunogenicity)

				≥0.05 µg/mL				≥0.2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
ANTI-1	Pn-Pn9 (9-12)	PIII(M3)	66	66	100	94.6	100	66	100	94.6	100	3.38	2.73	4.18
		PRE-BOOSTER	65	65	100	94.5	100	48	73.8	61.5	84.0	0.45	0.34	0.60
		PIV(M1)	61	61	100	94.1	100	61	100	94.1	100	4.92	4.01	6.05
		PIV(M15)	40	39	97.5	86.8	99.9	36	90.0	76.3	97.2	0.84	0.56	1.26
	Pn-Pn9 (13-18)	PIII(M3)	23	23	100	85.2	100	23	100	85.2	100	3.22	2.30	4.50
		PRE-BOOSTER	23	21	91.3	72.0	98.9	10	43.5	23.2	65.5	0.21	0.12	0.37
		PIV(M1)	19	19	100	82.4	100	18	94.7	74.0	99.9	4.36	2.28	8.35
		PIV(M15)	19	18	94.7	74.0	99.9	17	89.5	66.9	98.7	1.28	0.62	2.65
	Pn-Pn9	PIII(M3)	89	89	100	95.9	100	89	100	95.9	100	3.34	2.79	3.98
		PRE-BOOSTER	88	86	97.7	92.0	99.7	58	65.9	55.0	75.7	0.37	0.29	0.48
		PIV(M1)	80	80	100	95.5	100	79	98.8	93.2	100	4.78	3.87	5.91
		PIV(M15)	59	57	96.6	88.3	99.6	53	89.8	79.2	96.2	0.96	0.68	1.37
	Pn-Pn15	PIII(M3)	71	70	98.6	92.4	100	70	98.6	92.4	100	3.51	2.78	4.43
		PRE-BOOSTER	69	65	94.2	85.8	98.4	44	63.8	51.3	75.0	0.31	0.23	0.41
		PIV(M1)	61	61	100	94.1	100	60	98.4	91.2	100	5.98	4.54	7.90
		PIV(M9)	55	55	100	93.5	100	51	92.7	82.4	98.0	1.37	1.00	1.87
	Hib-Pn	PIII(M3)	81	12	14.8	7.9	24.4	1	1.2	0.0	6.7	0.03	0.03	0.04
		PRE-VACC	81	18	22.2	13.7	32.8	3	3.7	0.8	10.4	0.04	0.03	0.04
		PII(M3)	69	67	97.1	89.9	99.6	67	97.1	89.9	99.6	2.50	1.93	3.24
		PII(M6)	65	65	100	94.5	100	62	95.4	87.1	99.0	1.03	0.82	1.29
		PIII(M7)	54	54	100	93.4	100	54	100	93.4	100	3.32	2.69	4.10
ANTI-4	Pn-Pn9 (9-12)	PIII(M3)	66	66	100	94.6	100	63	95.5	87.3	99.1	3.60	2.74	4.74
		PRE-BOOSTER	65	65	100	94.5	100	59	90.8	81.0	96.5	1.03	0.79	1.34
		PIV(M1)	62	61	98.4	91.3	100	61	98.4	91.3	100	7.22	5.34	9.76
		PIV(M15)	40	40	100	91.2	100	37	92.5	79.6	98.4	1.09	0.75	1.59
	Pn-Pn9 (13-18)	PIII(M3)	23	23	100	85.2	100	23	100	85.2	100	3.66	2.58	5.21
		PRE-BOOSTER	23	21	91.3	72.0	98.9	14	60.9	38.5	80.3	0.33	0.18	0.62
		PIV(M1)	19	18	94.7	74.0	99.9	18	94.7	74.0	99.9	7.47	3.15	17.70
		PIV(M15)	19	18	94.7	74.0	99.9	18	94.7	74.0	99.9	1.61	0.87	3.00
	Pn-Pn9	PIII(M3)	89	89	100	95.9	100	86	96.6	90.5	99.3	3.62	2.91	4.50
		PRE-BOOSTER	88	86	97.7	92.0	99.7	73	83.0	73.4	90.1	0.76	0.58	1.00
		PIV(M1)	81	79	97.5	91.4	99.7	79	97.5	91.4	99.7	7.28	5.41	9.79
		PIV(M15)	59	58	98.3	90.9	100	55	93.2	83.5	98.1	1.24	0.90	1.70
	Pn-Pn15	PIII(M3)	71	70	98.6	92.4	100	70	98.6	92.4	100	4.25	3.31	5.47
		PRE-BOOSTER	68	67	98.5	92.1	100	56	82.4	71.2	90.5	0.58	0.44	0.75
		PIV(M1)	63	63	100	94.3	100	63	100	94.3	100	11.56	7.96	16.79
		PIV(M9)	55	53	96.4	87.5	99.6	53	96.4	87.5	99.6	2.29	1.53	3.42
	Hib-Pn	PIII(M3)	81	17	21.0	12.7	31.5	6	7.4	2.8	15.4	0.04	0.03	0.04
		PRE-VACC	80	21	26.3	17.0	37.3	7	8.8	3.6	17.2	0.04	0.03	0.05
		PII(M3)	71	68	95.8	88.1	99.1	68	95.8	88.1	99.1	5.89	4.23	8.22
		PII(M6)	65	65	100	94.5	100	65	100	94.5	100	2.23	1.85	2.69
		PIII(M7)	54	54	100	93.4	100	54	100	93.4	100	8.22	5.92	11.42

				≥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-5	Pn-Pn9 (9-12)	PIII(M3)	66	66	100	94.6	100	65	98.5	91.8	100	4.42	3.56	5.48
		PRE-BOOSTER	65	65	100	94.5	100	58	89.2	79.1	95.6	0.60	0.47	0.77
		PIV(M1)	62	62	100	94.2	100	62	100	94.2	100	6.06	4.91	7.48
		PIV(M15)	40	40	100	91.2	100	37	92.5	79.6	98.4	1.07	0.74	1.55
	Pn-Pn9 (13-18)	PIII(M3)	23	23	100	85.2	100	23	100	85.2	100	4.41	3.33	5.83
		PRE-BOOSTER	23	22	95.7	78.1	99.9	13	56.5	34.5	76.8	0.29	0.18	0.49
		PIV(M1)	19	19	100	82.4	100	18	94.7	74.0	99.9	5.25	2.59	10.63
		PIV(M15)	19	18	94.7	74.0	99.9	17	89.5	66.9	98.7	1.50	0.76	2.93
	Pn-Pn9	PIII(M3)	89	89	100	95.9	100	88	98.9	93.9	100	4.42	3.71	5.25
		PRE-BOOSTER	88	87	98.9	93.8	100	71	80.7	70.9	88.3	0.50	0.40	0.63
		PIV(M1)	81	81	100	95.5	100	80	98.8	93.3	100	5.86	4.69	7.32
		PIV(M15)	59	58	98.3	90.9	100	54	91.5	81.3	97.2	1.19	0.86	1.65
	Pn-Pn15	PIII(M3)	71	71	100	94.9	100	69	97.2	90.2	99.7	4.03	3.20	5.07
		PRE-BOOSTER	69	67	97.1	89.9	99.6	56	81.2	69.9	89.6	0.38	0.29	0.48
		PIV(M1)	62	62	100	94.2	100	61	98.4	91.3	100	7.20	5.25	9.86
		PIV(M9)	55	54	98.2	90.3	100	53	96.4	87.5	99.6	2.03	1.43	2.86
	Hib-Pn	PIII(M3)	81	35	43.2	32.2	54.7	8	9.9	4.4	18.5	0.05	0.04	0.06
		PRE-VACC	80	35	43.8	32.7	55.3	10	12.5	6.2	21.8	0.05	0.04	0.06
		PII(M3)	71	70	98.6	92.4	100	70	98.6	92.4	100	2.81	2.20	3.58
		PII(M6)	65	65	100	94.5	100	65	100	94.5	100	1.39	1.13	1.70
		PIII(M7)	54	54	100	93.4	100	54	100	93.4	100	5.32	4.21	6.72
ANTI-6B	Pn-Pn9 (9-12)	PIII(M3)	66	62	93.9	85.2	98.3	51	77.3	65.3	86.7	0.75	0.51	1.10
		PRE-BOOSTER	66	65	98.5	91.8	100	58	87.9	77.5	94.6	0.64	0.49	0.84
		PIV(M1)	62	61	98.4	91.3	100	59	95.2	86.5	99.0	2.78	2.03	3.80
		PIV(M15)	40	39	97.5	86.8	99.9	32	80.0	64.4	90.9	0.68	0.45	1.03
	Pn-Pn9 (13-18)	PIII(M3)	23	23	100	85.2	100	17	73.9	51.6	89.8	0.68	0.38	1.20
		PRE-BOOSTER	22	22	100	84.6	100	17	77.3	54.6	92.2	0.67	0.33	1.37
		PIV(M1)	19	19	100	82.4	100	19	100	82.4	100	2.97	1.72	5.14
		PIV(M15)	19	18	94.7	74.0	99.9	17	89.5	66.9	98.7	1.04	0.51	2.12
	Pn-Pn9	PIII(M3)	89	85	95.5	88.9	98.8	68	76.4	66.2	84.8	0.73	0.53	1.00
		PRE-BOOSTER	88	87	98.9	93.8	100	75	85.2	76.1	91.9	0.65	0.50	0.85
		PIV(M1)	81	80	98.8	93.3	100	78	96.3	89.6	99.2	2.82	2.16	3.68
		PIV(M15)	59	57	96.6	88.3	99.6	49	83.1	71.0	91.6	0.78	0.54	1.11
	Pn-Pn15	PIII(M3)	71	65	91.5	82.5	96.8	56	78.9	67.6	87.7	0.68	0.48	0.97
		PRE-BOOSTER	71	69	97.2	90.2	99.7	56	78.9	67.6	87.7	0.49	0.37	0.64
		PIV(M1)	64	61	95.3	86.9	99.0	60	93.8	84.8	98.3	2.98	2.05	4.32
		PIV(M9)	55	53	96.4	87.5	99.6	50	90.9	80.0	97.0	0.90	0.61	1.32
	Hib-Pn	PIII(M3)	81	31	38.3	27.7	49.7	7	8.6	3.5	17.0	0.05	0.04	0.06
		PRE-VACC	80	13	16.3	8.9	26.2	3	3.8	0.8	10.6	0.03	0.03	0.04
		PII(M3)	70	67	95.7	88.0	99.1	62	88.6	78.7	94.9	0.71	0.53	0.95
		PII(M6)	65	63	96.9	89.3	99.6	57	87.7	77.2	94.5	0.61	0.47	0.78
		PIII(M7)	54	52	96.3	87.3	99.5	52	96.3	87.3	99.5	1.40	1.04	1.88

