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Human Medicines Evaluation Division

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

Synflorix

pneumococcal polysaccharide conjugate vaccine (adsorbed)

Procedure no: EMEA/H/C/000973/P46/062

Note

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

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Introduction

On July 7 2016, the MAH submitted a completed paediatric study for Synflorix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

1. Scientific discussion

1.1. Information on the development program

The MAH stated that SPNG-003, *A phase II, randomized, controlled, observer-blind study to assess the safety, reactogenicity and immunogenicity of two formulations of GlaxoSmithKline (GSK) Biologicals' Streptococcus pneumoniae protein containing vaccine given as a 3-dose primary vaccination course coadministered with DTPa-HBV-IPV/Hib vaccine during the first 6 months of life and as a booster dose at 12-15 months of age,* is a stand-alone study.

1.2. Information on the pharmaceutical formulation used in the study

The commercial formulation was used in the study.

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted a final report for:

- SPNG-003, *A phase II, randomized, controlled, observer-blind study to assess the safety, reactogenicity and immunogenicity of two formulations of GlaxoSmithKline (GSK) Biologicals' Streptococcus pneumoniae protein containing vaccine given as a 3-dose primary vaccination course coadministered with DTPa-HBV-IPV/Hib vaccine during the first 6 months of life and as a booster dose at 12-15 months of age.*

1.3.2. Clinical study

Description

SPNG-003, *A phase II, randomized, controlled, observer-blind study to assess the safety, reactogenicity and immunogenicity of two formulations of GlaxoSmithKline (GSK) Biologicals' Streptococcus pneumoniae protein containing vaccine given as a 3-dose primary vaccination course coadministered with DTPa-HBV-IPV/Hib vaccine during the first 6 months of life and as a booster dose at 12-15 months of age.*

Methods

Objectives

First primary objective

- To support that GSK Biologicals' candidate pneumococcal protein-containing vaccine (dPly 10 µg and PhtD 10 µg), when administered as a 3-dose primary vaccination course, is non-inferior to GSK Biologicals' 10-valent pneumococcal conjugate vaccine (10Pn-PD-DiT), when coadministered with DTPa-HBV-IPV/Hib vaccine in infants, in terms of post-primary immunization febrile reactions with fever > 40.0° C (rectal temperature) with causal relationship to vaccination.

Second primary objective (sequential)

- To support that GSK Biologicals' candidate pneumococcal protein-containing vaccine (dPly 30 µg and PhtD 30 µg), when administered as a 3-dose primary vaccination course, is non-inferior to GSK Biologicals' 10-valent pneumococcal conjugate vaccine (10Pn-PD-DiT), when coadministered with DTPa-HBV-IPV/Hib vaccine in infants, in terms of post-primary immunization febrile reactions with fever > 40.0° C (rectal temperature) with causal relationship to vaccination.

Criteria for safety:

Non-inferiority was supported if one could rule out an increase, in terms of percentage of subjects with fever > 40.0°C (rectal measurement) with causal relationship to vaccination (10Pn+Proteins group as compared to 10Pn group) above 5% + half the incidence in the control group (= null hypothesis) as shown by a one-sided p-value < 5%.

Note: the second primary objective was assessed sequentially: it was not possible to conclude on the second primary objective if the first primary objective could not be demonstrated.

Secondary

- To compare the protein doses (10 µg-10 µg or 30 µg-30 µg) contained in GSK Biologicals' candidate pneumococcal protein-containing vaccine when given as a 3-dose primary vaccination course to infants and co-administered with DTPa-HBV-IPV/Hib vaccine, in terms of post-dose 3 immune response.

Criteria for superiority:

Superiority of one formulation over the other was demonstrated if the upper limit (UL) of the 95% confidence interval (CI) for the geometric mean concentration (GMC) ratio between the 10vPP30 group

and the 10vPP10 group was below 1.0 for anti-Ply and anti-PhtD antibody concentrations OR if the UL of the 95% CI for the GMC ratio between the 10vPP10 group and the 10vPP30 group was below 1.0 for anti-Ply and anti-PhtD antibody concentrations.

- To assess the immune responses to pneumococcal proteins, pneumococcal serotype-specific polysaccharides and to protein D, elicited by GSK Biologicals' candidate pneumococcal protein containing vaccine co-administered with DTPa-HBV-IPV/Hib vaccine after 3-dose primary vaccination course in infants at 2-3-4 months of age and after a booster vaccination at 12-15 months of age.
- To assess the safety and reactogenicity of GSK Biologicals' candidate pneumococcal protein containing vaccine after administration of any vaccine dose when co-administered with DTPa-HBV-IPV/Hib.
- To assess the persistence of pneumococcal antibodies elicited by GSK Biologicals' candidate pneumococcal protein-containing vaccine when co-administered with DTPa-HBV-IPV/Hib vaccine, 8 to 11 months after completion of the 3-dose primary vaccination course.
- To assess the immune response and safety of DTPa-HBV-IPV/Hib vaccine when co-administered with GSK Biologicals' candidate pneumococcal protein-containing vaccine, as a 3-dose primary vaccination course at 2-3-4 months of age and as a booster dose at 12-15 months of age.
- To assess the persistence of antibodies against DTPa-HBV-IPV/Hib vaccine when co-administered with GSK Biologicals' candidate pneumococcal protein-containing vaccine, 8 to 11 months after completion of the 3-dose primary vaccination course.

Study design

Phase II, multicentre, observer-blind, randomized (1:1:1:1), controlled study with 4 parallel groups.

Study population

Healthy male or female, between and including 6 and 14 weeks (42-104 days) of age at the time of the first vaccination, born after a gestation period of 36 to 42 weeks inclusive and for whom the investigator believed that their parents/legally acceptable representative(s) (LARs) could and would comply with the requirements of the protocol. Written informed consent was to be obtained from the parents/LAR(s) of the subject.

Treatments

- **Treatment study groups** were as follows:
- 10vPP10 group: approximately 150 subjects receiving GSK Biologicals' 10Pn-PD-DiT vaccine combined with the pneumococcal proteins dPly (10 µg) and PhtD (10 µg).
- 10vPP30 group: approximately 150 subjects receiving GSK Biologicals' 10Pn-PD-DiT vaccine combined with the pneumococcal proteins dPly (30 µg) and PhtD (30 µg).
- 10Pn group: approximately 150 subjects receiving GSK Biologicals' 10-valent pneumococcal conjugate vaccine (10Pn-PD-DiT).

