21 April 2017
EMA/288302/2017
Human Medicines Evaluation Division

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

Infanrix hexa

diphtheria (D), tetanus (T), pertussis (acellular, component) (Pa), hepatitis B (rDNA) (HBV), poliomyelitis (inactivated) (IPV) and Haemophilus influenzae type b (Hib) conjugate vaccine (adsorbed)

Procedure no: EMEA/H/C/000296/P46/126

Note

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

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1. Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

Paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. FINAL STUDY REPORT / Study No. SPNG-009, A phase II, randomized, controlled, partially-blind study to demonstrate immunogenicity and assess safety of GSK Biologicals' 11-valent and 12-valent pneumococcal polysaccharide and non-typeable *Haemophilus Influenzae* protein D conjugate vaccines administered as a 3-dose primary vaccination course during the first 6 months of life and as a booster dose at 12-15 months of age.

1.1. Steps taken for the assessment

Submission date:	21/12/2016
Start of procedure:	23/01/2017
CHMP Rapporteur's preliminary assessment report circulated on:	27/03/2017
CHMP Rapporteur's updated assessment report circulated on:	10/04/2017
CHMP opinion:	21/04/2017

2. Assessment of the post-authorisation measure PAM 126

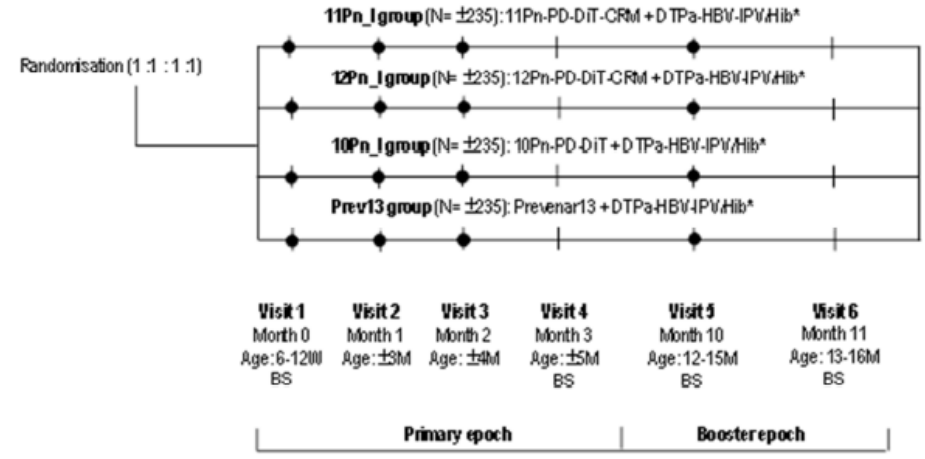
The safety and immunogenicity of the GSK Biologicals' 12-valent pneumococcal polysaccharide and non-typeable *H. influenzae* protein D conjugate vaccine (12Pn-PDDiT- CRM) containing serotypes 6A and 19A in addition to the 10 Synflorix serotypes, has been assessed for the first time in the study SPNG-007 (115373). The results from SPNG-007 study showed that 12Pn-PD-DiT-CRM was immunogenic and well tolerated when administered as single dose in toddlers 12-23 months of age, previously primed with three doses of Synflorix. No clinical pattern that would suggest a clinical safety concern was found.

This current study aimed to demonstrate non-inferiority of immune response to 11Pn-PDDiT- CRM and 12Pn-PD-DiT-CRM vaccines respectively when compared to immune responses of the licensed vaccines and when administered as a 3-dose primary immunization course in healthy infants at 3, 4 and 5 months of age and as a booster vaccination at 12-15 months of age. Pfizer's Prevenar 13 vaccine was used for the comparison of the immune response to the two additional pneumococcal serotypes 19A and/or 6A conjugated to CRM197 and GSK Biologicals' Synflorix was used for the comparison of the immune response to the 10 common pneumococcal serotypes. Evaluation of the safety of 11Pn-PD-DiT-CRM and 12Pn-PD-DiT-CRM vaccines was also performed in the study.

Summary of the study design

4 parallel groups were randomized.

Figure 1 Study design overview



● = vaccination
BS: blood sampling; W: weeks; M: months; Post-vacc: post-vaccination
* DTPa-HBV-IPV/Hib vaccine was co-administered with the pneumococcal study vaccines in order to comply with the routine infant immunisation programme and was considered as a non-investigational study vaccine.
Note: To comply with national immunization schedule, subjects in Spain received a licensed meningococcal serogroup C-tetanus toxoid conjugate (MenC-TT) vaccine (Baxter's *NeisVac-C*), concomitantly administered with the study vaccine at the time of the booster dose vaccination (Visit 5). This vaccine was not considered as study vaccine.

Duration of the study: approximately 11 to 14 months for each subject, depending on the age at the vaccination.

☐ Primary epoch: starting at Visit 1 (Month 0) and ending at Visit 4 (Month 3)

☐ Booster epoch: starting at Visit 5 (Month 10) and ending at Visit 6 (Month 11)

Control: active control

☐ Prevenar 13 for the serotypes 6A and 19A.

☐ Synflorix for the 10 common vaccine serotypes.

Vaccination schedule:

☐ 3 primary doses given at approximately 2, 3, 4 months of age.