				≥0.05 µg/mL				≥0.2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
ANTI-7F	Pn-Pn9 (9-12)	PIII(M3)	66	66	100	94.6	100	66	100	94.6	100	3.61	2.95	4.42
		PRE-BOOSTER	65	65	100	94.5	100	63	96.9	89.3	99.6	1.30	1.02	1.65
		PIV(M1)	62	61	98.4	91.3	100	61	98.4	91.3	100	6.52	4.87	8.73
		PIV(M15)	40	39	97.5	86.8	99.9	39	97.5	86.8	99.9	1.14	0.82	1.60
	Pn-Pn9 (13-18)	PIII(M3)	23	23	100	85.2	100	23	100	85.2	100	4.23	3.15	5.70
		PRE-BOOSTER	23	23	100	85.2	100	23	100	85.2	100	0.74	0.53	1.05
		PIV(M1)	19	19	100	82.4	100	18	94.7	74.0	99.9	5.61	2.75	11.45
		PIV(M15)	19	18	94.7	74.0	99.9	18	94.7	74.0	99.9	1.71	0.89	3.29
	Pn-Pn9	PIII(M3)	89	89	100	95.9	100	89	100	95.9	100	3.76	3.19	4.44
		PRE-BOOSTER	88	88	100	95.9	100	86	97.7	92.0	99.7	1.12	0.92	1.38
		PIV(M1)	81	80	98.8	93.3	100	79	97.5	91.4	99.7	6.30	4.80	8.25
		PIV(M15)	59	57	96.6	88.3	99.6	57	96.6	88.3	99.6	1.30	0.96	1.76
	Pn-Pn15	PIII(M3)	71	71	100	94.9	100	70	98.6	92.4	100	3.61	2.89	4.52
		PRE-BOOSTER	70	70	100	94.9	100	69	98.6	92.3	100	0.93	0.73	1.19
		PIV(M1)	63	63	100	94.3	100	63	100	94.3	100	7.89	5.91	10.54
		PIV(M9)	55	55	100	93.5	100	54	98.2	90.3	100	1.98	1.43	2.75
	Hib-Pn	PIII(M3)	81	36	44.4	33.4	55.9	10	12.3	6.1	21.5	0.05	0.04	0.07
		PRE-VACC	81	34	42.0	31.1	53.5	16	19.8	11.7	30.1	0.06	0.05	0.08
		PII(M3)	71	69	97.2	90.2	99.7	68	95.8	88.1	99.1	4.63	3.38	6.34
		PII(M6)	65	65	100	94.5	100	65	100	94.5	100	2.72	2.28	3.24
		PIII(M7)	54	54	100	93.4	100	54	100	93.4	100	7.41	5.87	9.34
ANTI-9V	Pn-Pn9 (9-12)	PIII(M3)	66	66	100	94.6	100	66	100	94.6	100	4.36	3.49	5.44
		PRE-BOOSTER	65	65	100	94.5	100	63	96.9	89.3	99.6	1.32	1.04	1.68
		PIV(M1)	62	61	98.4	91.3	100	61	98.4	91.3	100	8.64	6.53	11.43
		PIV(M15)	39	39	100	91.0	100	37	94.9	82.7	99.4	1.52	1.02	2.26
	Pn-Pn9 (13-18)	PIII(M3)	23	23	100	85.2	100	22	95.7	78.1	99.9	3.34	2.02	5.53
		PRE-BOOSTER	23	23	100	85.2	100	21	91.3	72.0	98.9	0.90	0.47	1.70
		PIV(M1)	19	18	94.7	74.0	99.9	18	94.7	74.0	99.9	6.30	2.64	15.04
		PIV(M15)	19	18	94.7	74.0	99.9	18	94.7	74.0	99.9	2.14	1.03	4.43
	Pn-Pn9	PIII(M3)	89	89	100	95.9	100	88	98.9	93.9	100	4.07	3.31	5.00
		PRE-BOOSTER	88	88	100	95.9	100	84	95.5	88.8	98.7	1.20	0.94	1.52
		PIV(M1)	81	79	97.5	91.4	99.7	79	97.5	91.4	99.7	8.03	6.03	10.69
		PIV(M15)	58	57	98.3	90.8	100	55	94.8	85.6	98.9	1.70	1.20	2.41
	Pn-Pn15	PIII(M3)	71	70	98.6	92.4	100	70	98.6	92.4	100	4.24	3.30	5.45
		PRE-BOOSTER	71	71	100	94.9	100	66	93.0	84.3	97.7	0.96	0.74	1.25
		PIV(M1)	64	63	98.4	91.6	100	63	98.4	91.6	100	9.76	7.08	13.44
		PIV(M9)	55	54	98.2	90.3	100	53	96.4	87.5	99.6	2.27	1.64	3.14
	Hib-Pn	PIII(M3)	81	37	45.7	34.6	57.1	15	18.5	10.8	28.7	0.06	0.05	0.08
		PRE-VACC	80	18	22.5	13.9	33.2	7	8.8	3.6	17.2	0.04	0.03	0.05
		PII(M3)	71	67	94.4	86.2	98.4	67	94.4	86.2	98.4	2.09	1.53	2.87
		PII(M6)	65	65	100	94.5	100	65	100	94.5	100	1.74	1.40	2.17
		PIII(M7)	54	54	100	93.4	100	54	100	93.4	100	4.88	3.73	6.37

				≥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-14	Pn-Pn9 (9-12)	PIII(M3)	66	66	100	94.6	100	66	100	94.6	100	5.22	3.99	6.83
		PRE-BOOSTER	66	64	97.0	89.5	99.6	57	86.4	75.7	93.6	2.09	1.33	3.30
		PIV(M1)	62	62	100	94.2	100	61	98.4	91.3	100	10.49	7.52	14.63
		PIV(M15)	40	40	100	91.2	100	40	100	91.2	100	2.70	1.83	3.98
	Pn-Pn9 (13-18)	PIII(M3)	23	23	100	85.2	100	23	100	85.2	100	4.43	2.57	7.66
		PRE-BOOSTER	23	23	100	85.2	100	22	95.7	78.1	99.9	1.06	0.61	1.83
		PIV(M1)	19	19	100	82.4	100	19	100	82.4	100	9.24	4.69	18.19
		PIV(M15)	19	18	94.7	74.0	99.9	18	94.7	74.0	99.9	3.82	1.62	9.03
	Pn-Pn9	PIII(M3)	89	89	100	95.9	100	89	100	95.9	100	5.01	3.94	6.36
		PRE-BOOSTER	89	87	97.8	92.1	99.7	79	88.8	80.3	94.5	1.76	1.22	2.53
		PIV(M1)	81	81	100	95.5	100	80	98.8	93.3	100	10.18	7.60	13.65
		PIV(M15)	59	58	98.3	90.9	100	58	98.3	90.9	100	3.02	2.09	4.37
	Pn-Pn15	PIII(M3)	71	71	100	94.9	100	71	100	94.9	100	5.44	4.18	7.10
		PRE-BOOSTER	70	70	100	94.9	100	64	91.4	82.3	96.8	1.52	1.08	2.15
		PIV(M1)	64	63	98.4	91.6	100	63	98.4	91.6	100	11.85	8.15	17.22
		PIV(M9)	55	55	100	93.5	100	55	100	93.5	100	4.11	2.98	5.67
	Hib-Pn	PIII(M3)	81	69	85.2	75.6	92.1	45	55.6	44.1	66.6	0.24	0.18	0.33
		PRE-VACC	80	46	57.5	45.9	68.5	10	12.5	6.2	21.8	0.06	0.05	0.08
		PII(M3)	71	70	98.6	92.4	100	70	98.6	92.4	100	5.01	3.75	6.69
		PII(M6)	65	65	100	94.5	100	65	100	94.5	100	2.84	2.25	3.57
		PIII(M7)	54	54	100	93.4	100	54	100	93.4	100	7.59	5.87	9.80
ANTI-18C	Pn-Pn9 (9-12)	PIII(M3)	66	66	100	94.6	100	66	100	94.6	100	15.37	11.96	19.75
		PRE-BOOSTER	66	66	100	94.6	100	66	100	94.6	100	3.09	2.35	4.07
		PIV(M1)	62	62	100	94.2	100	61	98.4	91.3	100	35.86	27.01	47.61
		PIV(M15)	40	40	100	91.2	100	39	97.5	86.8	99.9	4.67	3.15	6.91
	Pn-Pn9 (13-18)	PIII(M3)	23	23	100	85.2	100	23	100	85.2	100	15.03	8.46	26.70
		PRE-BOOSTER	23	23	100	85.2	100	21	91.3	72.0	98.9	1.37	0.78	2.39
		PIV(M1)	19	18	94.7	74.0	99.9	18	94.7	74.0	99.9	26.45	10.22	68.49
		PIV(M15)	19	18	94.7	74.0	99.9	18	94.7	74.0	99.9	8.05	3.49	18.56
	Pn-Pn9	PIII(M3)	89	89	100	95.9	100	89	100	95.9	100	15.28	12.12	19.27
		PRE-BOOSTER	89	89	100	95.9	100	87	97.8	92.1	99.7	2.51	1.94	3.23
		PIV(M1)	81	80	98.8	93.3	100	79	97.5	91.4	99.7	33.39	24.73	45.08
		PIV(M15)	59	58	98.3	90.9	100	57	96.6	88.3	99.6	5.56	3.84	8.05
	Pn-Pn15	PIII(M3)	71	70	98.6	92.4	100	70	98.6	92.4	100	13.35	9.65	18.46
		PRE-BOOSTER	71	71	100	94.9	100	69	97.2	90.2	99.7	1.55	1.19	2.03
		PIV(M1)	63	63	100	94.3	100	63	100	94.3	100	42.43	31.48	57.20
		PIV(M9)	55	55	100	93.5	100	54	98.2	90.3	100	10.04	6.55	15.37
	Hib-Pn	PIII(M3)	81	42	51.9	40.5	63.1	17	21.0	12.7	31.5	0.07	0.05	0.10
		PRE-VACC	80	15	18.8	10.9	29.0	7	8.8	3.6	17.2	0.04	0.03	0.05
		PII(M3)	70	69	98.6	92.3	100	67	95.7	88.0	99.1	29.10	19.86	42.64
		PII(M6)	65	65	100	94.5	100	65	100	94.5	100	12.44	9.16	16.91
		PIII(M7)	54	54	100	93.4	100	54	100	93.4	100	75.19	57.69	98.01