- Prev13 group: approximately 150 subjects receiving Pfizer's 13-valent pneumococcal conjugate vaccine (Prevenar 13).

Control: 10Pn-PD-DiT and *Prevenar* 13 vaccines

Vaccination schedule: 3 primary doses given at 2, 3, 4 months of age (with allowable intervals of 28-42 days between doses) and a booster dose at 12-15 months of age.

Four **blood samples** were to be collected for serology testing at the following timepoints: prior to dose 1 [Pre (M0)], one month post-dose 3 [Post-vacc III (M3)], prior to booster vaccination [Preboost (M10)] and one month post-booster vaccination [Post-boost (M11)].

Vaccine composition:

Vaccine	Formulation (per dose of 0.5 mL)	Lot number	Group
Study vaccine: GSK Biologicals' 10-valent Pn-PD-DiT-dPly-PhtD 10 vaccine	10 μg of each dPly and PhtD Protein D carrier: 1 μg of each capsular PS for serotypes 1, 5, 6B, 7F, 9V, 14 and 23F and 3 μg for serotype 4 conjugated to PD. Tetanus toxoid carrier: 3 μg of capsular PS of serotype 18C conjugated to TT. Diphtheria toxoid carrier: 3 μg of capsular PS of serotype 19F conjugated to DT. Protein carrier content: 9-16 μg PD, 3-6 μg DT, 5-10 μg TT. 0.5 mg aluminium (Al^{3+}) as aluminium phosphate	DSP2A008A	10vPP10
Study vaccine: GSK Biologicals' 10-valent Pn-PD-DiT-dPly-PhtD 30 vaccine	30 μg of each dPly and PhtD Protein D carrier: 1 μg of each capsular PS for serotypes 1, 5, 6B, 7F, 9V, 14 and 23F and 3 μg for serotype 4 conjugated to PD. Tetanus toxoid carrier: 3 μg of capsular PS of serotype 18C conjugated to TT. Diphtheria toxoid carrier: 3 μg of capsular PS of serotype 19F conjugated to DT. Protein carrier content: 9-16 μg PD, 3-6 μg DT, 5-10 μg TT. 0.5 mg aluminium (Al^{3+}) as aluminium phosphate	DSP2A009A	10vPP30
Control vaccine: GSK Biologicals' 10-valent Pn-PD-DiT vaccine (*Synflorix*)	Protein D carrier: 1 μg of each capsular PS for serotypes 1, 5, 6B, 7F, 9V, 14 and 23F and 3 μg for serotype 4 conjugated to PD. Tetanus toxoid carrier: 3 μg of capsular PS of serotype 18C conjugated to TT. Diphtheria toxoid carrier: 3 μg of capsular PS of serotype 19F conjugated to DT. Protein carrier content: 9-16 μg PD, 3-6 μg DT, 5-10 μg TT. 0.5 mg aluminium (Al^{3+}) as aluminium phosphate	ASPNA048A	10Pn
Control vaccine: Pfizer's *Prevenar* 13 vaccine	2.2 μg of each pneumococcal PS for serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F and 4.4 μg for serotype 6B conjugated to CRM_{197} carrier protein 0.125 mg aluminium as aluminium phosphate	DEXTA374AZ DEXTA404AZ DEXTA407AX	Prev13

Outcomes/endpoints

Primary endpoint:

- Occurrence of fever >40°C (rectal temperature) with causal relationship to vaccination within 7 days (Days 0-6) after at least one dose of the primary vaccination

Secondary endpoints:

Safety and Reactogenicity

- Occurrence of each solicited adverse event (AE) within 7 days (Days 0-6) after each vaccine dose:
    - Local AE (any, grade 3).
    - General AE (any, grade 3, related).
- Occurrence of any unsolicited AEs within 31 days (Days 0-30) after each vaccination.
- Occurrence of serious adverse events (SAEs) during the entire study period (from Visit 1 to Visit 6).

Immunogenicity

- Evaluation of the immune responses to components of the investigational vaccines, one month post-dose 3, prior to and one month post-booster.
    - Concentrations of antibodies against pneumococcal Ply and PhtD proteins.
    - Concentrations of antibodies against protein D.
    - Concentrations of antibodies against pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F.
    - Opsonophagocytic activity against pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A*, 19F, 23F.
    - Level of anti-Ply antibodies inhibiting Ply haemolysis activity**.

**OPA testing for the vaccine-related serotype 19A will be done with a multiplex assay and results will be presented in an Annex Report when available.*

***Inhibition of Ply haemolysis activity assay has been discontinued due to assay stability issues.*

Statistical Methods

Safety and reactogenicity

The primary safety analysis was performed on the Total vaccinated cohort (TVC).

Between group assessment (confirmatory analysis)

- Standardized asymptotic 95% CIs for the difference between groups (10Pn+Proteins groups minus 10Pn group) in terms of percentage of subjects reporting fever > 40.0°C (rectal temperature) with causal relationship to vaccination after the primary vaccination schedule.

The one-sided p-value for the null hypothesis, i.e. that the increase in the percentage of subjects with fever > 40.0°C (rectal temperature) with causal relationship to vaccination (10Pn+Proteins groups as compared to 10Pn group) would be above 5% + half the incidence in the control group, was also computed.

The first primary objective would be reached if the p-value is below 5%, when considering 10vPP10 group. The sequential second primary objective would be reached if the first primary objective is reached and if the p-value, when considering 10vPP30 group, is below 5%.

Within group assessment (descriptive analysis)

- The percentage of subjects reporting each individual solicited local and general AE during the 7- day (Days 0-6) solicited follow-up period was tabulated for each group, after each vaccine dose and overall primary doses, with exact 95% CI. The percentage of doses followed by each individual solicited local and general AE during the 7-day (Days 0-6) solicited follow-up period was tabulated for each group, over the full primary vaccination course, with exact 95% CI. The same tabulation was performed for grade 3 solicited AEs and for solicited AEs with causal relationship to vaccination. For redness and swelling, grade 2 or 3 AEs were also tabulated. Occurrence of fever was reported per 0.5°C cumulative increments. All the above tabulations for each individual solicited AE were also performed for the first 4 days after each vaccination (Days 0-3).
- The proportion of subjects/doses with at least one report of unsolicited AE classified by the Medical Dictionary for Regulatory Activities (MedDRA) and reported up to 30 days after primary or booster vaccination was tabulated with exact 95% CI for each group. The same tabulation was performed for grade 3 unsolicited AEs and for unsolicited AEs with a relationship to vaccination.
- SAEs and withdrawal(s) due to SAE(s) were described in detail.