☐ A booster dose at 12-15 months of age.

Study groups:

11Pn_I group: subjects were to receive GSK Biologicals' 11-valent pneumococcal polysaccharide and non-typeable *Haemophilus influenzae* protein D conjugate vaccine (11Pn-PD-DiT-CRM) **co-administered with DTPa-HBV-IPV/ Hib (Infanrix hexa) vaccine.**

12Pn_I group: subjects were to receive GSK Biologicals' 12-valent pneumococcal polysaccharide and non-typeable *Haemophilus influenzae* protein D conjugate vaccine (12Pn-PD-DiT-CRM) **co-administered with DTPa-HBV-IPV/ Hib (Infanrix hexa) vaccine.**

10Pn_I group: subjects were to receive GSK Biologicals' 10-valent pneumococcal polysaccharide non-typeable *Haemophilus influenzae* protein D conjugate vaccine (Synflorix or 10Pn-PD-DiT) **co-administered with DTPa- HBV-IPV/Hib (Infanrix hexa) vaccine.**

Prev13 group: subjects were to receive Pfizer's 13-valent pneumococcal conjugate vaccine (Prevenar 13) **co-administered with DTPa-HBV-IPV/Hib (Infanrix hexa) vaccine.**

Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age (Min/Max)*	Epochs	
			Primary	Booster
11Pn_I	235	6-12 weeks	x	x
12Pn_I	235	6-12 weeks	x	x
10Pn_I	235	6-12 weeks	x	x
Prev13	235	6-12 weeks	x	x

*Age at the time of first vaccination

Treatment allocation: randomised (1:1:1:1).

Table 2 Study groups

Treatment name	Vaccine/product name	Study groups			
		11Pn_I	12Pn_I	10Pn_I	Prev13
11Pn-PD-DiT-CRM	11Pn-PD-DiT-CRM	x			
12Pn-PD-DiT-CRM	12Pn-PD-DiT-CRM		x		
10Pn-PD-DiT	10Pn-PD-DiT			x	
Prevenar 13	*Prevenar 13*				x
Infanrix hexa	DTPa-HBV-IPV	x	x	x	x
	Hib	x	x	x	x

Note: DTPa-HBV-IPV/Hib (*Infanrix hexa*) was administered as part of the routine immunisation schedule and was considered as a non-investigational study vaccine. It had to be recorded in the "Non-investigational study vaccine" section of the eCRF.

Primary objectives This report addresses the objectives related to the booster epoch except for antibody concentrations for serotype 6A and immunogenicity measured by opsonophagocytic assay (OPA) for serotype 19A. As soon as data will be available, they will be presented in an Annex report. The sequential co-primary objectives were previously addressed and results are presented in the SPNG-009 (116485) Report (Primary Epoch) Amendment 1 dated 07 October2016.

First sequential co-primary objectives for the 11-valent formulation

- To demonstrate that GSK Biologicals' 11-valent pneumococcal polysaccharide and non-typeable Haemophilus influenzae protein D conjugate vaccine co-administered with DTPa-HBV-IPV/Hib as a three-dose primary vaccination course at approximately 2, 3, 4 months of age is non-inferior for at least 9 out of 11 vaccine pneumococcal serotypes to Prevenar 13 (for 19A) or Synflorix (for 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) in terms of percentage of subjects with antibody concentrations ≥ 0.2 μg/mL.
  AND
- To demonstrate that GSK Biologicals' 11-valent pneumococcal polysaccharide and non-typeable Haemophilus influenzae protein D conjugate vaccine co-administered with DTPa-HBV-IPV/Hib as a three-dose primary vaccination course at approximately 2, 3, 4 months of age is non-inferior for at least 9 out of 11 vaccine pneumococcal serotypes to Prevenar 13 (for 19A) or Synflorix (for 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) in terms of ELISA Geometric Mean Concentrations (GMCs).

Second sequential co-primary objectives for the 12-valent formulation

The co-primary objectives for the 12-valent formulation were assessed sequentially after demonstration of the co-primary objectives for the 11-valent formulation.

- To demonstrate that GSK Biologicals' 12-valent pneumococcal polysaccharide and non-typeable Haemophilus influenzae protein D conjugate vaccine co-administered with DTPa-HBV-IPV/Hib as a three-dose primary vaccination course at approximately 2, 3, 4 months of age is non-inferior for at least 10 out of 12 vaccine pneumococcal serotypes to Prevenar 13 (for 6A and 19A) or Synflorix (for 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) in terms of percentage of subjects with antibody concentrations ≥ 0.2 µg/mL.
  AND
- To demonstrate that GSK Biologicals' 12-valent pneumococcal polysaccharide and non-typeable Haemophilus influenzae protein D conjugate vaccine co-administered with DTPa-HBV-IPV/Hib as a three-dose primary vaccination course at approximately 2, 3, 4 months of age is non-inferior for at least 10 out of 12 vaccine pneumococcal serotypes to Prevenar 13 (for 6A and 19A) or Synflorix (for 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) in terms of ELISA GMCs.