				≥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-19F	Pn-Pn9 (9-12)	PIII(M3)	66	66	100	94.6	100	66	100	94.6	100	11.85	9.08	15.45
		PRE-BOOSTER	66	66	100	94.6	100	64	97.0	89.5	99.6	2.19	1.60	3.01
		PIV(M1)	62	61	98.4	91.3	100	61	98.4	91.3	100	14.17	10.12	19.83
		PIV(M15)	40	40	100	91.2	100	39	97.5	86.8	99.9	2.33	1.53	3.55
	Pn-Pn9 (13-18)	PIII(M3)	23	23	100	85.2	100	23	100	85.2	100	10.62	7.00	16.09
		PRE-BOOSTER	23	23	100	85.2	100	19	82.6	61.2	95.0	0.97	0.55	1.72
		PIV(M1)	19	18	94.7	74.0	99.9	18	94.7	74.0	99.9	12.20	4.78	31.09
		PIV(M15)	19	18	94.7	74.0	99.9	18	94.7	74.0	99.9	3.17	1.59	6.31
	Pn-Pn9	PIII(M3)	89	89	100	95.9	100	89	100	95.9	100	11.52	9.24	14.36
		PRE-BOOSTER	89	89	100	95.9	100	83	93.3	85.9	97.5	1.78	1.34	2.36
		PIV(M1)	81	79	97.5	91.4	99.7	79	97.5	91.4	99.7	13.68	9.86	18.97
		PIV(M15)	59	58	98.3	90.9	100	57	96.6	88.3	99.6	2.57	1.81	3.65
	Pn-Pn15	PIII(M3)	71	71	100	94.9	100	69	97.2	90.2	99.7	9.67	7.15	13.07
		PRE-BOOSTER	70	70	100	94.9	100	67	95.7	88.0	99.1	1.23	0.97	1.57
		PIV(M1)	64	64	100	94.4	100	63	98.4	91.6	100	13.64	9.42	19.76
		PIV(M9)	55	54	98.2	90.3	100	53	96.4	87.5	99.6	4.15	2.88	5.98
	Hib-Pn	PIII(M3)	81	61	75.3	64.5	84.2	30	37.0	26.6	48.5	0.12	0.09	0.16
		PRE-VACC	80	29	36.3	25.8	47.8	17	21.3	12.9	31.8	0.07	0.05	0.10
		PII(M3)	71	69	97.2	90.2	99.7	68	95.8	88.1	99.1	16.39	11.15	24.10
		PII(M6)	65	65	100	94.5	100	64	98.5	91.7	100	7.74	5.85	10.24
		PIII(M7)	54	54	100	93.4	100	54	100	93.4	100	30.71	23.76	39.68
ANTI-23F	Pn-Pn9 (9-12)	PIII(M3)	66	63	95.5	87.3	99.1	58	87.9	77.5	94.6	1.25	0.86	1.81
		PRE-BOOSTER	66	65	98.5	91.8	100	55	83.3	72.1	91.4	0.85	0.61	1.19
		PIV(M1)	62	61	98.4	91.3	100	60	96.8	88.8	99.6	5.94	4.21	8.39
		PIV(M15)	40	39	97.5	86.8	99.9	36	90.0	76.3	97.2	1.18	0.72	1.92
	Pn-Pn9 (13-18)	PIII(M3)	23	23	100	85.2	100	22	95.7	78.1	99.9	1.26	0.78	2.02
		PRE-BOOSTER	22	21	95.5	77.2	99.9	17	77.3	54.6	92.2	0.46	0.26	0.81
		PIV(M1)	19	18	94.7	74.0	99.9	18	94.7	74.0	99.9	4.41	1.90	10.22
		PIV(M15)	19	18	94.7	74.0	99.9	18	94.7	74.0	99.9	1.58	0.81	3.11
	Pn-Pn9	PIII(M3)	89	86	96.6	90.5	99.3	80	89.9	81.7	95.3	1.25	0.93	1.69
		PRE-BOOSTER	88	86	97.7	92.0	99.7	72	81.8	72.2	89.2	0.73	0.55	0.97
		PIV(M1)	81	79	97.5	91.4	99.7	78	96.3	89.6	99.2	5.54	4.02	7.63
		PIV(M15)	59	57	96.6	88.3	99.6	54	91.5	81.3	97.2	1.30	0.88	1.91
	Pn-Pn15	PIII(M3)	71	68	95.8	88.1	99.1	60	84.5	74.0	92.0	1.01	0.71	1.43
		PRE-BOOSTER	70	69	98.6	92.3	100	55	78.6	67.1	87.5	0.65	0.48	0.89
		PIV(M1)	63	62	98.4	91.5	100	62	98.4	91.5	100	6.48	4.69	8.96
		PIV(M9)	55	53	96.4	87.5	99.6	52	94.5	84.9	98.9	1.38	0.96	1.98
	Hib-Pn	PIII(M3)	81	24	29.6	20.0	40.8	10	12.3	6.1	21.5	0.04	0.04	0.05
		PRE-VACC	80	20	25.0	16.0	35.9	8	10.0	4.4	18.8	0.04	0.03	0.05
		PII(M3)	71	68	95.8	88.1	99.1	64	90.1	80.7	95.9	1.13	0.82	1.57
		PII(M6)	65	65	100	94.5	100	61	93.8	85.0	98.3	0.85	0.67	1.09
		PIII(M7)	54	54	100	93.4	100	53	98.1	90.1	100	2.15	1.69	2.75

Pn-Pn9 (9-12) = Primed group receiving booster dose of 10Pn-PD-DiT at 9-12 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Pn-Pn9 (13-18) = Primed group receiving booster dose of 10Pn-PD-DiT at 13-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Pn-Pn9 = Primed group receiving booster dose of 10Pn-PD-DiT at 9-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study (pooled Pn-Pn9 (9-12) and Pn-Pn9 (13-18) groups)
Pn-Pn15 = Primed group receiving booster dose of 10Pn-PD-DiT at 15-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Hib-Pn = Unprimed group receiving 2+1 catch up vaccination with 10Pn-PD-DiT in the second year of life
GMC = geometric mean antibody concentration
N = number of subiects with available results

Table 38 Seropositivity rates and GMCs for ANTI-6A and ANTI-19A antibodies (ATP cohort for immunogenicity)

				≥0.05 µg/mL				≥0.2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
ANTI-6A	Pn-Pn9 (9-12)	PIII(M3)	66	55	83.3	72.1	91.4	29	43.9	31.7	56.7	0.16	0.12	0.22
		PRE-BOOSTER	66	51	77.3	65.3	86.7	31	47.0	34.6	59.7	0.18	0.13	0.26
		PIV(M1)	62	58	93.5	84.3	98.2	52	83.9	72.3	92.0	0.86	0.57	1.29
		PIV(M15)	40	35	87.5	73.2	95.8	25	62.5	45.8	77.3	0.33	0.20	0.56
	Pn-Pn9 (13-18)	PIII(M3)	23	17	73.9	51.6	89.8	5	21.7	7.5	43.7	0.11	0.06	0.19
		PRE-BOOSTER	23	19	82.6	61.2	95.0	10	43.5	23.2	65.5	0.21	0.10	0.42
		PIV(M1)	19	19	100	82.4	100	15	78.9	54.4	93.9	0.69	0.38	1.28
		PIV(M15)	19	18	94.7	74.0	99.9	12	63.2	38.4	83.7	0.31	0.17	0.57
	Pn-Pn9	PIII(M3)	89	72	80.9	71.2	88.5	34	38.2	28.1	49.1	0.14	0.11	0.19
		PRE-BOOSTER	89	70	78.7	68.7	86.6	41	46.1	35.4	57.0	0.19	0.14	0.26
		PIV(M1)	81	77	95.1	87.8	98.6	67	82.7	72.7	90.2	0.82	0.59	1.14
		PIV(M15)	59	53	89.8	79.2	96.2	37	62.7	49.1	75.0	0.32	0.22	0.48
	Pn-Pn15	PIII(M3)	71	60	84.5	74.0	92.0	32	45.1	33.2	57.3	0.15	0.12	0.20
		PRE-BOOSTER	70	59	84.3	73.6	91.9	36	51.4	39.2	63.6	0.19	0.14	0.27
		PIV(M1)	62	58	93.5	84.3	98.2	51	82.3	70.5	90.8	0.95	0.63	1.44
		PIV(M9)	55	49	89.1	77.8	95.9	32	58.2	44.1	71.3	0.36	0.22	0.59
	Hib-Pn	PIII(M3)	81	42	51.9	40.5	63.1	9	11.1	5.2	20.0	0.06	0.05	0.08
		PRE-VACC	80	12	15.0	8.0	24.7	3	3.8	0.8	10.6	0.03	0.03	0.04
		PII(M3)	70	64	91.4	82.3	96.8	46	65.7	53.4	76.7	0.35	0.25	0.50
		PII(M6)	65	63	96.9	89.3	99.6	39	60.0	47.1	72.0	0.33	0.24	0.45
		PIII(M7)	54	53	98.1	90.1	100	47	87.0	75.1	94.6	0.76	0.53	1.09
ANTI-19A	Pn-Pn9 (9-12)	PIII(M3)	66	60	90.9	81.3	96.6	44	66.7	54.0	77.8	0.32	0.23	0.46
		PRE-BOOSTER	65	52	80.0	68.2	88.9	39	60.0	47.1	72.0	0.32	0.20	0.50
		PIV(M1)	62	61	98.4	91.3	100	51	82.3	70.5	90.8	2.29	1.36	3.86
		PIV(M15)	40	36	90.0	76.3	97.2	30	75.0	58.8	87.3	0.62	0.35	1.10
	Pn-Pn9 (13-18)	PIII(M3)	23	20	87.0	66.4	97.2	16	69.6	47.1	86.8	0.37	0.19	0.73
		PRE-BOOSTER	23	18	78.3	56.3	92.5	16	69.6	47.1	86.8	0.28	0.14	0.55
		PIV(M1)	19	18	94.7	74.0	99.9	16	84.2	60.4	96.6	3.57	1.24	10.31
		PIV(M15)	19	18	94.7	74.0	99.9	14	73.7	48.8	90.9	0.95	0.40	2.28
	Pn-Pn9	PIII(M3)	89	80	89.9	81.7	95.3	60	67.4	56.7	77.0	0.34	0.25	0.46
		PRE-BOOSTER	88	70	79.5	69.6	87.4	55	62.5	51.5	72.6	0.31	0.21	0.45
		PIV(M1)	81	79	97.5	91.4	99.7	67	82.7	72.7	90.2	2.54	1.61	4.03
		PIV(M15)	59	54	91.5	81.3	97.2	44	74.6	61.6	85.0	0.71	0.45	1.14
	Pn-Pn15	PIII(M3)	71	62	87.3	77.3	94.0	39	54.9	42.7	66.8	0.26	0.19	0.35
		PRE-BOOSTER	70	61	87.1	77.0	93.9	47	67.1	54.9	77.9	0.30	0.22	0.41
		PIV(M1)	64	63	98.4	91.6	100	56	87.5	76.8	94.4	2.87	1.78	4.61
		PIV(M9)	55	53	96.4	87.5	99.6	51	92.7	82.4	98.0	1.33	0.85	2.08
	Hib-Pn	PIII(M3)	81	47	58.0	46.5	68.9	14	17.3	9.8	27.3	0.07	0.06	0.09
		PRE-VACC	81	30	37.0	26.6	48.5	14	17.3	9.8	27.3	0.06	0.04	0.08
		PII(M3)	71	69	97.2	90.2	99.7	67	94.4	86.2	98.4	2.49	1.77	3.51
		PII(M6)	65	65	100	94.5	100	62	95.4	87.1	99.0	1.94	1.44	2.61
		PIII(M7)	54	54	100	93.4	100	54	100	93.4	100	7.91	5.62	11.13

Pn-Pn9 (9-12) = Primed group receiving booster dose of 10Pn-PD-DiT at 9-12 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Pn-Pn9 (13-18) = Primed group receiving booster dose of 10Pn-PD-DiT at 13-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Pn-Pn9 = Primed group receiving booster dose of 10Pn-PD-DiT at 9-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study (pooled Pn-Pn9 (9-12) and Pn-Pn9 (13-18) groups)
Pn-Pn15 = Primed group receiving booster dose of 10Pn-PD-DiT at 15-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study

Hib-Pn = Unprimed group receiving 2+1 catch up vaccination with 10Pn-PD-DiT in the second year of life
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(M3) = one month after dose III of 10Pn-PD-DiT (for Pn-Pn groups) and Hiberix (for Hib-Pn group)
PRE-BOOSTER = prior to booster dose
PRE-VACC = prior to catch-up vaccination
PIV(M1)= one month after booster dose
PIV(M9)= approximately 9 months after booster dose (for Pn-Pn15 group)
PIV(M15)= approximately 15 months after booster dose (for Pn-Pn9 groups)
PII(M3)= one month after dose 2 of 2+1 catch-up vaccination - Month 3
PII(M6)= four months after dose 2 of 2+1 catch-up vaccination - Month 6
PIII(M7)= one month after dose 3 catch-up vaccination - Month 7

Immune response to booster vaccination in primed Pn-Pn9 (9-12), Pn-Pn9 and Pn-Pn15 groups (opsonophagocytic activity):

One month after booster vaccination:

For each of the vaccine pneumococcal serotypes, at least 97.4% of subjects in the Pn-Pn9 group and 93.0% of subjects in the Pn-Pn15 groups had OPA titres ≥8 (Table 40).