Immunogenicity

The immunogenicity analysis was performed on the ATP cohort for immunogenicity (primary analysis) and on the TVC.

Between group assessment (confirmatory analysis)

- 95% CIs for the antibody GMC ratios (10vPP30 group over 10vPP10 group and 10vPP10 group over 10vPP30 group), one month after the third dose of the primary immunization course, were computed for anti-Ply and anti-PhtD antibody concentrations.

First secondary objective would be demonstrated if the UL of the 95% CI for the GMC ratio between the 10vPP30 group and the 10vPP10 group was below 1.0 for anti-Ply and anti-PhtD antibody concentrations OR if the UL of the 95% CI for GMC ratio between the 10vPP10 group and the 10vPP30 group was below 1.0 for anti-Ply and anti-PhtD antibody concentrations.

Within group assessment (descriptive analysis)

At each timepoint that a blood sample result was available and for each group:

- Geometric mean concentrations/titres (GMCs/GMTs) with 95% CIs were tabulated for each serotype*/antigen
- Seropositivity/seroprotection rates with exact 95% CIs were calculated for each appropriate serotype*/antigen
- Vaccine response rates with exact 95% CIs were calculated for HBs antigen.

Note: investigations on the quality of some serology assays revealed that the anti-HBs ELISA overestimated concentrations between 10-100 mIU/mL while values > 100 mIU/mL were confirmed valid. Therefore, all available samples at the one month post-dose 3 timepoint for which the anti-HBs

antibody concentration was between 10-100 mIU/mL by in-house ELISA were retested by the commercial assay Centaur™*, an FDA-approved and CE-marked CLIA with a cut-off defining seropositivity of 6.2 mIU/mL. Anti-HBs seroprotection was redefined as in-house ELISA concentration > 100 mIU/mL or CLIA concentration > 10 mIU/mL.*

- Vaccine response/booster vaccine response rates with exact 95% CIs were calculated for each pertussis antigen.
- The distribution of antibody concentrations/titres for each appropriate serotype*/antigen was displayed using tables and/or reverse cumulative distribution curves (RCCs).

**Note that opsonophagocytic activity against the vaccine-related serotype 19A will be measured with a multiplex OPA and results will be presented in an Annex Report when available.*

Results

Recruitment/ Number analysed

This multicentre study was conducted in 24 centres in 4 countries: Czech Republic, Germany, Poland and Sweden. A maximum of 104 subjects (18.1%) were enrolled in a single study centre (in Czech Republic).

Out of the 575 subjects vaccinated in this study, 564 completed this study and 11 were withdrawn. Among those:

- One subject from the 10Pn group was withdrawn due to an SAE (hypotonichyporesponsive episode) occurring during the primary epoch.
- One subject from the 10Pn group did not participate in the booster epoch due to an SAE (psychomotor retardation) occurring during the primary epoch.
- One subject from the 10vPP30 group was withdrawn due to an SAE (type I diabetes mellitus) occurring during the booster epoch.

Thus, the TVC for the primary epoch included 575 subjects (146 in the 10vPP10 group, 142 in the 10vPP30 group, 145 in the 10Pn group and 142 in the Prev13 group). Out of these, 558 subjects (97.0%) met the eligibility criteria for the inclusion in the ATP cohort for safety for the primary epoch. 537 subjects (93.4%) were included in the ATP cohort for immunogenicity for the primary epoch.

Efficacy results

Immunogenicity results:

Between group assessment (confirmatory analysis)

The first secondary objective to compare the protein doses contained in the 10Pn-PD-DiT-dPly-PhtD 10 and 10Pn-PD-DiT-dPly-PhtD 30 vaccines was reached. The superiority of 10Pn-PD-DiT-dPly-PhtD 30 vaccine over the 10Pn-PD-DiT-dPly-PhtD 10 vaccine in terms of post-dose 3 immune responses to Ply and PhtD pneumococcal proteins was demonstrated as the ULs of the 95% CI for the GMC ratio (10vPP10/10vPP30) for anti-Ply and anti-PhtD antibodies were below 1 (UL of 95% CI were 0.98 for anti-Ply and 0.94 for anti-PhtD).

Table 5: Adjusted ratios of post-dose III GMCs, between 10vPP10 and 10vPP30 study groups, with their 95%CIs for ANTI-Ply and ANTI-PhtD antibody concentrations (Epoch 001) (ATP cohort for immunogenicity)

					Adjusted GMC ratio (10vPP10 / 10vPP30)		
	10vPP10		10vPP30			95% CI	
Antibody	N	Adjusted GMC	N	Adjusted GMC	Value	LL	UL
ANTI-Ply	131	9527.68	129	11841.28	0.80	0.66	0.98
ANTI-PhtD	131	1498.46	129	1959.25	0.76	0.62	0.94

10vPP10 = 10Pn-PD-DiT vaccine combined with the pneumococcal protein vaccine containing the pneumococcal proteins dPly and PhtD (10 μg-10 μg), co-administered with DTPa-HBV-IPV/Hib

10vPP30 = 10Pn-PD-DiT vaccine combined with the pneumococcal protein vaccine containing the pneumococcal proteins dPly and PhtD (30 μg-30 μg), co-administered with DTPa-HBV-IPV/Hib

Adjusted GMC = geometric mean antibody concentration adjusted for baseline concentration

N = Number of subjects with both pre- and post-vaccination results available

95% CI = 95% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for baseline concentration - pooled variance); LL = lower limit, UL = upper limit

Assessor's comment: The above results are not relevant to Synflorix, and will not be further commented.