Secondary objectives

To assess the immune responses to pneumococcal serotype specific polysaccharides and to protein D, elicited by GSK Biologicals' 11-valent and 12-valent pneumococcal polysaccharide and non-typeable *Haemophilus influenzae* protein D conjugate vaccines co-administered with DTPa-HBV-IPV/Hib vaccine after 3-dose primary vaccination course in infants at approximately 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' 11-valent and 12-valent pneumococcal polysaccharide and non-typeable *Haemophilus influenzae* protein D conjugate vaccines after administration of any primary and booster vaccine dose when co-administered with DTPa-HBV-IPV/Hib.

To assess the antibody persistence induced by GSK Biologicals' 11-valent and 12-valent pneumococcal polysaccharide and non-typeable Haemophilus influenzae protein D vaccines, 8-11 months after completion of the 3-dose primary vaccination course.

Selection of study population

The target enrolment was approximately 940 subjects (± 235 subjects in each group), in a 1:1:1:1 ratio in order to have 800 evaluable subjects (± 200 subjects in each group) for the immunogenicity analysis on the according-to-protocol (ATP) cohort.

Inclusion criteria for enrolment

All subjects had to satisfy ALL the following criteria at study entry:

- Subjects who the investigator believed that their parent(s)/LAR(s) could and would comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).
- A male or female between, and including 6 to 12 weeks (42-90 days) of age at the time of the first vaccination. In addition, the first pneumococcal and DTPa-HBVIPV/ Hib vaccination was to be given in accordance with the official national recommendations for the immunisation schedule of infants.
- Written informed consent obtained from the parents/LAR(s) of the subject.
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Born after a gestation period of at least 36 weeks.

Exclusion criteria

The following criteria had to be checked at the time of study entry. If ANY exclusion criterion applied, the subject could not be included in the study:

- Child in care.
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccines within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs since birth. For corticosteroids, this meant prednisone ≥ 0.5 mg/kg/day, or equivalent. Inhaled and topical steroids were allowed.
- Planned administration/administration of a vaccine containing diphtheria toxoid, tetanus toxoid (except MenC-TT in Spain) or CRM197 and not foreseen by the study protocol during any time of the study period, or of any other vaccines not foreseen by the protocol in the period starting from 30 days before each dose and ending 30 days after each dose of vaccine(s), with the following exceptions:
    - Licensed influenza vaccines were always allowed, even if concomitantly administered with the study vaccines.

- Licensed rotavirus vaccine was allowed if administered at least 7 days before or after each dose of study of vaccines.
- Licensed MenC-TT vaccine was allowed for subjects in Spain and was to be concomitantly administered with the study vaccine at around 2, 4 and 12-15 months of age.
- In case an emergency mass vaccination for an unforeseen public health threat (e.g. a pandemic) was organised by the public health authorities, outside the routine immunization program, that vaccine could be administered at any time during the study period provided it was licensed and used according to its Summary of Product Characteristics (SPC) or Prescribing Information (PI) and according to the local governmental recommendations.

Administration of any of the vaccines mentioned above had to be documented in the "Concomitant vaccination" of the eCRF.

- Concurrently participating in another clinical study, at any time during the study period, in which the subject had been or was exposed to an investigational or a non-investigational product (pharmaceutical product or device).
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Family history of congenital or hereditary immunodeficiency.
- History of any reaction or hypersensitivity likely to be exacerbate
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine(s).
- Major congenital defects or serious chronic illness, including Kawasaki's syndrome.
- History of any neurological disorders or seizures, including conditions such as hypotensive-hyporesponsive episodes, encephalopathy and any convulsions (afebrile and febrile).
- Acute disease and/or fever at the time of enrolment:
  - Fever was defined as temperature ≥ 38.0°C (rectal measurement) or ≥37.5°C (oral or axillary measurement).
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever could be enrolled at the discretion of the investigator.
- Administration of immunoglobulins and/or any blood products since birth or planned administration during study period.
- Previous vaccination against diphtheria, tetanus, pertussis, polio, H. influenzae type b.
- Previous vaccination against S. pneumoniae.
- History of or intercurrent diphtheria, tetanus, pertussis, hepatitis B, polio, H. influenzae type b disease.
- Any medical condition which could interfere with the assessment of the study objectives in the opinion of the investigator.

History of any neurological disorders or seizures, including conditions such as hypotensive-hyporesponsive episodes, encephalopathy and any convulsions (afebrile and febrile). The following adverse events constituted additional precautions specific to DTPa-HBV-IPV/ Hib vaccine administration. If any of these adverse events occurred, booster vaccination with a DTPa-HBV-IPV/Hib based vaccine remained at the discretion of the investigator:

- Temperature of ≥ 40.0°C within 48 hours, not due to another identifiable cause.

- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
- Persistent crying lasting ≥ 3 hours, occurring within 48 hours.
- Convulsions with or without fever, occurring within 3 days of vaccination.

Safety summary of Results of the SPNG-009 after Primary vaccination

During the 4-days post-vaccination period:

Pain was the most frequently reported solicited local AE in each group (after 37.5%, 40.2%, 37.9% and 35.4% of doses in the 11Pn_I, 12Pn_I, 10Pn_I and Prev13 groups, respectively). The overall/dose incidence of grade 3 solicited local AEs ranged from 0.3% (redness in the Prev13 group) to 4.5% (pain in the 11Pn_I group).