For cross-reactive serotypes, the observed percentage of subjects with OPA titres ≥8 was 73.4% for 6A and 76.9% for 19A in the Pn-Pn9 group and 77.2% for 6A and 87.7% for 19A in the Pn-Pn15 group (Table 42).

Approximately 9 to 15 months after booster vaccination,

For each of the vaccine pneumococcal serotypes, at least 80.4% of subjects in the Pn-Pn9 group and 83.6% of subjects Pn-Pn15 group had OPA titres ≥8, except for serotype 1 in the Pn-Pn9 group (71.9%).

For cross-reactive serotype, the observed percentage of subjects with OPA titres ≥8 was 64.8% for 6A and 37.7% for 19A in the Pn-Pn9 group and 62.3% for 6A and 72.5% for 19A in the Pn-Pn15 group.

Immune response to catch-up (2+1 schedule) vaccination in unprimed Hib-Pn group (opsonophagocytic activity):

One month after dose 2 of catch-up vaccination:

For each of the vaccine pneumococcal serotypes, at least 90.6% of subjects had OPA titres ≥8 except for serotypes 6B (71.4%) and 1 (79.4%) (Table 40).

For cross-reactive serotypes, the observed percentage of subjects with OPA titres ≥8 was 78.5% for 6A and 87.5% for 19A (Table 42).

Four months after dose 2 of catch-up vaccination:

For each of the vaccine pneumococcal serotypes, at least 87.1% of subjects had OPA titres ≥8 except for serotypes 1 (45.3%), 6B (70.5%) and 5 (73.0%) (Table 40).

For cross-reactive serotypes, the observed percentage of subjects with OPA titres ≥8 was 81.0% for 6A and 90.2% for 19A.

One month after dose 3 of catch-up vaccination:

For each of the vaccine pneumococcal serotypes, at least 90.6% of subjects had OPA titres ≥8 (Table 40).

For cross-reactive serotypes, the observed percentage of subjects with OPA titres ≥8 was 92.3% for 6A and 98.1% for 19A (Table 42).

Table 40 Seropositivity rates and GMTs for OPSONO-1, OPSONO-4, OPSONO- 5, OPSONO-6B, OPSONO-7F, OPSONO-9V, OPSONO-14, OPSONO-18C, OPSONO- 19F and OPSONO-23F titres (ATP cohort for immunogenicity)

				≥8				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
OPSONO-1	Pn-Pn9 (9-12)	PIII(M3)	36	33	91.7	77.5	98.2	171.6	102.5	287.3
		PRE-BOOSTER	66	29	43.9	31.7	56.7	18.1	11.5	28.6
		PIV(M1)	61	59	96.7	88.7	99.6	1053.0	724.4	1530.7
		PIV(M15)	38	26	68.4	51.3	82.5	52.6	26.7	103.6
	Pn-Pn9 (13-18)	PIII(M3)	13	11	84.6	54.6	98.1	111.7	37.1	336.3
		PRE-BOOSTER	21	7	33.3	14.6	57.0	12.3	5.6	27.1
		PIV(M1)	18	18	100	81.5	100	1481.9	790.7	2777.5
		PIV(M15)	19	15	78.9	54.4	93.9	122.3	45.5	328.3
	Pn-Pn9	PIII(M3)	49	44	89.8	77.8	96.6	153.1	96.7	242.5
		PRE-BOOSTER	87	36	41.4	30.9	52.4	16.5	11.2	24.3
		PIV(M1)	79	77	97.5	91.2	99.7	1138.3	828.6	1563.7
		PIV(M15)	57	41	71.9	58.5	83.0	69.6	40.1	121.0
	Pn-Pn15	PIII(M3)	40	36	90.0	76.3	97.2	151.7	90.3	254.7
		PRE-BOOSTER	65	25	38.5	26.7	51.4	14.3	9.3	22.1
		PIV(M1)	58	57	98.3	90.8	100	2096.7	1464.8	3001.1
		PIV(M9)	54	47	87.0	75.1	94.6	173.8	105.5	286.5
	Hib-Pn	PIII(M3)	39	2	5.1	0.6	17.3	4.5	3.8	5.4
		PRE-VACC	74	2	2.7	0.3	9.4	4.3	3.9	4.8
		PII(M3)	68	54	79.4	67.9	88.3	76.1	49.0	118.2
		PII(M6)	64	29	45.3	32.8	58.3	18.1	11.5	28.4
		PIII(M7)	54	51	94.4	84.6	98.8	309.8	203.0	472.9
OPSONO-4	Pn-Pn9 (9-12)	PIII(M3)	36	36	100	90.3	100	738.8	462.3	1180.7
		PRE-BOOSTER	65	52	80.0	68.2	88.9	80.5	48.4	133.7
		PIV(M1)	61	61	100	94.1	100	2803.0	2121.2	3703.9
		PIV(M15)	39	31	79.5	63.5	90.7	325.2	131.4	804.4
	Pn-Pn9 (13-18)	PIII(M3)	13	13	100	75.3	100	945.8	469.8	1903.9
		PRE-BOOSTER	20	11	55.0	31.5	76.9	45.2	13.6	150.8
		PIV(M1)	18	18	100	81.5	100	6282.3	3727.6	10587.8
		PIV(M15)	18	18	100	81.5	100	1791.8	934.9	3434.0
	Pn-Pn9	PIII(M3)	49	49	100	92.7	100	788.8	539.7	1153.1
		PRE-BOOSTER	85	63	74.1	63.5	83.0	70.3	43.9	112.5
		PIV(M1)	79	79	100	95.4	100	3368.8	2618.0	4334.9
		PIV(M15)	57	49	86.0	74.2	93.7	557.4	284.0	1093.9
	Pn-Pn15	PIII(M3)	40	39	97.5	86.8	99.9	861.8	531.3	1398.1
		PRE-BOOSTER	63	52	82.5	70.9	90.9	101.6	62.6	164.9
		PIV(M1)	58	58	100	93.8	100	7202.1	5336.1	9720.6
		PIV(M9)	54	51	94.4	84.6	98.8	2525.6	1474.5	4325.9
	Hib-Pn	PIII(M3)	38	16	42.1	26.3	59.2	14.7	8.6	25.2
		PRE-VACC	64	4	6.3	1.7	15.2	5.8	4.0	8.6
		PII(M3)	66	66	100	94.6	100	2256.3	1840.0	2766.8
		PII(M6)	63	63	100	94.3	100	959.7	727.2	1266.6
		PIII(M7)	54	54	100	93.4	100	2946.2	2097.9	4137.4

				≥8				GMT		
						95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
OPSONO-5	Pn-Pn9 (9-12)	PIII(M3)	36	35	97.2	85.5	99.9	106.3	69.0	164.0
		PRE-BOOSTER	66	36	54.5	41.8	66.9	13.7	9.7	19.3
		PIV(M1)	61	60	98.4	91.2	100	434.8	328.2	576.1
		PIV(M15)	38	29	76.3	59.8	88.6	34.2	20.1	58.1
	Pn-Pn9 (13-18)	PIII(M3)	13	13	100	75.3	100	73.8	35.4	153.8
		PRE-BOOSTER	21	6	28.6	11.3	52.2	7.6	4.4	13.2
		PIV(M1)	18	18	100	81.5	100	519.0	289.4	930.7
		PIV(M15)	18	16	88.9	65.3	98.6	84.7	40.3	178.2
	Pn-Pn9	PIII(M3)	49	48	98.0	89.1	99.9	96.5	67.2	138.6
		PRE-BOOSTER	87	42	48.3	37.4	59.2	11.9	8.9	15.9
		PIV(M1)	79	78	98.7	93.1	100	452.7	353.0	580.6
		PIV(M15)	56	45	80.4	67.6	89.8	45.7	29.6	70.7
	Pn-Pn15	PIII(M3)	40	38	95.0	83.1	99.4	100.1	66.2	151.4
		PRE-BOOSTER	62	27	43.5	31.0	56.7	9.7	7.2	13.1
		PIV(M1)	58	57	98.3	90.8	100	834.6	610.9	1140.2
		PIV(M9)	55	46	83.6	71.2	92.2	90.6	54.8	149.8
	Hib-Pn	PIII(M3)	39	1	2.6	0.1	13.5	4.1	3.9	4.2
		PRE-VACC	75	1	1.3	0.0	7.2	4.2	3.8	4.7
		PII(M3)	64	58	90.6	80.7	96.5	76.3	53.3	109.3
		PII(M6)	63	46	73.0	60.3	83.4	24.6	17.0	35.6
		PIII(M7)	54	54	100	93.4	100	212.0	148.9	301.7
OPSONO-6B	Pn-Pn9 (9-12)	PIII(M3)	36	30	83.3	67.2	93.6	364.0	159.1	833.0
		PRE-BOOSTER	66	42	63.6	50.9	75.1	48.1	27.5	83.9
		PIV(M1)	61	59	96.7	88.7	99.6	1459.4	936.2	2274.8
		PIV(M15)	35	31	88.6	73.3	96.8	242.4	110.1	533.7
	Pn-Pn9 (13-18)	PIII(M3)	13	12	92.3	64.0	99.8	669.8	202.9	2211.1
		PRE-BOOSTER	21	14	66.7	43.0	85.4	57.6	18.6	178.1
		PIV(M1)	18	18	100	81.5	100	1937.1	1194.8	3140.5
		PIV(M15)	16	13	81.3	54.4	96.0	239.2	71.6	799.2
	Pn-Pn9	PIII(M3)	49	42	85.7	72.8	94.1	428.0	219.3	835.0
		PRE-BOOSTER	87	56	64.4	53.4	74.4	50.2	30.7	82.1
		PIV(M1)	79	77	97.5	91.2	99.7	1556.6	1090.0	2223.0
		PIV(M15)	51	44	86.3	73.7	94.3	241.4	127.7	456.4
	Pn-Pn15	PIII(M3)	40	34	85.0	70.2	94.3	478.3	229.7	995.8
		PRE-BOOSTER	63	44	69.8	57.0	80.8	60.0	32.9	109.3
		PIV(M1)	57	53	93.0	83.0	98.1	1781.2	1042.5	3043.6
		PIV(M9)	52	46	88.5	76.6	95.6	287.5	149.0	555.0
	Hib-Pn	PIII(M3)	37	4	10.8	3.0	25.4	5.5	3.8	8.0
		PRE-VACC	68	4	5.9	1.6	14.4	5.3	3.9	7.2
		PII(M3)	63	45	71.4	58.7	82.1	348.2	165.7	731.6
		PII(M6)	61	43	70.5	57.4	81.5	201.5	98.2	413.5
		PIII(M7)	53	48	90.6	79.3	96.9	740.5	419.6	1306.8