Within group assessment (descriptive analysis)

Immune response to the pneumococcal proteins Ply and PhtD

The immune response to Ply and PhtD antigens are presented in the following tables:

Table 31 Seropositivity rates and GMCs for ANTI-Ply antibodies (ATP cohort for immunogenicity adapted for each epoch)

				≥ 12 EL.U/mL				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
ANTI-Ply	10vPP10	PRE	132	132	100	97.2	100	1212.46	1014.12	1449.60
		PIII(M3)	130	130	100	97.2	100	9408.42	8182.15	10818.47
		PRE-BOOSTER	130	130	100	97.2	100	6674.42	5628.57	7914.60
		POST-BOOSTER	129	129	100	97.2	100	24720.40	21863.04	27951.19
	10vPP30	PRE	131	131	100	97.2	100	1117.49	941.97	1325.73
		PIII(M3)	134	134	100	97.3	100	12137.96	10641.83	13844.44
		PRE-BOOSTER	128	128	100	97.2	100	5592.85	4750.83	6584.10
		POST-BOOSTER	129	129	100	97.2	100	29838.18	26892.53	33106.48
	10Pn	PRE	134	134	100	97.3	100	1205.81	1031.29	1409.87
		PIII(M3)	136	136	100	97.3	100	459.97	398.31	531.18
		PRE-BOOSTER	129	129	100	97.2	100	495.02	393.19	623.22
		POST-BOOSTER	129	129	100	97.2	100	582.85	463.40	733.09
	Prev13	PRE	130	130	100	97.2	100	1058.99	899.97	1246.11
		PIII(M3)	131	131	100	97.2	100	472.88	404.48	552.86
		PRE-BOOSTER	129	129	100	97.2	100	737.71	587.67	926.06
		POST-BOOSTER	125	125	100	97.1	100	791.42	628.23	997.00

10vPP10 = 10Pn-PD-DiT vaccine combined with the pneumococcal protein vaccine containing the pneumococcal proteins dPly and PhtD (10 μg-10 μg), co-administered with DTPa-HBV-IPV/Hib

10vPP30 = 10Pn-PD-DiT vaccine combined with the pneumococcal protein vaccine containing the pneumococcal proteins dPly and PhtD (30 μg-30 μg), co-administered with DTPa-HBV-IPV/Hib

10Pn = 10Pn-PD-DiT vaccine co-administered with DTPa-HBV-IPV/Hib

Prev13 = Prevenar 13 vaccine co-administered with DTPa-HBV-IPV/Hib

GMC = geometric mean concentration

N = number of subjects with available results

n/% = number/percentage of subjects with concentration within the specified range

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

PRE = Pre-vaccination blood sample

PIII(M3) = One month after third dose of primary vaccination

PRE-BOOSTER = Prior to booster dose

POST-BOOSTER = One month after booster dose

Table 32 Seropositivity rates and GMCs for ANTI-PhtD antibodies (ATP cohort for immunogenicity adapted for each epoch)

				≥ 17 EL.U/mL				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
ANTI-PhtD	10vPP10	PRE	132	132	100	97.2	100	1536.31	1337.66	1764.47
		PIII(M3)	130	130	100	97.2	100	1456.57	1250.65	1696.39
		PRE-BOOSTER	130	130	100	97.2	100	910.80	718.85	1154.00
		POST-BOOSTER	129	129	100	97.2	100	3528.25	2952.68	4216.01
	10vPP30	PRE	131	131	100	97.2	100	1582.51	1367.71	1831.05
		PIII(M3)	134	134	100	97.3	100	1996.61	1734.17	2298.75
		PRE-BOOSTER	128	128	100	97.2	100	829.12	671.12	1024.32
		POST-BOOSTER	129	129	100	97.2	100	3777.39	3181.74	4484.55
	10Pn	PRE	134	134	100	97.3	100	1565.21	1343.30	1823.77
		PIII(M3)	136	136	100	97.3	100	523.61	453.71	604.28
		PRE-BOOSTER	129	126	97.7	93.4	99.5	209.27	153.16	285.95
		POST-BOOSTER	129	124	96.1	91.2	98.7	266.58	190.06	373.91
	Prev13	PRE	130	130	100	97.2	100	1410.48	1216.47	1635.43
		PIII(M3)	131	131	100	97.2	100	552.01	469.55	648.95
		PRE-BOOSTER	129	127	98.4	94.5	99.8	381.66	274.64	530.39
		POST-BOOSTER	125	125	100	97.1	100	469.16	335.29	656.46

10vPP10 = 10Pn-PD-DiT vaccine combined with the pneumococcal protein vaccine containing the pneumococcal proteins dPly and PhtD (10 μg-10 μg), co-administered with DTPa-HBV-IPV/Hib

10vPP30 = 10Pn-PD-DiT vaccine combined with the pneumococcal protein vaccine containing the pneumococcal proteins dPly and PhtD (30 μg-30 μg), co-administered with DTPa-HBV-IPV/Hib

10Pn = 10Pn-PD-DiT vaccine co-administered with DTPa-HBV-IPV/Hib

Prev13 = Prevenar 13 vaccine co-administered with DTPa-HBV-IPV/Hib

GMC = geometric mean concentration

N = number of subjects with available results

n/% = number/percentage of subjects with concentration within the specified range

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

PRE = Pre-vaccination blood sample

PIII(M3) = One month after third dose of primary vaccination
PRE-BOOSTER = Prior to booster dose
POST-BOOSTER = One month after booster dose

Assessor's comment: As expected the control groups, (Synflorix and Prevenar 13) did not respond to the protein antigens.

Antibody concentrations against pneumococcal serotypes

The immune responses to the vaccine pneumococcal serotypes are presented in the following tables:

Table 33 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 adapted for each epoch)