Table Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period followingeach dose and overall (Epoch 001) (Total vaccinated cohort)

		11Pn_I					12Pn_I					10Pn_I					Prev13				
					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
Overall/subject																					
Drowsiness	All	240	185	77.1	71.2	82.2	236	178	75.4	69.4	80.8	228	162	71.1	64.7	76.8	238	168	70.6	64.4	76.3
	Grade 3	240	13	5.4	2.9	9.1	236	13	5.5	3.0	9.2	228	15	6.6	3.7	10.6	238	20	8.4	5.2	12.7
	Related	240	155	64.6	58.2	70.6	236	143	60.6	54.0	66.9	228	130	57.0	50.3	63.5	238	138	58.0	51.4	64.3
	Grade 3 Related	240	13	5.4	2.9	9.1	236	12	5.1	2.7	8.7	228	12	5.3	2.7	9.0	238	19	8.0	4.9	12.2
	Medical advice	240	0	0.0	0.0	1.5	236	2	0.8	0.1	3.0	228	0	0.0	0.0	1.6	238	0	0.0	0.0	1.5
Irritability / fussiness	All	240	202	84.2	78.9	88.5	236	203	86.0	80.9	90.2	228	185	81.1	75.4	86.0	238	186	78.2	72.4	83.2
	Grade 3	240	36	15.0	10.7	20.2	236	27	11.4	7.7	16.2	228	32	14.0	9.8	19.2	238	20	8.4	5.2	12.7
	Related	240	173	72.1	65.9	77.7	236	174	73.7	67.6	79.2	228	153	67.1	60.6	73.2	238	153	64.3	57.8	70.4
	Grade 3 Related	240	32	13.3	9.3	18.3	236	26	11.0	7.3	15.7	228	27	11.8	8.0	16.8	238	17	7.1	4.2	11.2
	Medical advice	240	2	0.8	0.1	3.0	236	4	1.7	0.5	4.3	228	2	0.9	0.1	3.1	238	1	0.4	0.0	2.3
Loss of appetite	All	240	124	51.7	45.1	58.1	236	132	55.9	49.3	62.4	228	125	54.8	48.1	61.4	238	125	52.5	46.0	59.0
	Grade 3	240	4	1.7	0.5	4.2	236	8	3.4	1.5	6.6	228	7	3.1	1.2	6.2	238	9	3.8	1.7	7.1
	Related	240	93	38.8	32.6	45.2	236	103	43.6	37.2	50.2	228	101	44.3	37.7	51.0	238	101	42.4	36.1	49.0
	Grade 3 Related	240	4	1.7	0.5	4.2	236	8	3.4	1.5	6.6	228	5	2.2	0.7	5.0	238	6	2.5	0.9	5.4
	Medical advice	240	1	0.4	0.0	2.3	236	4	1.7	0.5	4.3	228	3	1.3	0.3	3.8	238	0	0.0	0.0	1.5
Temperature/(Rectally) (°C)	All	240	153	63.8	57.3	69.8	236	144	61.0	54.5	67.3	228	148	64.9	58.3	71.1	238	143	60.1	53.6	66.4
	>38.5	240	59	24.6	19.3	30.5	236	55	23.3	18.1	29.2	228	65	28.5	22.7	34.8	238	53	22.3	17.1	28.1
	>39.0	240	12	5.0	2.6	8.6	236	14	5.9	3.3	9.8	228	22	9.6	6.1	14.2	238	24	10.1	6.6	14.6
	>39.5	240	1	0.4	0.0	2.3	236	5	2.1	0.7	4.9	228	6	2.6	1.0	5.6	238	2	0.8	0.1	3.0
	>40.0	240	0	0.0	0.0	1.5	236	0	0.0	0.0	1.6	228	0	0.0	0.0	1.6	238	0	0.0	0.0	1.5
	Related	240	140	58.3	51.8	64.6	236	132	55.9	49.3	62.4	228	136	59.6	53.0	66.1	238	133	55.9	49.3	62.3
	>40.0 Related	240	0	0.0	0.0	1.5	236	0	0.0	0.0	1.6	228	0	0.0	0.0	1.6	238	0	0.0	0.0	1.5
	Medical advice	240	4	1.7	0.5	4.2	236	3	1.3	0.3	3.7	228	5	2.2	0.7	5.0	238	5	2.1	0.7	4.8

11Pn_I = 11Pn-PD-DiT-CRM co-administered with DTPa-HBV-IPV/Hib
12Pn_I = 12Pn-PD-DiT-CRM co-administered with DTPa-HBV-IPV/Hib
10Pn_I = 10Pn-PD-DiT co-administered with DTPa-HBV-IPV/Hib
Prev13 = Prevenar 13 co-administered with DTPa-HBV-IPV/Hib
For each dose and overall/subject:
N= number of subjects with at least one documented dose
n/%= number/percentage of subjects reporting the symptom at least once
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

Irritability / fussiness was the most frequently reported solicited general AE in each group (after 58.4%, 61.7%, 57.7% and 53.5% of doses in the 11Pn_I, 12Pn_I, 10Pn_I and Prev13 groups, respectively). Grade 3 solicited general AEs were reported following maximum 5.6% of doses in the

11Pn_I and 12Pn_I groups (irritability in 11Pn_I group) and maximum 6.2% of doses in the control 10Pn_I and Prev13 groups (irritability in the 10Pn_I group). Grade 3 solicited general AEs considered by the investigator to be causally related to vaccination were reported following maximum 4.9% of doses in the 11Pn_I and 12Pn_I groups (irritability in the 11Pn_I group) and maximum 5.0% of doses in the control 10Pn_I and Prev13 groups (irritability in the 10Pn_I group).