					≥8			GMT		
						95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
OPSONO-7F	Pn-Pn9 (9-12)	PIII(M3)	36	36	100	90.3	100	1690.5	1259.0	2269.9
		PRE-BOOSTER	66	66	100	94.6	100	1050.0	796.1	1385.0
		PIV(M1)	61	61	100	94.1	100	7229.8	5338.9	9790.5
		PIV(M15)	36	35	97.2	85.5	99.9	2399.1	1462.6	3935.1
	Pn-Pn9 (13-18)	PIII(M3)	13	13	100	75.3	100	1719.0	1080.1	2735.7
		PRE-BOOSTER	21	21	100	83.9	100	1600.4	932.1	2747.8
		PIV(M1)	18	18	100	81.5	100	10172.4	5569.2	18580.2
		PIV(M15)	19	19	100	82.4	100	4117.2	2106.4	8047.4
	Pn-Pn9	PIII(M3)	49	49	100	92.7	100	1698.0	1335.1	2159.7
		PRE-BOOSTER	87	87	100	95.8	100	1162.5	910.0	1485.0
		PIV(M1)	79	79	100	95.4	100	7814.8	5984.8	10204.3
		PIV(M15)	55	54	98.2	90.3	100	2891.2	1954.4	4276.9
	Pn-Pn15	PIII(M3)	40	40	100	91.2	100	1621.7	1112.7	2363.7
		PRE-BOOSTER	65	65	100	94.5	100	1539.1	1262.9	1875.6
		PIV(M1)	57	57	100	93.7	100	11064.4	8182.9	14960.5
		PIV(M9)	52	52	100	93.2	100	5371.9	3712.4	7773.4
	Hib-Pn	PIII(M3)	36	23	63.9	46.2	79.2	63.7	29.8	136.0
		PRE-VACC	63	52	82.5	70.9	90.9	1106.8	540.7	2265.9
		PII(M3)	67	67	100	94.6	100	7462.5	5653.9	9849.6
		PII(M6)	63	63	100	94.3	100	6295.9	4545.0	8721.4
		PIII(M7)	54	54	100	93.4	100	10104.0	7377.8	13837.4
OPSONO-9V	Pn-Pn9 (9-12)	PIII(M3)	36	35	97.2	85.5	99.9	1398.6	886.3	2207.1
		PRE-BOOSTER	63	60	95.2	86.7	99.0	373.3	261.3	533.4
		PIV(M1)	61	61	100	94.1	100	3755.9	2710.5	5204.4
		PIV(M15)	31	31	100	88.8	100	1384.3	844.8	2268.3
	Pn-Pn9 (13-18)	PIII(M3)	12	12	100	73.5	100	1844.9	1095.2	3107.6
		PRE-BOOSTER	20	20	100	83.2	100	673.7	308.8	1469.7
		PIV(M1)	18	18	100	81.5	100	7828.6	4018.5	15251.2
		PIV(M15)	18	18	100	81.5	100	3402.3	1967.1	5884.7
	Pn-Pn9	PIII(M3)	48	47	97.9	88.9	99.9	1498.9	1047.1	2145.6
		PRE-BOOSTER	83	80	96.4	89.8	99.2	430.4	310.7	596.1
		PIV(M1)	79	79	100	95.4	100	4440.0	3305.4	5964.2
		PIV(M15)	49	49	100	92.7	100	1926.1	1316.6	2817.9
	Pn-Pn15	PIII(M3)	40	39	97.5	86.8	99.9	1350.0	848.6	2147.7
		PRE-BOOSTER	63	63	100	94.3	100	704.9	533.7	931.1
		PIV(M1)	58	58	100	93.8	100	7870.3	5634.4	10993.4
		PIV(M9)	52	52	100	93.2	100	3504.5	2501.0	4910.6
	Hib-Pn	PIII(M3)	38	5	13.2	4.4	28.1	6.8	4.2	10.8
		PRE-VACC	58	40	69.0	55.5	80.5	205.9	98.7	429.4
		PII(M3)	61	61	100	94.1	100	5792.5	4586.3	7315.9
		PII(M6)	62	62	100	94.2	100	3463.4	2716.3	4416.1
		PIII(M7)	53	53	100	93.3	100	7000.0	5265.1	9306.6

				≥8				GMT		
						95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
OPSONO-14	Pn-Pn9 (9-12)	PIII(M3)	36	33	91.7	77.5	98.2	800.3	400.3	1600.1
		PRE-BOOSTER	64	54	84.4	73.1	92.2	196.6	115.7	334.2
		PIV(M1)	61	60	98.4	91.2	100	1970.8	1452.1	2674.8
		PIV(M15)	37	35	94.6	81.8	99.3	517.4	277.2	965.8
	Pn-Pn9 (13-18)	PIII(M3)	12	11	91.7	61.5	99.8	602.4	155.4	2334.7
		PRE-BOOSTER	21	21	100	83.9	100	239.2	116.3	491.8
		PIV(M1)	18	18	100	81.5	100	2378.7	1257.3	4500.0
		PIV(M15)	19	18	94.7	74.0	99.9	1101.0	447.2	2710.7
	Pn-Pn9	PIII(M3)	48	44	91.7	80.0	97.7	745.4	411.1	1351.8
		PRE-BOOSTER	85	75	88.2	79.4	94.2	206.4	134.2	317.5
		PIV(M1)	79	78	98.7	93.1	100	2057.1	1569.6	2696.1
		PIV(M15)	56	53	94.6	85.1	98.9	668.5	403.1	1108.6
	Pn-Pn15	PIII(M3)	40	39	97.5	86.8	99.9	1159.8	675.8	1990.4
		PRE-BOOSTER	62	53	85.5	74.2	93.1	184.0	109.8	308.2
		PIV(M1)	57	57	100	93.7	100	4407.5	3193.2	6083.5
		PIV(M9)	53	51	96.2	87.0	99.5	1641.2	944.2	2852.9
	Hib-Pn	PIII(M3)	38	9	23.7	11.4	40.2	7.4	4.9	11.0
		PRE-VACC	67	14	20.9	11.9	32.6	12.4	7.1	21.6
		PII(M3)	65	63	96.9	89.3	99.6	2359.8	1576.1	3533.2
		PII(M6)	63	61	96.8	89.0	99.6	1293.6	886.8	1887.2
		PIII(M7)	54	53	98.1	90.1	100	3709.4	2463.5	5585.2
OPSONO-18C	Pn-Pn9 (9-12)	PIII(M3)	36	36	100	90.3	100	1023.7	762.5	1374.4
		PRE-BOOSTER	65	48	73.8	61.5	84.0	37.9	25.4	56.5
		PIV(M1)	61	60	98.4	91.2	100	1565.0	1131.9	2163.8
		PIV(M15)	34	31	91.2	76.3	98.1	123.1	68.7	220.6
	Pn-Pn9 (13-18)	PIII(M3)	12	12	100	73.5	100	1106.5	514.2	2381.2
		PRE-BOOSTER	20	7	35.0	15.4	59.2	14.8	5.4	40.4
		PIV(M1)	18	18	100	81.5	100	3579.4	2222.4	5765.0
		PIV(M15)	18	18	100	81.5	100	783.6	406.3	1511.2
	Pn-Pn9	PIII(M3)	48	48	100	92.6	100	1043.8	791.7	1376.1
		PRE-BOOSTER	85	55	64.7	53.6	74.8	30.4	20.7	44.6
		PIV(M1)	79	78	98.7	93.1	100	1889.7	1429.4	2498.1
		PIV(M15)	52	49	94.2	84.1	98.8	233.6	142.2	383.8
	Pn-Pn15	PIII(M3)	40	38	95.0	83.1	99.4	774.4	461.9	1298.5
		PRE-BOOSTER	62	37	59.7	46.4	71.9	22.2	14.1	35.0
		PIV(M1)	58	57	98.3	90.8	100	3643.2	2572.2	5160.2
		PIV(M9)	53	50	94.3	84.3	98.8	1155.0	662.0	2015.0
	Hib-Pn	PIII(M3)	37	1	2.7	0.1	14.2	4.5	3.5	5.8
		PRE-VACC	71	3	4.2	0.9	11.9	4.8	3.8	6.1
		PII(M3)	66	62	93.9	85.2	98.3	2487.5	1541.2	4014.8
		PII(M6)	62	62	100	94.2	100	2546.4	1755.0	3694.7
		PIII(M7)	54	54	100	93.4	100	8814.6	6810.9	11407.7

				≥8				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
OPSONO-19F	Pn-Pn9 (9-12)	PIII(M3)	36	36	100	90.3	100	890.2	600.1	1320.4
		PRE-BOOSTER	65	54	83.1	71.7	91.2	50.2	33.2	75.9
		PIV(M1)	60	59	98.3	91.1	100	1645.0	1020.1	2652.8
		PIV(M15)	32	25	78.1	60.0	90.7	73.7	36.5	148.6
	Pn-Pn9 (13-18)	PIII(M3)	13	13	100	75.3	100	1057.7	469.5	2382.8
		PRE-BOOSTER	21	15	71.4	47.8	88.7	26.6	12.3	57.6
		PIV(M1)	18	17	94.4	72.7	99.9	1769.4	651.9	4802.5
		PIV(M15)	19	17	89.5	66.9	98.7	202.4	79.6	514.7
	Pn-Pn9	PIII(M3)	49	49	100	92.7	100	931.8	659.6	1316.5
		PRE-BOOSTER	86	69	80.2	70.2	88.0	43.0	29.9	61.7
		PIV(M1)	78	76	97.4	91.0	99.7	1672.9	1096.3	2552.7
		PIV(M15)	51	42	82.4	69.1	91.6	107.3	61.4	187.6
	Pn-Pn15	PIII(M3)	40	38	95.0	83.1	99.4	670.0	401.1	1119.2
		PRE-BOOSTER	63	49	77.8	65.5	87.3	34.7	23.4	51.6
		PIV(M1)	58	57	98.3	90.8	100	2404.4	1583.1	3651.6
		PIV(M9)	53	50	94.3	84.3	98.8	357.9	218.9	585.0
	Hib-Pn	PIII(M3)	38	5	13.2	4.4	28.1	5.4	4.1	7.1
		PRE-VACC	73	2	2.7	0.3	9.5	4.2	3.9	4.6
		PII(M3)	65	62	95.4	87.1	99.0	1768.6	1120.3	2792.0
		PII(M6)	62	60	96.8	88.8	99.6	753.8	497.3	1142.5
		PIII(M7)	51	51	100	93.0	100	3808.8	2689.5	5393.9
OPSONO-23F	Pn-Pn9 (9-12)	PIII(M3)	36	35	97.2	85.5	99.9	1611.5	965.1	2691.0
		PRE-BOOSTER	66	46	69.7	57.1	80.4	193.2	96.0	388.6
		PIV(M1)	61	59	96.7	88.7	99.6	2828.0	1829.7	4370.9
		PIV(M15)	35	28	80.0	63.1	91.6	1015.3	354.7	2906.3
	Pn-Pn9 (13-18)	PIII(M3)	13	13	100	75.3	100	2351.3	1185.8	4662.3
		PRE-BOOSTER	20	10	50.0	27.2	72.8	79.3	16.9	372.6
		PIV(M1)	18	18	100	81.5	100	10489.7	6411.7	17161.6
		PIV(M15)	19	19	100	82.4	100	6915.3	4363.2	10960.1
	Pn-Pn9	PIII(M3)	49	48	98.0	89.1	99.9	1781.4	1183.9	2680.5
		PRE-BOOSTER	86	56	65.1	54.1	75.1	157.0	83.2	296.3
		PIV(M1)	79	77	97.5	91.2	99.7	3812.3	2630.8	5524.5
		PIV(M15)	54	47	87.0	75.1	94.6	1994.1	959.7	4143.4
	Pn-Pn15	PIII(M3)	40	39	97.5	86.8	99.9	1356.3	818.3	2247.9
		PRE-BOOSTER	61	46	75.4	62.7	85.5	498.2	231.4	1072.9
		PIV(M1)	58	56	96.6	88.1	99.6	5937.2	3587.6	9825.5
		PIV(M9)	55	48	87.3	75.5	94.7	3018.5	1389.0	6559.6
	Hib-Pn	PIII(M3)	37	5	13.5	4.5	28.8	7.9	4.4	14.2
		PRE-VACC	69	22	31.9	21.2	44.2	38.7	17.1	87.5
		PII(M3)	67	62	92.5	83.4	97.5	3378.1	2014.8	5664.0
		PII(M6)	62	54	87.1	76.1	94.3	1868.2	956.9	3647.5
		PIII(M7)	53	48	90.6	79.3	96.9	4357.3	2246.9	8449.8