				≥ 0.05 µg/mL				≥ 0.2 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
ANTI-1	10vPP10	PRE	128	45	35.2	26.9	44.1	13	10.2	5.5	16.7	0.05	0.04	0.06
		PIII(M3)	131	130	99.2	95.8	100	130	99.2	95.8	100	1.57	1.36	1.80
		PRE-BOOSTER	126	124	98.4	94.4	99.8	87	69.0	60.2	77.0	0.30	0.25	0.35
		POST-BOOSTER	130	130	100	97.2	100	129	99.2	95.8	100	2.62	2.27	3.04
	10vPP30	PRE	127	45	35.4	27.2	44.4	10	7.9	3.8	14.0	0.05	0.04	0.06
		PIII(M3)	131	130	99.2	95.8	100	129	98.5	94.6	99.8	1.58	1.36	1.83
		PRE-BOOSTER	124	124	100	97.1	100	81	65.3	56.3	73.6	0.30	0.26	0.36
		POST-BOOSTER	131	131	100	97.2	100	131	100	97.2	100	2.61	2.27	3.00
	10Pn	PRE	132	45	34.1	26.1	42.8	11	8.3	4.2	14.4	0.04	0.04	0.05
		PIII(M3)	134	133	99.3	95.9	100	132	98.5	94.7	99.8	1.49	1.28	1.74
		PRE-BOOSTER	130	128	98.5	94.6	99.8	74	56.9	48.0	65.6	0.26	0.22	0.31
		POST-BOOSTER	131	131	100	97.2	100	131	100	97.2	100	2.41	2.06	2.82
	Prev13	PRE	129	50	38.8	30.3	47.7	9	7.0	3.2	12.8	0.05	0.04	0.05
		PIII(M3)	132	129	97.7	93.5	99.5	129	97.7	93.5	99.5	2.20	1.86	2.60
		PRE-BOOSTER	129	129	100	97.2	100	114	88.4	81.5	93.3	0.49	0.43	0.55
		POST-BOOSTER	127	127	100	97.1	100	127	100	97.1	100	3.78	3.34	4.28
ANTI-4	10vPP10	PRE	128	46	35.9	27.7	44.9	17	13.3	7.9	20.4	0.05	0.04	0.06
		PIII(M3)	131	130	99.2	95.8	100	129	98.5	94.6	99.8	2.04	1.74	2.39
		PRE-BOOSTER	125	125	100	97.1	100	109	87.2	80.0	92.5	0.50	0.43	0.58
		POST-BOOSTER	130	130	100	97.2	100	129	99.2	95.8	100	4.10	3.54	4.74
	10vPP30	PRE	125	39	31.2	23.2	40.1	11	8.8	4.5	15.2	0.05	0.04	0.06
		PIII(M3)	133	132	99.2	95.9	100	132	99.2	95.9	100	2.11	1.83	2.43
		PRE-BOOSTER	121	120	99.2	95.5	100	108	89.3	82.3	94.2	0.51	0.43	0.61
		POST-BOOSTER	129	129	100	97.2	100	129	100	97.2	100	3.90	3.35	4.53
	10Pn	PRE	131	38	29.0	21.4	37.6	10	7.6	3.7	13.6	0.04	0.04	0.05
		PIII(M3)	133	132	99.2	95.9	100	130	97.7	93.5	99.5	1.82	1.55	2.14
		PRE-BOOSTER	126	126	100	97.1	100	109	86.5	79.3	91.9	0.58	0.49	0.70
		POST-BOOSTER	131	131	100	97.2	100	131	100	97.2	100	3.98	3.51	4.52
	Prev13	PRE	128	43	33.6	25.5	42.5	14	10.9	6.1	17.7	0.05	0.04	0.06
		PIII(M3)	132	130	98.5	94.6	99.8	128	97.0	92.4	99.2	2.43	2.05	2.88
		PRE-BOOSTER	128	128	100	97.2	100	103	80.5	72.5	86.9	0.40	0.35	0.46
		POST-BOOSTER	127	127	100	97.1	100	127	100	97.1	100	4.36	3.77	5.05
ANTI-5	10vPP10	PRE	127	70	55.1	46.0	63.9	13	10.2	5.6	16.9	0.06	0.05	0.07
		PIII(M3)	132	132	100	97.2	100	130	98.5	94.6	99.8	2.46	2.13	2.85
		PRE-BOOSTER	128	128	100	97.2	100	114	89.1	82.3	93.9	0.59	0.50	0.69
		POST-BOOSTER	129	129	100	97.2	100	129	100	97.2	100	3.48	2.98	4.05
	10vPP30	PRE	127	66	52.0	42.9	60.9	17	13.4	8.0	20.6	0.06	0.05	0.07
		PIII(M3)	134	133	99.3	95.9	100	133	99.3	95.9	100	2.55	2.22	2.92
		PRE-BOOSTER	123	123	100	97.0	100	114	92.7	86.6	96.6	0.58	0.49	0.68
		POST-BOOSTER	129	129	100	97.2	100	129	100	97.2	100	3.44	2.98	3.96