During the 31-days post-vaccination period:

24.2%, 23.4%, 27.2% and 23.6% of doses in the 11Pn_I, 12Pn_I, 10Pn_I and Prev13 group, respectively were followed by at least one unsolicited AE.

Grade 3 unsolicited AEs were reported after 2.1%, 1.4%, 1.2% and 0.8% of doses in the 11Pn_I, 12Pn_I, 10Pn_I and Prev13 group, respectively. Of these, three grade 3 AEs, two in the 12Pn_I group (both pyrexia) and one in the Prev13 group (vomiting), were considered by the investigator to be causally related to vaccination.

Unsolicited AEs considered by the investigator to be causally related to vaccination were reported for 0.6%, 0.8%, 1.5% and 1.0% of doses in the 11Pn_I, 12Pn_I, 10Pn_I and Prev13 group, respectively).

During the primary epoch (from dose 1 up to visit 4), at least one SAE was reported for 52 subjects: 12 out of 240 (5.0%) vaccinated subjects in the 11Pn_I group, 11 out of 240 (4.6%) vaccinated subjects in the 12Pn_I group, 17 out of 230 (7.4%) vaccinated subjects in the 10Pn_I group and 12 out of 241 (5.0%) vaccinated subjects in the Prev13 group. Of these, three SAEs were considered by the investigator to be causally related to vaccination, one in the 10Pn_I group (pyrexia) and two in the 12Pn_I group (both pyrexia). All SAEs resolved without sequelae except one (chronic bronchitis, resolving).

No fatal SAEs were reported during the primary epoch of the study (from dose 1 up to visit 4). There were no subjects withdrawn from the study due to a SAE. One subject was withdrawn due to a non-serious adverse event not related to vaccination.

Safety summary of Results of the SPNG-009 after Booster

During the 4-day post-booster vaccination period, pain was the most frequently reported solicited local symptom (reported for 47.7%, 54.9%, 54.3% and 47.6% of subjects in the 11Pn_I, 12Pn_I, 10Pn_I and Prev13 groups, respectively). The percentage of subjects with grade 3 solicited local symptom ranged from 2.1% (redness in the 11Pn_I group) to 8.2% (pain in the 10Pn_I group). Six large swelling reactions were reported after administration of the booster dose of pneumococcal conjugate vaccines (three in each of the 12Pn_I and 10Pn_I groups).

During the 4-day post-booster vaccination period, irritability was the most frequently reported solicited general symptom (reported for 59.6%, 60.7%, 62.6% and 55.8% of subjects in the 11Pn_I, 12Pn_I, 10Pn_I and Prev13 groups, respectively). The percentage of subjects reporting fever (a rectal temperature of $\geq 38.0^{\circ}$ C) was 34.0%, 32.1 %, 31.1 5 and 32.5 % in 11Pn_I, 12Pn_I, 10Pn_I and Prev13 groups, respectively. Grade 3 solicited general symptoms were reported for a maximum of 6.3% of subjects (irritability in the 12Pn_I group). The percentage of subjects with solicited general symptom with causal relationship to vaccination (as assessed by the investigator) ranged from 19.5% (loss of appetite in the Prev13 group) to 52.2% (irritability in the 12Pn_I group).

Table Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-booster period (Epoch 002) (Total vaccinated cohort)