Pn-Pn9 (9-12) = Primed group receiving booster dose of 10Pn-PD-DiT at 9-12 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Pn-Pn9 (13-18) = Primed group receiving booster dose of 10Pn-PD-DiT at 13-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Pn-Pn9 = Primed group receiving booster dose of 10Pn-PD-DiT at 9-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study (pooled Pn-Pn9 (9-12) and Pn-Pn9 (13-18) groups)
Pn-Pn15 = Primed group receiving booster dose of 10Pn-PD-DiT at 15-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Hib-Pn = Unprimed group receiving 2+1 catch up vaccination with 10Pn-PD-DiT in the second year of life
GMT = geometric mean titre

N = number of subjects with available results

Table 42 Seropositivity rates and GMTs for OPSONO-6A and OPSONO-19A titres (ATP cohort for immunogenicity)

				≥8				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
OPSONO-6A	Pn-Pn9 (9-12)	PIII(M3)	32	16	50.0	31.9	68.1	24.7	12.0	50.8
		PRE-BOOSTER	65	28	43.1	30.8	56.0	22.1	13.1	37.0
		PIV(M1)	61	44	72.1	59.2	82.9	164.2	85.3	316.4
		PIV(M15)	35	24	68.6	50.7	83.1	67.4	31.6	143.5
	Pn-Pn9 (13-18)	PIII(M3)	12	6	50.0	21.1	78.9	29.0	7.6	110.9
		PRE-BOOSTER	21	7	33.3	14.6	57.0	18.3	5.9	56.1
		PIV(M1)	18	14	77.8	52.4	93.6	184.6	56.8	600.2
		PIV(M15)	19	11	57.9	33.5	79.7	53.7	17.1	169.0
	Pn-Pn9	PIII(M3)	44	22	50.0	34.6	65.4	25.8	14.0	47.5
		PRE-BOOSTER	86	35	40.7	30.2	51.8	21.1	13.2	33.6
		PIV(M1)	79	58	73.4	62.3	82.7	168.7	96.3	295.5
		PIV(M15)	54	35	64.8	50.6	77.3	62.2	33.7	114.8
	Pn-Pn15	PIII(M3)	39	17	43.6	27.8	60.4	19.0	10.0	36.0
		PRE-BOOSTER	63	29	46.0	33.4	59.1	27.1	15.7	47.0
		PIV(M1)	57	44	77.2	64.2	87.3	262.5	135.4	509.0
		PIV(M9)	53	33	62.3	47.9	75.2	96.6	45.4	205.6
	Hib-Pn	PIII(M3)	39	5	12.8	4.3	27.4	5.7	4.1	7.8
		PRE-VACC	69	12	17.4	9.3	28.4	10.2	6.1	17.1
		PII(M3)	65	51	78.5	66.5	87.7	324.9	176.1	599.5
		PII(M6)	63	51	81.0	69.1	89.8	329.0	181.0	598.2
		PIII(M7)	52	48	92.3	81.5	97.9	616.2	369.2	1028.5
OPSONO-19A	Pn-Pn9 (9-12)	PIII(M3)	36	9	25.0	12.1	42.2	10.6	5.8	19.4
		PRE-BOOSTER	66	14	21.2	12.1	33.0	8.9	6.0	13.3
		PIV(M1)	60	44	73.3	60.3	83.9	115.2	61.9	214.4
		PIV(M15)	36	10	27.8	14.2	45.2	11.7	6.1	22.5
	Pn-Pn9 (13-18)	PIII(M3)	12	5	41.7	15.2	72.3	21.2	5.0	89.6
		PRE-BOOSTER	20	8	40.0	19.1	63.9	12.8	6.0	27.1
		PIV(M1)	18	16	88.9	65.3	98.6	498.5	170.7	1456.0
		PIV(M15)	17	10	58.8	32.9	81.6	43.2	12.9	144.7
	Pn-Pn9	PIII(M3)	48	14	29.2	17.0	44.1	12.6	7.2	22.0
		PRE-BOOSTER	86	22	25.6	16.8	36.1	9.7	6.8	13.7
		PIV(M1)	78	60	76.9	66.0	85.7	161.6	93.7	278.5
		PIV(M15)	53	20	37.7	24.8	52.1	17.8	9.8	32.1
	Pn-Pn15	PIII(M3)	36	9	25.0	12.1	42.2	10.7	5.7	19.9
		PRE-BOOSTER	63	14	22.2	12.7	34.5	7.0	5.3	9.3
		PIV(M1)	57	50	87.7	76.3	94.9	385.6	223.4	665.5
		PIV(M9)	51	37	72.5	58.3	84.1	60.0	33.0	109.2
	Hib-Pn	PIII(M3)	39	0	0.0	0.0	9.0	4.0	4.0	4.0
		PRE-VACC	75	5	6.7	2.2	14.9	4.8	4.0	5.8
		PII(M3)	64	56	87.5	76.8	94.4	506.6	305.5	840.1
		PII(M6)	61	55	90.2	79.8	96.3	402.1	248.9	649.5
		PIII(M7)	54	53	98.1	90.1	100	1770.9	1190.6	2634.0

- Safety results

Exposure

	Pn-Pn9 (9-12) N = 74		Pn-Pn9 (13-18) N = 26		Pn-Pn9 N = 100		Pn-Pn15 N = 95		Hib-Pn N = 87	
Total number of doses received	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
1	74	100	26	100	100	100	95	100	7	8.0
2	-	-	-	-	-	-	-	-	9	10.3
3	-	-	-	-	-	-	-	-	71	81.6
Any	74	100	26	100	100	100	95	100	87	100

Pn-Pn9 (9-12) = Primed group receiving booster dose of 10Pn-PD-DiT at 9-12 months of age following 3-dose primary
vaccination in the 10PN-PD-DIT-037 study
Pn-Pn9 (13-18) = Primed group receiving booster dose of 10Pn-PD-DiT at 13-18 months of age following 3-dose
primary vaccination in the 10PN-PD-DIT-037 study
Pn-Pn9 = Primed group receiving booster dose of 10Pn-PD-DiT at 9-18 months of age following 3-dose primary
vaccination in the 10PN-PD-DIT-037 study (pooled Pn-Pn9 (9-12) and Pn-Pn9 (13-18) groups)
Pn-Pn15 = Primed group receiving booster dose of 10Pn-PD-DiT at 15-18 months of age following 3-dose primary
vaccination in the 10PN-PD-DIT-037 study
Hib-Pn = Unprimed group receiving 2+1 catch up vaccination with 10Pn-PD-DiT in the second year of life
N = number of subjects in each group included in the considered cohort
n/% = number/percentage of subjects receiving the specified total number of doses
Any = number and percentage of subjects receiving at least one dose

Overall incidence of adverse events

The overall incidence of AEs (solicited and/or unsolicited, local and/or general) reported during the 31-day post-vaccination period and the overall incidence of AEs (solicited and/or unsolicited, local and/or general) with are presented in Table 80 for primed groups (Pn-Pn9 and Pn-Pn15 groups) and Table 81 for the unprimed group.

Table 80 Incidence and nature of symptoms (solicited and unsolicited) reported during the 31-day (Days 0-30) post-vaccination period – Primed groups (Total vaccinated cohort)

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Pn-Pn9 (9-12)	71	37	52.1	39.9	64.1	70	28	40.0	28.5	52.4	71	29	40.8	29.3	53.2
Pn-Pn9 (13-18)	22	13	59.1	36.4	79.3	22	11	50.0	28.2	71.8	22	7	31.8	13.9	54.9
Pn-Pn9	93	50	53.8	43.1	64.2	92	39	42.4	32.1	53.1	93	36	38.7	28.8	49.4
Pn-Pn15	85	29	34.1	24.2	45.2	85	18	21.2	13.1	31.4	85	25	29.4	20.0	40.3

Pn-Pn9 (9-12) = Primed group receiving booster dose of 10Pn-PD-DiT at 9-12 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Pn-Pn9 (13-18) = Primed group receiving booster dose of 10Pn-PD-DiT at 13-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Pn-Pn9 = Primed group receiving booster dose of 10Pn-PD-DiT at 9-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study (pooled Pn-Pn9 (9-12) and Pn-Pn9 (13-18) groups)
Pn-Pn15 = Primed group receiving booster dose of 10Pn-PD-DiT at 15-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
N= number of subjects with the documented dose
n/%= number/percentage of subjects presenting at least one type of symptom
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Table 81 Incidence and nature of symptoms (solicited and unsolicited) reported during the 31-day (Days 0-30) post-vaccination period – Unprimed group (Total vaccinated cohort)

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	Hib-Pn	82	36	43.9	33.0	55.3	82	25	30.5	20.8	41.6	82	27	32.9	22.9	44.2
Dose 2	Hib-Pn	77	15	19.5	11.3	30.1	77	11	14.3	7.4	24.1	77	11	14.3	7.4	24.1
Dose 3	Hib-Pn	62	15	24.2	14.2	36.7	62	7	11.3	4.7	21.9	62	14	22.6	12.9	35.0
Overall/dose	Hib-Pn	221	66	29.9	23.9	36.4	221	43	19.5	14.5	25.3	221	52	23.5	18.1	29.7
Overall/subject	Hib-Pn	82	38	46.3	35.3	57.7	82	26	31.7	21.9	42.9	82	30	36.6	26.2	48.0

Hib-Pn = Unprimed group receiving 2+1 catch up vaccination with 10Pn-PD-DiT in the second year of life
For each dose and overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects reporting at least once the symptom
For overall/dose:
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

During the 31-day post-booster vaccination period:

- AEs (solicited and/or unsolicited, local and/or general) were reported for 53.8% and 34.1% of subjects in the Pn-Pn9 and Pn-Pn15 groups respectively.
- Grade 3 AEs (solicited and/or unsolicited, local and/or general) were reported for 7.5% and 8.2% of subjects in the Pn-Pn9 and Pn-Pn15 groups respectively. All these AEs were considered by the investigator to be causally related to study vaccination.
- AEs (solicited and/or unsolicited, local and/or general) with medically attended visits were reported for 5.4% and 1.2% of subjects in the Pn-Pn9 and Pn-Pn15 groups respectively.
- Any AEs (solicited and/or unsolicited, local and/or general) were reported following 29.9% of overall doses (46.3% of subjects) in the unprimed group.
- Grade 3 AEs (solicited and/or unsolicited, local and/or general) were reported following 4.1% of overall doses (8.5% of subjects) in the unprimed group. There was no increase in the incidence of adverse events over successive doses. All these AEs were considered by the investigator to be causally related to study vaccination.
- AEs (solicited and/or unsolicited, local and/or general) with medically attended visits were reported following 2.3% of doses (6.1% of subjects) in the unprimed group.

Solicited local adverse events

The results are detailed in Tables 90 (primed groups) and 91 (unprimed group).