				≥ 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
	10Pn	PRE	126	69	54.8	45.7	63.6	13	10.3	5.6	17.0	0.06	0.05	0.07
		PIII(M3)	134	133	99.3	95.9	100	133	99.3	95.9	100	2.31	2.00	2.67
		PRE-BOOSTER	128	128	100	97.2	100	110	85.9	78.7	91.4	0.55	0.47	0.65
		POST-BOOSTER	131	131	100	97.2	100	131	100	97.2	100	3.33	2.87	3.87
	Prev13	PRE	127	64	50.4	41.4	59.4	18	14.2	8.6	21.5	0.06	0.05	0.07
		PIII(M3)	132	129	97.7	93.5	99.5	127	96.2	91.4	98.8	2.77	2.27	3.38
		PRE-BOOSTER	129	129	100	97.2	100	122	94.6	89.1	97.8	0.85	0.74	0.99
		POST-BOOSTER	127	127	100	97.1	100	127	100	97.1	100	7.52	6.52	8.68
ANTI-6B	10vPP10	PRE	126	59	46.8	37.9	55.9	25	19.8	13.3	27.9	0.07	0.05	0.08
		PIII(M3)	130	120	92.3	86.3	96.2	94	72.3	63.8	79.8	0.36	0.29	0.46
		PRE-BOOSTER	126	123	97.6	93.2	99.5	107	84.9	77.5	90.7	0.45	0.38	0.53
		POST-BOOSTER	129	128	99.2	95.8	100	127	98.4	94.5	99.8	2.04	1.77	2.36
	10vPP30	PRE	127	68	53.5	44.5	62.4	32	25.2	17.9	33.7	0.08	0.06	0.10
		PIII(M3)	129	123	95.3	90.2	98.3	95	73.6	65.2	81.0	0.37	0.31	0.45
		PRE-BOOSTER	125	122	97.6	93.1	99.5	106	84.8	77.3	90.6	0.47	0.39	0.56
		POST-BOOSTER	129	127	98.4	94.5	99.8	126	97.7	93.4	99.5	1.96	1.67	2.30
	10Pn	PRE	130	52	40.0	31.5	49.0	21	16.2	10.3	23.6	0.06	0.05	0.07
		PIII(M3)	133	122	91.7	85.7	95.8	97	72.9	64.5	80.3	0.40	0.32	0.51
		PRE-BOOSTER	126	123	97.6	93.2	99.5	99	78.6	70.4	85.4	0.46	0.38	0.55
		POST-BOOSTER	131	130	99.2	95.8	100	127	96.9	92.4	99.2	2.28	1.94	2.68
	Prev13	PRE	128	55	43.0	34.3	52.0	18	14.1	8.6	21.3	0.06	0.05	0.07
		PIII(M3)	132	122	92.4	86.5	96.3	100	75.8	67.5	82.8	0.46	0.37	0.57
		PRE-BOOSTER	129	118	91.5	85.3	95.7	83	64.3	55.4	72.6	0.25	0.21	0.31
		POST-BOOSTER	127	126	99.2	95.7	100	126	99.2	95.7	100	3.11	2.65	3.64
ANTI-7F	10vPP10	PRE	129	94	72.9	64.3	80.3	54	41.9	33.2	50.9	0.14	0.11	0.17
		PIII(M3)	130	129	99.2	95.8	100	129	99.2	95.8	100	2.12	1.86	2.41
		PRE-BOOSTER	127	126	99.2	95.7	100	124	97.6	93.3	99.5	0.94	0.82	1.09
		POST-BOOSTER	129	129	100	97.2	100	129	100	97.2	100	4.72	4.13	5.40
	10vPP30	PRE	127	95	74.8	66.3	82.1	51	40.2	31.6	49.2	0.13	0.10	0.16
		PIII(M3)	131	131	100	97.2	100	130	99.2	95.8	100	2.21	1.97	2.48
		PRE-BOOSTER	126	126	100	97.1	100	123	97.6	93.2	99.5	1.00	0.88	1.15
		POST-BOOSTER	129	129	100	97.2	100	129	100	97.2	100	4.70	4.19	5.27
	10Pn	PRE	131	97	74.0	65.7	81.3	52	39.7	31.3	48.6	0.13	0.11	0.17
		PIII(M3)	134	133	99.3	95.9	100	133	99.3	95.9	100	2.20	1.92	2.50
		PRE-BOOSTER	127	127	100	97.1	100	123	96.9	92.1	99.1	0.98	0.85	1.13
		POST-BOOSTER	131	131	100	97.2	100	131	100	97.2	100	4.87	4.32	5.50
	Prev13	PRE	129	92	71.3	62.7	78.9	42	32.6	24.6	41.4	0.11	0.09	0.14
		PIII(M3)	132	130	98.5	94.6	99.8	129	97.7	93.5	99.5	2.94	2.51	3.46
		PRE-BOOSTER	129	129	100	97.2	100	127	98.4	94.5	99.8	1.34	1.18	1.53
		POST-BOOSTER	127	127	100	97.1	100	127	100	97.1	100	7.68	6.84	8.61
ANTI-9V	10vPP10	PRE	130	61	46.9	38.1	55.9	28	21.5	14.8	29.6	0.07	0.05	0.08
		PIII(M3)	132	131	99.2	95.9	100	131	99.2	95.9	100	1.83	1.59	2.12
		PRE-BOOSTER	127	126	99.2	95.7	100	120	94.5	89.0	97.8	0.77	0.65	0.90
		POST-BOOSTER	129	129	100	97.2	100	129	100	97.2	100	4.48	3.90	5.14
	10vPP30	PRE	129	53	41.1	32.5	50.1	18	14.0	8.5	21.2	0.05	0.04	0.06
		PIII(M3)	135	135	100	97.3	100	134	99.3	95.9	100	1.95	1.73	2.20
		PRE-BOOSTER	126	126	100	97.1	100	124	98.4	94.4	99.8	0.97	0.84	1.12
		POST-BOOSTER	129	129	100	97.2	100	129	100	97.2	100	4.91	4.32	5.58
	10Pn	PRE	135	63	46.7	38.0	55.4	20	14.8	9.3	21.9	0.06	0.05	0.07
		PIII(M3)	137	136	99.3	96.0	100	134	97.8	93.7	99.5	1.99	1.72	2.30
		PRE-BOOSTER	128	128	100	97.2	100	124	96.9	92.2	99.1	0.99	0.85	1.16
		POST-BOOSTER	131	131	100	97.2	100	131	100	97.2	100	5.20	4.52	5.97