		11Pn_I					12Pn_I					10Pn_I					Prev13				
					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	235	109	46.4	39.9	53.0	224	100	44.6	38.0	51.4	219	84	38.4	31.9	45.1	231	96	41.6	35.1	48.2
	Grade 3	235	9	3.8	1.8	7.1	224	6	2.7	1.0	5.7	219	4	1.8	0.5	4.6	231	2	0.9	0.1	3.1
	Related	235	93	39.6	33.3	46.1	224	79	35.3	29.0	41.9	219	68	31.1	25.0	37.6	231	81	35.1	28.9	41.6
	Grade 3 Related	235	7	3.0	1.2	6.0	224	4	1.8	0.5	4.5	219	4	1.8	0.5	4.6	231	2	0.9	0.1	3.1
	Medical advice	235	1	0.4	0.0	2.3	224	1	0.4	0.0	2.5	219	1	0.5	0.0	2.5	231	2	0.9	0.1	3.1
Irritability	All	235	140	59.6	53.0	65.9	224	136	60.7	54.0	67.2	219	137	62.6	55.8	69.0	231	129	55.8	49.2	62.4
	Grade 3	235	14	6.0	3.3	9.8	224	14	6.3	3.5	10.3	219	12	5.5	2.9	9.4	231	9	3.9	1.8	7.3
	Related	235	107	45.5	39.0	52.1	224	117	52.2	45.5	58.9	219	109	49.8	43.0	56.6	231	107	46.3	39.8	53.0
	Grade 3 Related	235	13	5.5	3.0	9.3	224	12	5.4	2.8	9.2	219	10	4.6	2.2	8.2	231	9	3.9	1.8	7.3
	Medical advice	235	4	1.7	0.5	4.3	224	3	1.3	0.3	3.9	219	2	0.9	0.1	3.3	231	2	0.9	0.1	3.1
Loss of appetite	All	235	80	34.0	28.0	40.5	224	85	37.9	31.6	44.7	219	83	37.9	31.4	44.7	231	61	26.4	20.8	32.6
	Grade 3	235	6	2.6	0.9	5.5	224	3	1.3	0.3	3.9	219	9	4.1	1.9	7.7	231	7	3.0	1.2	6.1
	Related	235	66	28.1	22.4	34.3	224	64	28.6	22.8	35.0	219	65	29.7	23.7	36.2	231	45	19.5	14.6	25.2
	Grade 3 Related	235	4	1.7	0.5	4.3	224	2	0.9	0.1	3.2	219	7	3.2	1.3	6.5	231	5	2.2	0.7	5.0
	Medical advice	235	1	0.4	0.0	2.3	224	3	1.3	0.3	3.9	219	1	0.5	0.0	2.5	231	2	0.9	0.1	3.1
Temperature (Rectal) (°C)	All	235	80	34.0	28.0	40.5	224	72	32.1	26.1	38.7	219	68	31.1	25.0	37.6	231	75	32.5	26.5	38.9
	>38.5	235	39	16.6	12.1	22.0	224	32	14.3	10.0	19.6	219	33	15.1	10.6	20.5	231	34	14.7	10.4	20.0
	>39.0	235	11	4.7	2.4	8.2	224	10	4.5	2.2	8.1	219	12	5.5	2.9	9.4	231	13	5.6	3.0	9.4
	>39.5	235	4	1.7	0.5	4.3	224	3	1.3	0.3	3.9	219	4	1.8	0.5	4.6	231	2	0.9	0.1	3.1
	>40.0	235	2	0.9	0.1	3.0	224	0	0.0	0.0	1.6	219	1	0.5	0.0	2.5	231	0	0.0	0.0	1.6
	Related	235	72	30.6	24.8	37.0	224	66	29.5	23.6	35.9	219	60	27.4	21.6	33.8	231	67	29.0	23.2	35.3
	>40.0 Related	235	2	0.9	0.1	3.0	224	0	0.0	0.0	1.6	219	0	0.0	0.0	1.7	231	0	0.0	0.0	1.6
	Medical advice	235	4	1.7	0.5	4.3	224	2	0.9	0.1	3.2	219	2	0.9	0.1	3.3	231	4	1.7	0.5	4.4

11Pn_I = 11Pn-PD-DiT-CRM co-administered with DTPa-HBV-IPV/Hib
12Pn_I = 12Pn-PD-DiT-CRM co-administered with DTPa-HBV-IPV/Hib
10Pn_I = 10Pn-PD-DiT co-administered with DTPa-HBV-IPV/Hib
Prev13 = Prevenar 13 co-administered with DTPa-HBV-IPV/Hib
N = number of subjects with the documented dose

During the 31-day post-booster vaccination period, at least one unsolicited symptom was reported for 29.1%, 30.1%, 33.3% and 22.6% of subjects in the 11Pn_I, 12Pn_I, 10Pn_I and Prev13 groups, respectively. At least one unsolicited symptom with causal relationship to vaccination was reported for 3.0%, 0.4%, 2.3% and 0.9% of subjects in the 11Pn_I, 12Pn_I, 10Pn_I and Prev13 groups, respectively.

During the booster epoch (from booster dose up to study end), at least one SAE was reported for 11 subjects: two subjects in the 11Pn_I group, three subjects in the 12Pn_I group, four subjects in the 10Pn_I group and two subjects in the Prev13 group. Of these, one SAE in the 11Pn_I group (head injury) was considered by the investigator to be causally related to vaccination. All SAEs recovered/resolved.

During the entire study period, at least one SAE was reported for 117 subjects: 29 subjects in the 11Pn_I group, 26 subjects in the 12Pn_I group, 38 subjects in the 10Pn_I group and 24 subjects in the Prev13 group. Of these, four SAEs were considered by the investigator to be causally related to vaccination. All SAEs recovered/resolved, except for three events (head injury (11Pn_I group) and three events of pyrexia (two in the 12Pn_I group and one in the 10Pn_I group). All SAEs recovered/resolved, except for three events: retinoblastoma in the 11Pn_I group, hypotonia in the 10Pn_I group (both not recovered/not resolved) and pneumonia in the 12Pn_I group (recovered/resolved with sequelae). Please refer to the appendix for the narratives.

During the entire study period, one subject was withdrawn due to a non-serious AE (central hypotonic syndrome) and two subjects were withdrawn due to SAEs (conjunctivitis and retinoblastoma).

Overall conclusion

During the 31-day post-primary vaccination period, 24.2%, 23.4%, 27.2% and 23.6% of doses in the 11Pn_I, 12Pn_I, 10Pn_I and Prev13 group, respectively were followed by at least one unsolicited AE.