Table 90 Incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period – Primed groups (Total vaccinated cohort)

		Pn-Pn9 (9-12)					Pn-Pn9 (13-18)					Pn-Pn9					Pn-Pn15				
					95 % CI					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Pain	All	71	24	33.8	23.0	46.0	22	7	31.8	13.9	54.9	93	31	33.3	23.9	43.9	85	25	29.4	20.0	40.3
	Grade 3	71	2	2.8	0.3	9.8	22	0	0.0	0.0	15.4	93	2	2.2	0.3	7.6	85	4	4.7	1.3	11.6
	Medical advice	71	0	0.0	0.0	5.1	22	0	0.0	0.0	15.4	93	0	0.0	0.0	3.9	85	0	0.0	0.0	4.2
Redness (mm)	All	71	14	19.7	11.2	30.9	22	2	9.1	1.1	29.2	93	16	17.2	10.2	26.4	85	12	14.1	7.5	23.4
	>20	71	3	4.2	0.9	11.9	22	0	0.0	0.0	15.4	93	3	3.2	0.7	9.1	85	0	0.0	0.0	4.2
	>30	71	2	2.8	0.3	9.8	22	0	0.0	0.0	15.4	93	2	2.2	0.3	7.6	85	0	0.0	0.0	4.2
	Medical advice	71	0	0.0	0.0	5.1	22	0	0.0	0.0	15.4	93	0	0.0	0.0	3.9	85	0	0.0	0.0	4.2
Swelling (mm)	All	71	12	16.9	9.0	27.7	22	2	9.1	1.1	29.2	93	14	15.1	8.5	24.0	85	14	16.5	9.3	26.1
	>20	71	5	7.0	2.3	15.7	22	0	0.0	0.0	15.4	93	5	5.4	1.8	12.1	85	4	4.7	1.3	11.6
	>30	71	4	5.6	1.6	13.8	22	0	0.0	0.0	15.4	93	4	4.3	1.2	10.6	85	1	1.2	0.0	6.4
	Medical advice	71	0	0.0	0.0	5.1	22	0	0.0	0.0	15.4	93	0	0.0	0.0	3.9	85	0	0.0	0.0	4.2

Pn-Pn9 (9-12) = Primed group receiving booster dose of 10Pn-PD-DiT at 9-12 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study

Pn-Pn9 (13-18) = Primed group receiving booster dose of 10Pn-PD-DiT at 13-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study

Pn-Pn9 = Primed group receiving booster dose of 10Pn-PD-DiT at 9-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study (pooled Pn-Pn9 (9-12) and Pn-Pn9 (13-18) groups)

Pn-Pn15 = Primed group receiving booster dose of 10Pn-PD-DiT at 15-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study

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

Table 91 Incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period following each dose and overall – Unprimed group (Total vaccinated cohort)

		Hib-Pn				
					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**
		Dose 1				
Pain	All	82	23	28.0	18.7	39.1
	Grade 3	82	4	4.9	1.3	12.0
	Medical advice	82	0	0.0	0.0	4.4
Redness (mm)	All	82	9	11.0	5.1	19.8
	>20	82	1	1.2	0.0	6.6
	>30	82	1	1.2	0.0	6.6
	Medical advice	82	0	0.0	0.0	4.4
Swelling (mm)	All	82	11	13.4	6.9	22.7
	>20	82	2	2.4	0.3	8.5
	>30	82	2	2.4	0.3	8.5
	Medical advice	82	0	0.0	0.0	4.4
		Dose 2				
Pain	All	77	10	13.0	6.4	22.6
	Grade 3	77	0	0.0	0.0	4.7
	Medical advice	77	0	0.0	0.0	4.7
Redness (mm)	All	77	1	1.3	0.0	7.0
	>20	77	0	0.0	0.0	4.7
	>30	77	0	0.0	0.0	4.7
	Medical advice	77	0	0.0	0.0	4.7
Swelling (mm)	All	77	6	7.8	2.9	16.2
	>20	77	1	1.3	0.0	7.0
	>30	77	1	1.3	0.0	7.0
	Medical advice	77	0	0.0	0.0	4.7
		Dose 3				
Pain	All	62	12	19.4	10.4	31.4
	Grade 3	62	2	3.2	0.4	11.2
	Medical advice	62	0	0.0	0.0	5.8
Redness (mm)	All	62	4	6.5	1.8	15.7
	>20	62	0	0.0	0.0	5.8
	>30	62	0	0.0	0.0	5.8
	Medical advice	62	0	0.0	0.0	5.8
Swelling (mm)	All	62	7	11.3	4.7	21.9
	>20	62	1	1.6	0.0	8.7
	>30	62	0	0.0	0.0	5.8
	Medical advice	62	0	0.0	0.0	5.8
		Overall/dose				
Pain	All	221	45	20.4	15.3	26.3
	Grade 3	221	6	2.7	1.0	5.8
	Medical advice	221	0	0.0	0.0	1.7
Redness (mm)	All	221	14	6.3	3.5	10.4
	>20	221	1	0.5	0.0	2.5
	>30	221	1	0.5	0.0	2.5
	Medical advice	221	0	0.0	0.0	1.7
Swelling (mm)	All	221	24	10.9	7.1	15.7
	>20	221	4	1.8	0.5	4.6
	>30	221	3	1.4	0.3	3.9
	Medical advice	221	0	0.0	0.0	1.7

		Hib-Pn				
					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**
Overall/subject						
Pain	All	82	26	31.7	21.9	42.9
	Grade 3	82	5	6.1	2.0	13.7
	Medical advice	82	0	0.0	0.0	4.4
Redness (mm)	All	82	11	13.4	6.9	22.7
	>20	82	1	1.2	0.0	6.6
	>30	82	1	1.2	0.0	6.6
	Medical advice	82	0	0.0	0.0	4.4
Swelling (mm)	All	82	16	19.5	11.6	29.7
	>20	82	3	3.7	0.8	10.3
	>30	82	2	2.4	0.3	8.5
	Medical advice	82	0	0.0	0.0	4.4

Hib-Pn = Unprimed group receiving 2+1 catch up vaccination with 10Pn-PD-DiT in the second year of life
For each dose and overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects reporting at least once the symptom
For Overall/dose:
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

Assessor's comment: The rate of solicited local adverse events does not cause any new concern regarding Synflorix.

Solicited general adverse events
The results are detailed in Tables 93 (primed groups) and 94 (unprimed group).

Table 93 Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period – Primed groups (Total vaccinated cohort)

		Pn-Pn9 (9-12)					Pn-Pn9 (13-18)					Pn-Pn9					Pn-Pn15				
					95 % CI					95 % CI					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Drowsiness	All	70	4	5.7	1.6	14.0	22	1	4.5	0.1	22.8	92	5	5.4	1.8	12.2	85	4	4.7	1.3	11.6
	Grade 3	70	0	0.0	0.0	5.1	22	0	0.0	0.0	15.4	92	0	0.0	0.0	3.9	85	0	0.0	0.0	4.2
	Related	70	3	4.3	0.9	12.0	22	1	4.5	0.1	22.8	92	4	4.3	1.2	10.8	85	4	4.7	1.3	11.6
	Grade 3 & Related	70	0	0.0	0.0	5.1	22	0	0.0	0.0	15.4	92	0	0.0	0.0	3.9	85	0	0.0	0.0	4.2
	Medical advice	70	0	0.0	0.0	5.1	22	0	0.0	0.0	15.4	92	0	0.0	0.0	3.9	85	0	0.0	0.0	4.2
Fever (Axillary) (°C)	All	70	13	18.6	10.3	29.7	22	7	31.8	13.9	54.9	92	20	21.7	13.8	31.6	85	13	15.3	8.4	24.7
	>38.0	70	1	1.4	0.0	7.7	22	3	13.6	2.9	34.9	92	4	4.3	1.2	10.8	85	5	5.9	1.9	13.2
	>38.5	70	1	1.4	0.0	7.7	22	2	9.1	1.1	29.2	92	3	3.3	0.7	9.2	85	3	3.5	0.7	10.0
	>39.0	70	0	0.0	0.0	5.1	22	0	0.0	0.0	15.4	92	0	0.0	0.0	3.9	85	1	1.2	0.0	6.4
	>39.5	70	0	0.0	0.0	5.1	22	0	0.0	0.0	15.4	92	0	0.0	0.0	3.9	85	1	1.2	0.0	6.4
	Related	70	13	18.6	10.3	29.7	22	6	27.3	10.7	50.2	92	19	20.7	12.9	30.4	85	13	15.3	8.4	24.7
	>39.5 & Related	70	0	0.0	0.0	5.1	22	0	0.0	0.0	15.4	92	0	0.0	0.0	3.9	85	1	1.2	0.0	6.4
	Medical advice	70	0	0.0	0.0	5.1	22	0	0.0	0.0	15.4	92	0	0.0	0.0	3.9	85	0	0.0	0.0	4.2
Irritability	All	70	15	21.4	12.5	32.9	22	4	18.2	5.2	40.3	92	19	20.7	12.9	30.4	85	9	10.6	5.0	19.2
	Grade 3	70	1	1.4	0.0	7.7	22	0	0.0	0.0	15.4	92	1	1.1	0.0	5.9	85	1	1.2	0.0	6.4
	Related	70	11	15.7	8.1	26.4	22	4	18.2	5.2	40.3	92	15	16.3	9.4	25.5	85	9	10.6	5.0	19.2
	Grade 3 & Related	70	1	1.4	0.0	7.7	22	0	0.0	0.0	15.4	92	1	1.1	0.0	5.9	85	1	1.2	0.0	6.4
	Medical advice	70	0	0.0	0.0	5.1	22	0	0.0	0.0	15.4	92	0	0.0	0.0	3.9	85	0	0.0	0.0	4.2
Loss of appetite	All	70	12	17.1	9.2	28.0	22	2	9.1	1.1	29.2	92	14	15.2	8.6	24.2	85	9	10.6	5.0	19.2
	Grade 3	70	0	0.0	0.0	5.1	22	0	0.0	0.0	15.4	92	0	0.0	0.0	3.9	85	2	2.4	0.3	8.2
	Related	70	7	10.0	4.1	19.5	22	2	9.1	1.1	29.2	92	9	9.8	4.6	17.8	85	8	9.4	4.2	17.7
	Grade 3 & Related	70	0	0.0	0.0	5.1	22	0	0.0	0.0	15.4	92	0	0.0	0.0	3.9	85	2	2.4	0.3	8.2
	Medical advice	70	0	0.0	0.0	5.1	22	0	0.0	0.0	15.4	92	0	0.0	0.0	3.9	85	0	0.0	0.0	4.2

Pn-Pn9 (9-12) = Primed group receiving booster dose of 10Pn-PD-DiT at 9-12 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Pn-Pn9 (13-18) = Primed group receiving booster dose of 10Pn-PD-DiT at 13-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
Pn-Pn9 = Primed group receiving booster dose of 10Pn-PD-DiT at 9-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study (pooled Pn-Pn9 (9-12) and Pn-Pn9 (13-18) groups)
Pn-Pn15 = Primed group receiving booster dose of 10Pn-PD-DiT at 15-18 months of age following 3-dose primary vaccination in the 10PN-PD-DIT-037 study
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

Table 94 Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period following each dose and overall – Unprimed group (Total vaccinated cohort)