				≥ 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
	Prev13	PRE	129	51	39.5	31.0	48.5	16	12.4	7.3	19.4	0.05	0.04	0.06
		PIII(M3)	132	129	97.7	93.5	99.5	128	97.0	92.4	99.2	2.33	1.96	2.76
		PRE-BOOSTER	128	128	100	97.2	100	116	90.6	84.2	95.1	0.58	0.50	0.68
		POST-BOOSTER	127	127	100	97.1	100	127	100	97.1	100	6.57	5.67	7.60
ANTI-14	10vPP10	PRE	130	123	94.6	89.2	97.8	87	66.9	58.1	74.9	0.44	0.34	0.57
		PIII(M3)	132	132	100	97.2	100	131	99.2	95.9	100	3.57	3.08	4.14
		PRE-BOOSTER	129	128	99.2	95.8	100	123	95.3	90.2	98.3	1.36	1.12	1.65
		POST-BOOSTER	129	129	100	97.2	100	129	100	97.2	100	6.06	5.18	7.09
	10vPP30	PRE	128	123	96.1	91.1	98.7	89	69.5	60.8	77.4	0.47	0.37	0.61
		PIII(M3)	133	133	100	97.3	100	133	100	97.3	100	3.72	3.30	4.18
		PRE-BOOSTER	126	126	100	97.1	100	122	96.8	92.1	99.1	1.43	1.18	1.73
		POST-BOOSTER	129	129	100	97.2	100	129	100	97.2	100	7.18	6.14	8.39
	10Pn	PRE	130	123	94.6	89.2	97.8	83	63.8	55.0	72.1	0.39	0.30	0.50
		PIII(M3)	135	135	100	97.3	100	135	100	97.3	100	3.91	3.41	4.48
		PRE-BOOSTER	128	128	100	97.2	100	123	96.1	91.1	98.7	1.57	1.28	1.93
		POST-BOOSTER	131	131	100	97.2	100	130	99.2	95.8	100	6.63	5.59	7.86
	Prev13	PRE	130	122	93.8	88.2	97.3	82	63.1	54.2	71.4	0.42	0.32	0.55
		PIII(M3)	132	131	99.2	95.9	100	128	97.0	92.4	99.2	4.18	3.41	5.13
		PRE-BOOSTER	129	129	100	97.2	100	126	97.7	93.4	99.5	2.06	1.72	2.47
		POST-BOOSTER	127	127	100	97.1	100	127	100	97.1	100	11.43	9.81	13.30
ANTI-18C	10vPP10	PRE	130	90	69.2	60.5	77.0	48	36.9	28.6	45.8	0.13	0.10	0.17
		PIII(M3)	132	131	99.2	95.9	100	130	98.5	94.6	99.8	2.27	1.93	2.67
		PRE-BOOSTER	126	125	99.2	95.7	100	120	95.2	89.9	98.2	0.75	0.64	0.87
		POST-BOOSTER	129	129	100	97.2	100	128	99.2	95.8	100	6.68	5.76	7.75
	10vPP30	PRE	128	83	64.8	55.9	73.1	39	30.5	22.6	39.2	0.10	0.08	0.13
		PIII(M3)	132	131	99.2	95.9	100	131	99.2	95.9	100	2.18	1.84	2.59
		PRE-BOOSTER	124	124	100	97.1	100	118	95.2	89.8	98.2	0.76	0.65	0.89
		POST-BOOSTER	129	129	100	97.2	100	129	100	97.2	100	6.38	5.48	7.42
	10Pn	PRE	132	86	65.2	56.4	73.2	42	31.8	24.0	40.5	0.11	0.09	0.14
		PIII(M3)	135	134	99.3	95.9	100	132	97.8	93.6	99.5	2.45	2.04	2.95
		PRE-BOOSTER	126	126	100	97.1	100	122	96.8	92.1	99.1	0.92	0.77	1.10
		POST-BOOSTER	131	131	100	97.2	100	131	100	97.2	100	7.65	6.76	8.67
	Prev13	PRE	129	74	57.4	48.4	66.0	36	27.9	20.4	36.5	0.09	0.07	0.11
		PIII(M3)	132	130	98.5	94.6	99.8	128	97.0	92.4	99.2	2.56	2.14	3.07
		PRE-BOOSTER	129	128	99.2	95.8	100	124	96.1	91.2	98.7	0.75	0.65	0.85
		POST-BOOSTER	127	126	99.2	95.7	100	126	99.2	95.7	100	6.40	5.50	7.45
ANTI-19F	10vPP10	PRE	127	111	87.4	80.3	92.6	74	58.3	49.2	67.0	0.29	0.22	0.38
		PIII(M3)	132	132	100	97.2	100	130	98.5	94.6	99.8	4.29	3.63	5.07
		PRE-BOOSTER	127	127	100	97.1	100	122	96.1	91.1	98.7	1.25	1.05	1.47
		POST-BOOSTER	130	130	100	97.2	100	129	99.2	95.8	100	6.73	5.77	7.83
	10vPP30	PRE	127	105	82.7	75.0	88.8	73	57.5	48.4	66.2	0.28	0.21	0.37
		PIII(M3)	132	132	100	97.2	100	131	99.2	95.9	100	4.13	3.52	4.85
		PRE-BOOSTER	126	126	100	97.1	100	124	98.4	94.4	99.8	1.13	0.96	1.33
		POST-BOOSTER	129	129	100	97.2	100	129	100	97.2	100	7.22	6.25	8.33
	10Pn	PRE	131	113	86.3	79.2	91.6	74	56.5	47.6	65.1	0.27	0.21	0.34
		PIII(M3)	135	135	100	97.3	100	135	100	97.3	100	4.51	3.79	5.36
		PRE-BOOSTER	127	126	99.2	95.7	100	122	96.1	91.1	98.7	1.30	1.06	1.58
		POST-BOOSTER	131	131	100	97.2	100	131	100	97.2	100	7.84	6.78	9.06
	Prev13	PRE	127	101	79.5	71.5	86.2	68	53.5	44.5	62.4	0.19	0.15	0.25
		PIII(M3)	132	129	97.7	93.5	99.5	128	97.0	92.4	99.2	3.50	2.94	4.18
		PRE-BOOSTER	128	128	100	97.2	100	116	90.6	84.2	95.1	0.66	0.53	0.82
		POST-BOOSTER	127	127	100	97.1	100	127	100	97.1	100	7.43	6.35	8.69

				≥ 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	10vPP10	PRE	128	74	57.8	48.8	66.5	37	28.9	21.2	37.6	0.09	0.07	0.11
		PIII(M3)	131	129	98.5	94.6	99.8	111	84.7	77.4	90.4	0.67	0.54	0.82
		PRE-BOOSTER	126	123	97.6	93.2	99.5	104	82.5	74.8	88.7	0.46	0.38	0.56
		POST-BOOSTER	129	127	98.4	94.5	99.8	127	98.4	94.5	99.8	3.20	2.68	3.83
	10vPP30	PRE	129	67	51.9	43.0	60.8	31	24.0	16.9	32.3	0.08	0.06	0.10
		PIII(M3)	133	128	96.2	91.4	98.8	110	82.7	75.2	88.7	0.62	0.50	0.78
		PRE-BOOSTER	123	119	96.7	91.9	99.1	102	82.9	75.1	89.1	0.47	0.38	0.58
		POST-BOOSTER	129	127	98.4	94.5	99.8	127	98.4	94.5	99.8	3.20	2.70	3.78
	10Pn	PRE	131	69	52.7	43.8	61.5	33	25.2	18.0	33.5	0.08	0.07	0.11
		PIII(M3)	135	133	98.5	94.8	99.8	112	83.0	75.5	88.9	0.67	0.54	0.82
		PRE-BOOSTER	125	124	99.2	95.6	100	108	86.4	79.1	91.9	0.57	0.48	0.68
		POST-BOOSTER	131	131	100	97.2	100	131	100	97.2	100	3.72	3.21	4.31
	Prev13	PRE	129	63	48.8	39.9	57.8	17	13.2	7.9	20.3	0.06	0.05	0.08
		PIII(M3)	132	128	97.0	92.4	99.2	121	91.7	85.6	95.8	1.48	1.17	1.88
		PRE-BOOSTER	128	122	95.3	90.1	98.3	92	71.9	63.2	79.5	0.37	0.30	0.44
		POST-BOOSTER	127	127	100	97.1	100	127	100	97.1	100	7.10	6.05	8.35

Assessor's comment: The immune responses to the 10 vaccine serotypes following vaccination with Synflorix were in agreement with previously reported results, and do not cause concern regarding immunogenicity.

Safety results

Between group assessment (confirmatory analysis)

No fever > 40.0°C (rectal temperature) considered by the investigator to be causally related to primary vaccination was reported in any of the 4 study groups.

Within group assessment (descriptive analysis)

Primary epoch

During the 7-day post-primary vaccination period:

Redness was the most frequently reported solicited local symptom at the pneumococcal vaccine injection site (reported after 37.2%, 38.1%, 33.6% and 34.5% of doses in the 10vPP10, 10vPP30, 10Pn and Prev13 groups, respectively). No more than 2.7% of doses were followed by grade 3 solicited local symptoms of given category, in each group.

Irritability was the most frequently reported solicited general symptom (reported after 55.5%, 55.5%, 55.0% and 56.6% of doses in the 10vPP10, 10vPP30, 10Pn and Prev13 groups, respectively). General symptoms assessed by the investigator to be causally related to vaccination were reported after a maximum of 43.6%, 43.1%, 41.8% and 41.5% of doses (irritability) in the 10vPP10, 10vPP30, 10Pn and Prev13 groups, respectively. No more than 4.8% of doses (irritability) were followed by grade 3 general solicited symptoms in each group and most of them were considered by the investigator to be causally related to vaccination.

No increase in the incidence of solicited local and general symptoms was observed with consecutive doses of either 10Pn-PD-DiT-dPly-PhtD 10 or 10Pn-PD-DiT-dPly-PhtD 30 vaccines, during the 3-dose primary vaccination course.

During the 31-day post-primary vaccination period:

At least one unsolicited symptom was reported after 16.9%, 21.4%, 20.1% and 20.0% of doses in the 10vPP10, 10vPP30, 10Pn and Prev13 group, respectively.

Grade 3 unsolicited symptoms were reported after 0.2%, 0.5% and 0.2% of doses in the 10vPP30, 10Pn and Prev13 group, respectively. Of these, one grade 3 symptom (hypotonic-hyporesponsive episode in one subject in the 10Pn group) was considered by the investigator to be causally related to vaccination.

Unsolicited symptoms considered by the investigator to be causally related to vaccination were reported after 0.2%, 0.5%, 0.9% and 0.2% of doses in the 10vPP10, 10vPP30, 10Pn and Prev13 groups, respectively.

Booster epoch

During the 7-day post-booster vaccination period:

The most frequently reported solicited local symptoms at the pneumococcal vaccine injection site were redness in the 10vPP10 and 10Pn groups (reported for 47.9% and 41.0% of subjects, respectively) and pain in the 10vPP30 and Prev13 groups (reported for 45.7% and 44.3% of subjects). No more than 5.7% of subjects were reported with grade 3 solicited local symptoms of given category, in each group.

Rates of pain for both 10vPP10 and 10vPP30 investigational groups seem to be higher after booster dose than after primary doses of the same vaccines; however similar observation can be made for the control 10Pn and Prev13 groups.

Irritability was the most frequently reported solicited general symptom (reported for 66.0%, 60.0%, 59.0% and 64.3% of subjects in the 10vPP10, 10vPP30, 10Pn and Prev13 groups, respectively).

General symptoms assessed by the investigator to be causally related to vaccination were reported for a maximum of 59.7%, 58.6%, 54.7% and 59.3% of subjects (irritability) in the 10vPP10, 10vPP30, 10Pn and Prev13 groups, respectively. No more than 8.3% of subjects (irritability) were reported with grade 3 general solicited symptoms in each group and most of them were considered by the investigator to be causally related to vaccination.

For some solicited general AEs (e.g. loss of appetite and fever), a trend for higher rate of symptoms reported after booster dose when compared to the last primary dose can be observed; however similar observation can be made for the control 10Pn and Prev13 groups.

During the 31-day post-booster vaccination period:

At least one unsolicited symptom was reported for 27.8%, 18.6%, 19.3% and 24.3% of subjects in the 10vPP10, 10vPP30, 10Pn and Prev13 groups, respectively.

Grade 3 unsolicited symptoms were reported for 1.4% and 2.1% of subjects in the 10vPP10 and Prev13 groups, respectively. None were considered by the investigator to be causally related to vaccination.

Unsolicited symptoms assessed by the investigator to be causally related to vaccination were reported for 1.4% and 0.7% of subjects in the 10Pn and Prev13 groups, respectively.

No fatal SAEs were reported during the entire study period. At least one non-fatal SAE was reported for 56 out of 575 subjects during the primary epoch and for 4 out of 564 subjects during the booster epoch.

One SAE (hypotonic-hyporesponsive episode in one subject in the 10Pn group on the day of vaccination dose 1) was assessed by the investigator to be causally related to vaccination. All events recovered/resolved by the time of study end, except for 4 events (2 cases of psychomotor retardation, type I diabetes mellitus and thermal burn).

During the primary epoch, one subject from the 10Pn group was withdrawn from the study due to a SAE (hypotonic-hyporesponsive episode). During the booster epoch, 2 subjects were withdrawn from the study due to an SAE (psychomotor retardation in the 10Pn group and type I diabetes mellitus in the 10vPP30 group).

Assessor's comment: The safety results were in agreement with previous studies, and no new safety concern was raised.

1.3.3. Discussion on clinical aspects

The MAH has submitted a clinical study of a new pneumococcal candidate vaccine, in which Synflorix was one of the comparators. The immunogenicity and safety results for the Synflorix group were in agreement with previous studies, and no new concerns are raised.

2. Rapporteur's overall conclusion and recommendation

Overall conclusion

The procedure is considered fulfilled. No new concerns are raised by this study.

Recommendation

☒ **Fulfilled:**

No regulatory action required.

Additional clarifications requested

Not applicable.