During the primary epoch (from dose 1 up to visit 4), at least one SAE was reported for 52 subjects: 12 out of 240 (5.0%) vaccinated subjects in the 11Pn_I group, 11 out of 240 (4.6%) vaccinated subjects in the 12Pn_I group, 17 out of 230 (7.4%) vaccinated subjects in the 10Pn_I group and 12 out of 241 (5.0%) vaccinated subjects in the Prev13 group. Of these, three SAEs were considered by the investigator to be causally related to vaccination, one in the 10Pn_I group (pyrexia) and two in the 12Pn_I group (both pyrexia).

During the 31-day post-booster vaccination period, at least one unsolicited symptom was reported for 29.1%, 30.1%, 33.3% and 22.6% of subjects in the 11Pn_I, 12Pn_I, 10Pn_I and Prev13 groups, respectively.

During the booster epoch (from booster dose up to study end), at least one SAE was reported for 11 subjects. Of these, one SAE in the 11Pn_I group (head injury) was assessed by the investigator to be causally related to vaccination. All SAEs recovered/resolved.

During the entire study period, at least one SAE was reported for 117 subjects. Of these, four SAEs were considered by the investigator to be causally related to vaccination: head injury (11Pn_I group) and three events of pyrexia (two in the 12Pn_I group and one in the 10Pn_I group). All SAEs recovered/resolved, except for three events: retinoblastoma in the 11Pn_I group, hypotonia in the 10Pn_I group (both not recovered/not resolved) and pneumonia in the 12Pn_I group (recovered/resolved with sequelae).

In this study, the 11Pn-PD-DiT-CRM and 12Pn-PD-DiT-CRM vaccines given as a booster dose to children of 12-15 months of age and co-administered with DTPa- HBV-IPV/Hib were generally well-tolerated and induced immune responses to all vaccine antigens (i.e. pneumococcal serotype-specific capsular polysaccharides and protein D).

3. Rapporteur's overall conclusion

The solicited/unsolicited AEs and SAEs – such as HHE and febrile convulsions - were addressed correctly in this study.

In clinical studies in which some of the vaccines received Infanrix hexa concomitantly with Prevenar (PCV7) as a booster (4th) dose of both vaccines, fever $\geq$ 38.0° C was reported in 43.4% of infants receiving Prevenar and Infanrix hexa at the same time as compared to 30.5% of infants receiving the hexavalent vaccine alone. Fever $\geq$39.5° C was observed in 2.6% and 1.5% of infants receiving Infanrix hexa with or without Prevenar, respectively. The incidence and severity of fever following co-

administration of the two vaccines in the primary series was lower than that observed after the booster dose.

The physician should be aware that the rate of febrile reactions is higher when Infanrix hexa is co-administered with a pneumococcal conjugate vaccine (PCV7, PCV10, PCV13) compared to that occurring following the administration of Infanrix hexa alone. These reactions were mostly moderate (less than or equal to 39°C) and transient.

The results of this SPNG-009 study confirm and are consistent with the above results. The benefit/risk balance remains favourable and there is no need for further actions.

☒ PAM fulfilled (all commitments fulfilled) - No further action required

☐ PAM not fulfilled (not all commitments fulfilled) and further action required:

Appendix

Case ID: - Serious Events: Hypotonia

This female subject was enrolled in the partially blind study 116485 (SPNG-009).On she received the1st, 2nd, 3rd and booster dose of either 11-valent pneumococcal polysaccharide protein D conjugate vaccine (11Pn-PD-DiT-CRM), 12-valent pneumococcal polysaccharide protein D conjugate vaccine (12Pn-PD-DiT-CRM), 10-valent pneumococcal polysaccharide protein D conjugate vaccine (Synflorix) coadministered with combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated polio, Haemophilus influenzae type b vaccine (Infanrix hexa)., four months after the 3rd dose of Blinded vaccine, four months after the 3rd dose of Infanrix hexa, this eight-month-old subject developed hypotonia. The subject was hospitalised and the event was disabling. The event was unresolved at time of reporting. The investigator considered that there was no reasonable possibility that the hypotonia may have been caused by investigational product and Infanrix hexa. The time to onset is pointing at other causes, no relation with a GSK product suspected.

Investigator Comments: Infant of 13 months derived from another hospital to study hypotonia (She was admitted on and discharged on). At 8 months is referred by her doctor to the other hospital for assessment of marked kyphoscoliosis and hypotonia (the patient was admitted on and she was discharged on). At that age does not get stable seating but head control (5 months) with predominantly distal hypotonia. On admission to study performs the following test: cranial MRI and column that are not pathological findings, blood chemistry (CPK 117 AST 40 ALT 16 LDH 256). EMG reported as systemic demyelinating peripheral motor neuropathy (VCM 8,53 m/s) and genetic study espinal muscular atrophy with negative results. After making the initial study is derived to our hospital for further test and performing additional evidence if necessary (genetic study). Comments The EMG is suggestive of peripheral motor neuropathy, but its just a sign, like hypotonia is a symptom. The final diagnosis remains unknown at this moment. Currently the patient has improved her clinical hypotonia, although it persists. Complementary studies have not been conclusive for a final diagnosis and continuous monitoring currently ongoing in our hospital. The time to onset is pointing at other causes, no relation with a GSK product suspected.

Case ID: - Serious Events: Hypotonic-hyporesponsive episode

This female subject was enrolled in the partially blind study 116485 (SPNG-009). On and, she received the 1st and 2nd dose of Pfizer's 13 valent pneumococcal vaccine (Prevenar 13) co-administered with combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated polio, Haemophilus influenzae type b vaccine (Infanrix hexa). On 12 days after the 1st dose of Prevnar 13, 12 days after the 1st dose of Infanrix hexa, this two-month-old subject developed hypotonic crisis. The subject was hospitalised. The event resolved on The investigator considered that there was no reasonable possibility that the hypotonic crisis may have been caused by Prevnar 13 and Infanrix hexa .

Investigator Comments: Patient with two months of age was hospitalized on due to a cerebral inhibition crisis in study. The subject had on episode of apnea 30 minutes before she arrival to the hospital. The duration of the episode was of 1 minute. The subject has no family history of neurological diseases. Her evolution has been favourable during the hospitalization. The subject was discharged on She will be subjected to a study of neurology. The patient has made brain ultrasound and a wakefulness and sleep EEG spontaneous that they have been normal. The neurologist will assess its evolution and raise apneas study if they recur. The patient is in good condition in the actuality. The event is a crisis of hypotonia during sleep. The testing was performed to reach this diagnosis. This event does not need treatment at present.

Case ID: - Serious Events: Febrile convulsions

On she received the 1st,2nd, 3rd and booster dose of Pfizer's 13 valent pneumococcal vaccine (Prevenar 13) co-administered with combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated polio, Haemophilus influenza type b vaccine (Infanrix hexa). On30 days after the 4th dose of Prevnar 13, 30 days after the 4th dose of Infanrix hexa, this 13-month-old subject developed febrile convulsion. The subject was hospitalised. The subject was treated with paracetamol. The event resolved on

The investigator considered that there was no reasonable possibility that the febrile convulsion may have been caused by Prevnar 13 and Infanrix hexa. This subject developed febrile convulsion 30 days after the 4th dose of Prevnar 13 (non GSK), 30 days after the 4th dose of Infanrix hexa. The convulsion was probably caused by the fever, a relation with Infanrix hexa is unlikely, although febrile convulsion is a listed event for the vaccine.

In the SmPC, different wordings address the increased risk of certain SAEs related to concomitant administration of Pneumococcal vaccine and Infanrix hexa.

4.4 Warnings

The physician should be aware that the rate of febrile reactions is higher when Infanrix hexa is co-administered with a pneumococcal conjugate vaccine (PCV7, PCV10, PCV13), or with a measles-mumps-rubella-varicella (MMRV) vaccine, compared to that occurring following the administration of Infanrix hexa alone. These reactions were mostly moderate (less than or equal to 39°C) and transient (see sections 4.5 and 4.8).

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If any of the following events are known to have occurred in temporal relation to receipt of pertussis-containing vaccine, the decision to give further doses of pertussis-containing vaccines should be carefully considered:

☐ Temperature of ☐40.0°C within 48 hours, not due to another identifiable cause;

☐ Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination;

☐ Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours of vaccination;

☐ Convulsions with or without fever, occurring within 3 days of vaccination.

There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks.

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Increased reporting rates of convulsions (with or without fever) and hypotonic hyporesponsive episode (HHE) were observed with concomitant administration of Infanrix hexa and Prevenar 13 (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Infanrix hexa can be given concomitantly with pneumococcal conjugate vaccine (PCV7, PCV10 and PCV13), meningococcal serogroup C conjugate vaccine (CRM197 and TT conjugates), meningococcal serogroups A, C, W-135 and Y conjugate vaccine (TT conjugate), oral rotavirus vaccine and measles-mumps-rubella-varicella (MMRV) vaccine.

Data have shown no clinically relevant interference in the antibody response to each of the individual antigens, although inconsistent antibody response to poliovirus type 2 in co-administration with Synflorix was observed (seroprotection ranging from 78% to 100%) and the immune response rates to the PRP (Hib) antigen of Infanrix hexa after 2 doses given at 2 and 4 months of age were higher if co-administered with a tetanus toxoid conjugate pneumococcal or meningococcal vaccine (see section 5.1). The clinical relevance of these observations remains unknown.

4.8 Experience in co-administration:

Analysis of post-marketing reporting rates suggests a potential increased risk of convulsions (with or without fever) and HHE when comparing groups which reported use of Infanrix hexa with Prevenar 13 to those which reported use of Infanrix hexa alone.

In clinical studies in which some of the vaccinees received Infanrix hexa concomitantly with Prevenar (PCV7) as a booster (4th) dose of both vaccines, fever ≥ 38.0°C was reported in 43.4% of infants receiving Prevenar and Infanrix hexa at the same time as compared to 30.5% of infants receiving the hexavalent vaccine alone. Fever ≥39.5°C was observed in 2.6% and 1.5% of infants receiving Infanrix hexa with or without Prevenar, respectively (see sections 4.4 and 4.5). The incidence and severity of fever following co-administration of the two vaccines in the primary series was lower than that observed after the booster dose.

Data from clinical studies show similar incidences of fever when Infanrix hexa is co-administered with other pneumococcal saccharide conjugated vaccine.