		Hib-Pn				
					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**
	Dose 1					
Drowsiness	All	82	5	6.1	2.0	13.7
	Grade 3	82	2	2.4	0.3	8.5
	Related	82	2	2.4	0.3	8.5
	Grade 3 & Related	82	1	1.2	0.0	6.6
	Medical advice	82	0	0.0	0.0	4.4
Fever (Axillary) (°C)	All	82	16	19.5	11.6	29.7
	>38.0	82	7	8.5	3.5	16.8
	>38.5	82	3	3.7	0.8	10.3
	>39.0	82	1	1.2	0.0	6.6
	>39.5	82	0	0.0	0.0	4.4
	Related	82	14	17.1	9.7	27.0
	>39.5 & Related	82	0	0.0	0.0	4.4
	Medical advice	82	0	0.0	0.0	4.4
Irritability	All	82	9	11.0	5.1	19.8
	Grade 3	82	1	1.2	0.0	6.6
	Related	82	5	6.1	2.0	13.7
	Grade 3 & Related	82	0	0.0	0.0	4.4
	Medical advice	82	0	0.0	0.0	4.4
Loss of appetite	All	82	9	11.0	5.1	19.8
	Grade 3	82	0	0.0	0.0	4.4
	Related	82	7	8.5	3.5	16.8
	Grade 3 & Related	82	0	0.0	0.0	4.4
	Medical advice	82	0	0.0	0.0	4.4
	Dose 2					
Drowsiness	All	77	1	1.3	0.0	7.0
	Grade 3	77	0	0.0	0.0	4.7
	Related	77	1	1.3	0.0	7.0
	Grade 3 & Related	77	0	0.0	0.0	4.7
	Medical advice	77	0	0.0	0.0	4.7
Fever (Axillary) (°C)	All	77	8	10.4	4.6	19.4
	>38.0	77	2	2.6	0.3	9.1
	>38.5	77	1	1.3	0.0	7.0
	>39.0	77	0	0.0	0.0	4.7
	>39.5	77	0	0.0	0.0	4.7
	Related	77	8	10.4	4.6	19.4
	>39.5 & Related	77	0	0.0	0.0	4.7
	Medical advice	77	1	1.3	0.0	7.0
Irritability	All	77	5	6.5	2.1	14.5
	Grade 3	77	0	0.0	0.0	4.7
	Related	77	5	6.5	2.1	14.5
	Grade 3 & Related	77	0	0.0	0.0	4.7
	Medical advice	77	0	0.0	0.0	4.7
Loss of appetite	All	77	2	2.6	0.3	9.1
	Grade 3	77	0	0.0	0.0	4.7
	Related	77	2	2.6	0.3	9.1
	Grade 3 & Related	77	0	0.0	0.0	4.7
	Medical advice	77	0	0.0	0.0	4.7

		Hib-Pn				
					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**
		Dose 3				
Drowsiness	All	62	2	3.2	0.4	11.2
	Grade 3	62	0	0.0	0.0	5.8
	Related	62	1	1.6	0.0	8.7
	Grade 3 & Related	62	0	0.0	0.0	5.8
	Medical advice	62	0	0.0	0.0	5.8
Fever (Axillary) (°C)	All	62	6	9.7	3.6	19.9
	>38.0	62	1	1.6	0.0	8.7
	>38.5	62	0	0.0	0.0	5.8
	>39.0	62	0	0.0	0.0	5.8
	>39.5	62	0	0.0	0.0	5.8
	Related	62	6	9.7	3.6	19.9
	>39.5 & Related	62	0	0.0	0.0	5.8
	Medical advice	62	0	0.0	0.0	5.8
Irritability	All	62	2	3.2	0.4	11.2
	Grade 3	62	0	0.0	0.0	5.8
	Related	62	1	1.6	0.0	8.7
	Grade 3 & Related	62	0	0.0	0.0	5.8
	Medical advice	62	0	0.0	0.0	5.8
Loss of appetite	All	62	3	4.8	1.0	13.5
	Grade 3	62	0	0.0	0.0	5.8
	Related	62	2	3.2	0.4	11.2
	Grade 3 & Related	62	0	0.0	0.0	5.8
	Medical advice	62	0	0.0	0.0	5.8
		Overall/dose				
Drowsiness	All	221	8	3.6	1.6	7.0
	Grade 3	221	2	0.9	0.1	3.2
	Related	221	4	1.8	0.5	4.6
	Grade 3 & Related	221	1	0.5	0.0	2.5
	Medical advice	221	0	0.0	0.0	1.7
Fever (Axillary) (°C)	All	221	30	13.6	9.3	18.8
	>38.0	221	10	4.5	2.2	8.2
	>38.5	221	4	1.8	0.5	4.6
	>39.0	221	1	0.5	0.0	2.5
	>39.5	221	0	0.0	0.0	1.7
	Related	221	28	12.7	8.6	17.8
	>39.5 & Related	221	0	0.0	0.0	1.7
	Medical advice	221	1	0.5	0.0	2.5
Irritability	All	221	16	7.2	4.2	11.5
	Grade 3	221	1	0.5	0.0	2.5
	Related	221	11	5.0	2.5	8.7
	Grade 3 & Related	221	0	0.0	0.0	1.7
	Medical advice	221	0	0.0	0.0	1.7
Loss of appetite	All	221	14	6.3	3.5	10.4
	Grade 3	221	0	0.0	0.0	1.7
	Related	221	11	5.0	2.5	8.7
	Grade 3 & Related	221	0	0.0	0.0	1.7
	Medical advice	221	0	0.0	0.0	1.7

		Hib-Pn				
					95 % CI	
Symptom	Type	N	n	%	LL	UL
Overall/subject						
Drowsiness	All	82	5	6.1	2.0	13.7
	Grade 3	82	2	2.4	0.3	8.5
	Related	82	3	3.7	0.8	10.3
	Grade 3 & Related	82	1	1.2	0.0	6.6
	Medical advice	82	0	0.0	0.0	4.4
Fever (Axillary) (°C)	All	82	22	26.8	17.6	37.8
	>38.0	82	9	11.0	5.1	19.8
	>38.5	82	4	4.9	1.3	12.0
	>39.0	82	1	1.2	0.0	6.6
	>39.5	82	0	0.0	0.0	4.4
	Related	82	21	25.6	16.6	36.4
	>39.5 & Related	82	0	0.0	0.0	4.4
	Medical advice	82	1	1.2	0.0	6.6
Irritability	All	82	12	14.6	7.8	24.2
	Grade 3	82	1	1.2	0.0	6.6
	Related	82	9	11.0	5.1	19.8
	Grade 3 & Related	82	0	0.0	0.0	4.4
	Medical advice	82	0	0.0	0.0	4.4
Loss of appetite	All	82	10	12.2	6.0	21.3
	Grade 3	82	0	0.0	0.0	4.4
	Related	82	9	11.0	5.1	19.8
	Grade 3 & Related	82	0	0.0	0.0	4.4
	Medical advice	82	0	0.0	0.0	4.4

Hib-Pn = Unprimed group receiving 2+1 catch up vaccination with 10Pn-PD-DiT in the second year of life
For each dose and overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects reporting at least once the symptom
For Overall/dose:
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

Assessor's comment: The rate of solicited general adverse events does not cause any new concern regarding Synflorix.

Unsolicited adverse events
At least one unsolicited AE was reported by 7.0% and 1.1% of subjects in the Pn-Pn9 and Pn-Pn15 groups, respectively, within the 31-day post-vaccination period. Unsolicited AEs with medically attended visits were reported by 6.0% and 1.1% of subjects in the Pn-Pn9 and Pn-Pn15 groups, respectively.

In the unprimed Hib-Pn group, 2.5% of administered doses were followed by at least one unsolicited AE within the 31-day post-vaccination period. For the unsolicited AEs with medically attended visits, this percentage was 2.1% of administered doses.

Serious adverse events
Three subjects reported at least one SAE during the entire study period: two out of 100 subjects boosted at 9-18 months of age and one out of 87 subjects that received 2+1 dose catch-up vaccination in second year of life. None of the reported SAEs were fatal or considered by the investigator to be causally related to vaccination.

Fatal events

No fatal SAEs were reported during the entire study period.

Non-fatal events

During the entire study period, three subjects reported at least one SAE (two out of 100 vaccinated subjects in the Pn-Pn9 group and one out of 87 vaccinated subjects in the Hib-Pn group). None of the SAEs were considered by the investigator to be causally related to vaccination. All SAEs were recovered/resolved without sequelae.

Adverse events leading to premature discontinuation of study vaccine and/or study

None of the subjects withdrew due to an AE or SAE during the study period.

MAH conclusions

- The data in this study showed that the 10Pn-PD-DiT vaccine induced an immune response against vaccine pneumococcal serotypes when given as an early or late booster dose at either 9-12 or 15-18 months of age, respectively, following 3-dose primary immunization course at 6, 10 and 14 weeks of age in Indian children. One month after booster vaccination, for each of the 10 vaccine pneumococcal serotypes, at least 96.8% and 98.4% of subjects boosted with 10Pn-PD-DiT at 9-12 or 15-18 months of age, respectively had antibody concentrations ≥0.2 µg/mL except for serotype 6B (95.2% of subjects boosted at 9-12 months of age and 93.8% of subjects boosted at 15-18 months of age).
- 10Pn-PD-DiT vaccine was generally well tolerated.
- During the 31-day post-booster vaccination period, at least one unsolicited AE was reported by 7.0% and 1.1% of subjects boosted at either 9-18 or 15-18 months of age, respectively. In the group that received 3-dose (2+1 schedule) catch-up vaccination with 10Pn-PD-DiT in second year of life, at least one unsolicited AE was reported following the administration of 2.5% of doses (5.7% of subjects).
- Three subjects reported at least one SAE during the entire study period: two out of 100 subjects boosted at 9-18 months of age and one out of 87 subjects that received 2+1 dose catch-up vaccination in second year of life. None of the reported SAEs were fatal or considered by the investigator to be causally related to vaccination.
- No confirmatory analysis was performed with regards to the primary and secondary immunogenicity and reactogenicity/safety objectives.

3. Discussion on clinical aspects

The submitted study report describes booster responses at 9-12 months of age or 15-18 months of age in Indian children who had received three primary doses according to the EPI schedule, i.e. at 6, 10 and 14 weeks of age. In addition, a secondary objective was to study immune responses to 2 catch-up doses followed by a single booster dose within the second year of life. The catch-up part of this study fulfils FUM, regarding boostability of the catch-up vaccination. The study design was not optimal to achieve the primary objective, since the children were recruited to either the 9-18 months group or 15-18 months group, instead of the intended 9-12 and 15-18 months age groups. This was apparently done for practical reasons, as the study start was delayed.

The study was not powered to detect differences between an early or late booster dose. The titres had generally declined more in the late booster group before the booster dose, compared to the early booster group, and the responses tended to be higher in the late booster group. However, the groups were relatively small, and the relevance of these data for a European population is unclear. Therefore, in conclusion, there is no need to make any SPC changes based on the booster data presented in this submission.

The catch-up part of this study was a secondary objective, but represents the first data on boostability of a 2-dose catch-up schedule during the second year of life. The responses to a third dose given during the second year of life have the characteristics of a booster response, i.e. higher GMCs and GMTs following the third dose compared to the second priming dose. The interval between the two primary doses and the booster dose was relatively short, and no data on duration of the immunological memory are available. Taken together, the catch-up data indicate that a third dose given during the second year of life increases the antibody titres, but these data are not considered sufficient to change the dosing recommendations for the catch-up schedule. In addition, the relevance of the data from this study conducted in India to a European population is questioned.

No new safety signal was detected in this study.

Thus, no further regulatory action is required.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➢ **Overall conclusion**

This Paediatric submission is considered fulfilled, and in addition FUM is also considered fulfilled. The presented data on a booster dose following the 2-dose catch-up during the second year of life are considered novel, but not sufficient to request a change to the booster recommendations for the catch-up dose in the EU SPC.

➢ **Recommendation**

☒ **Fulfilled –**

No further action required

☐ **Not fulfilled:**

IV. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable