15 December 2016
EMA/793306/2016
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/P46/121

Note

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

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1. Introduction

On 27 June 2016, the MAH submitted the final study report of a candidate 10-valent pneumococcal conjugate vaccine safety study in which Infanrix hexa was coadministered, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

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

Infanrix hexa Stand-alone submission of study results in the paediatric population - SPNG-003

1.1. Steps taken for the assessment

Submission date:	13/07/2016
Start of procedure:	15/08/2016
CHMP Rapporteur's preliminary assessment report circulated on:	30/11/2016
CHMP Rapporteur's updated assessment report circulated on:	n/a
CHMP outcome:	15/12/2016

2. Assessment of the post-authorisation measure SPNG-003 (113994) study – Article 46

This study was a phase II, randomized, controlled, multicentre, 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 co-administered with DTPa-HBV-IPV/Hib vaccine during the first 6 months of life and as a booster dose at 12-15 months of age. Following identification of new subjects receiving concomitant vaccine(s) outside the protocol-defined intervals, there were changes in the according-to-protocol cohort for immunogenicity; therefore the decision has been made to re-analyse all available data from the primary epoch and to present the results in this Study Report, along with reactogenicity/safety and immunogenicity data of the booster epoch and immunogenicity results of the co-administered DTPa-HBV-IPV/Hib vaccine for both epochs. Note that for the confirmatory objectives, the results of first analysis (included in the SPNG-003 (113994) Report (Epoch 001) Amendment 1 dated 09 January 2014) are considered final and are presented below.

Methods

Study Design

First primary objective was 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 10Pn-PD-DiT (Synflorix), ***when coadministered with DTPa-HBV-IPV/Hib***

***vaccine (Infanrix hexa) in infants**, **in terms of post-primary immunization febrile reactions with fever > 40.0° C (rectal temperature) with causal relationship to vaccination**.*

The **second primary objective** (sequential)[1] was 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 10Pn-PD-DiT (Synflorix), ***when coadministered with DTPa-HBV-IPV/Hib vaccine (Infanrix hexa) 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:

Each 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%.

Fig. 1 Study Design

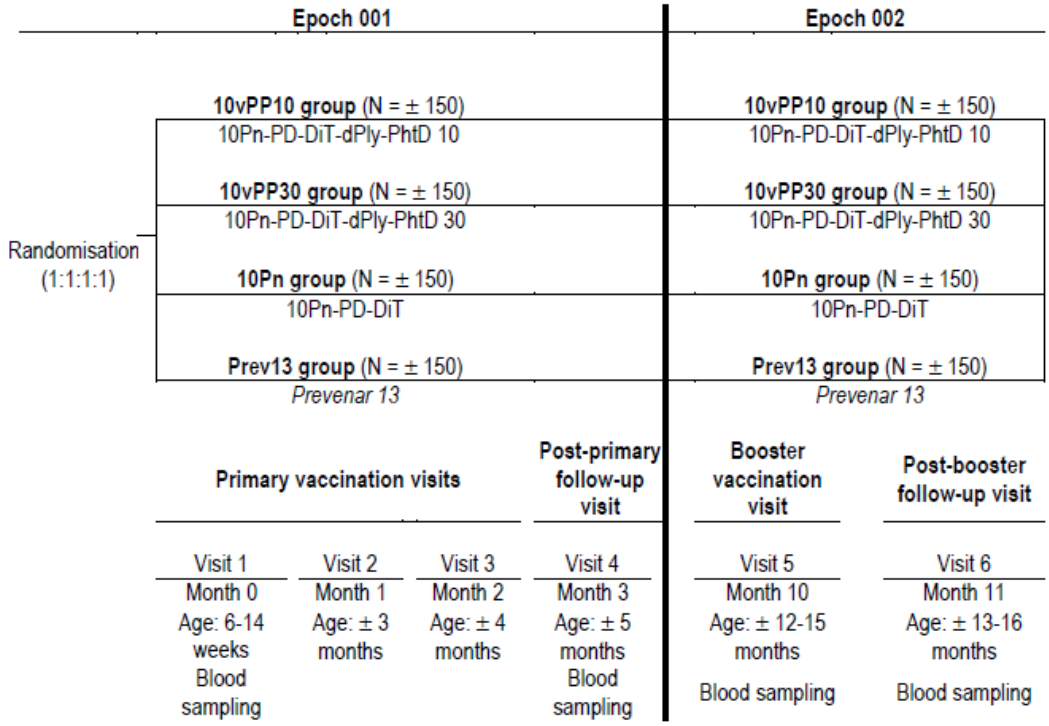

Table 1 illustrates the power to rule out an increase according to various incidences in the control group. Study Population was a healthy male or female, between and including 6 and 14 weeks (42-104 days) of age at the time of the first vaccination, born after a gestation period of 36 to 42 weeks inclusive.

Table 1. Power to rule out the null hypothesis that the increase in the percentage of subjects with fever greater than 40.0 degree Celsius (rectal temperature) with causal relationship to vaccination (10Pn+Proteins group as compared to the 10Pn group) is above a pre-defined boundary (delta) (N=150 in each group)

[1] 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.

Non-inferiority N = 150/150 subjects in 10Pn+Proteins / 10Pn groups				
Endpoint	**% in 10Pn group***	**% in 10Pn+Proteins group**	**δ****	**Power*****
Fever > 40.0°C (rectal temperature) with causal relationship to vaccination	0.5%	0.5%	5.3%	99.6%
	1.0%	1.0%	5.5%	97.2%
	1.5%	1.5%	5.8%	93.6%
	2.0%	2.0%	6.0%	90.0%

*Based on previous experiences with 10Pn-PD-DiT vaccine, incidence of fever > 40.0°C (rectal temperature) with causal relationship to vaccination varied from 0.0% to 1.4% (reported in 10PN-PD-DIT-003 (105554) study)
**These boundaries have been obtained from a linear curve (5%+0.5*rate in the control group) based on the hypothesis that a 3-fold increase and a 10% increase for an incidence rate of 2% and 10%, respectively, were considered acceptable.
***Power obtained using Kem Phillips' approach [Phillips, 2003] to derive P-value for ruling out an increase above the boundary. The null hypothesis is rejected for a one-sided P-value < 5.0%.

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.

Evaluation of the immune responses to components of the co-administered DTPa-HBV-IPV/Hib vaccine, one month post-dose 3, prior to and one month post-booster.

- Anti-tetanus, anti-diphtheria, anti-pertussis toxoid (PT), anti-filamentous haemagglutinin (FHA), anti-pertactin (PRN), anti-hepatitis B surface antigen (HBs) and anti-polyribosylribitol phosphate (PRP) antibody concentrations.
- Anti-poliovirus type 1, 2 and 3 titres.

Statistical methods:

Demography

- Demographic characteristics (age, gender, geographic ancestry) of each study cohort were tabulated per group.
- The mean age (plus range and standard deviation) of subjects at each vaccination was calculated.
- The distribution of subjects enrolled among the study centres was tabulated.

Synopsis Table 1: Study population – Primary Epoch (Total vaccinated cohort [TVC])				
Number of subjects	**10vPP10**	**10vPP30**	**10Pn**	**Prev13**
Planned, N	150	150	150	150
Randomised, N (TVC)	146	142	145	142
Completed up to Visit 4, n (%)	146 (100)	142 (100)	144 (99.3)	142 (100)
Demographics	**10vPP10**	**10vPP30**	**10Pn**	**Prev13**
N (TVC)	146	142	145	142
Females: Males	65:81	67:75	70:75	66:76
Mean age at dose 1, weeks (SD)	10.3 (2.5)	10.1 (2.7)	10.1 (2.6)	10.2 (2.6)
Median age at dose 1, weeks (minimum, maximum)	10 (6, 14)	10 (4, 14)	10 (6, 14)	11 (6, 14)
White - Caucasian / European heritage, n (%)	144 (98.6)	140 (98.6)	144 (99.3)	141 (99.3)
White - Arabic / North African heritage, n (%)	2 (1.4)	0	0	0
Other*, n (%)	0	2 (1.4)	1 (0.7)	1 (0.7)
10vPP10 = 10Pn-PD-DiT vaccine combined with the pneumococcal protein vaccine containing the pneumococcal proteins dPly and PhtD (10µg-10µg), 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 (30µg-30µg), 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 *Other = Gypsy				

Synopsis Table 2: Study population – Booster Epoch (Total vaccinated cohort for booster)				
Number of subjects	**10vPP10**	**10vPP30**	**10Pn**	**Prev13**
Planned for Visit 5, N	150	150	150	150
Returning for Visit 5, N (TVC for booster)	144	140	140	140
Completed, n (%)	144 (100)	140 (100)	140 (100)	140 (100)
Demographics	**10vPP10**	**10vPP30**	**10Pn**	**Prev13**
N (TVC for booster)	144	140	140	140
Females: Males	64:80	66:74	66:74	65:75
Mean age, months (SD)	12.4 (0.6)	12.3 (0.5)	12.3 (0.6)	12.3 (0.6)
Median age, months (minimum, maximum)	12.0 (11, 15)	12.0 (11, 14)	12.0 (10, 15)	12.0 (11, 15)
White - Caucasian / European heritage, n (%)	142 (98.6)	138 (98.6)	140 (100)	139 (99.3)
White - Arabic / North African heritage, n (%)	2 (1.4)	0	0	0
Other*, n (%)	0	2 (1.4)	0	1 (0.7)

Safety and reactogenicity

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

1. *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%.

Assessor's comment

Based on previous experiences with 10Pn-PD-DiT vaccine, incidence of fever >40.0°C (rectal temperature) with causal relationship to vaccination varied from 0.0% to 1.4% (reported in 10PN-PD-DIT-003 (105554) study).

In the Infanrix hexa SmPC last update (22 december 2015), the following wordings are presented :

Section 4.4

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).

Section 4.8

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.

Meanwhile, in the SPNG003 study protocol the MAH addresses the causal relationship by the following :

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of general AEs to the individual vaccines administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines.

....

Causality of all other AEs was to be assessed by the investigator using the following question: Was there a reasonable possibility that the AE might have been caused by the investigational product?

NO: The AE was not causally related to administration of the study vaccine(s). There were other, more likely causes and administration of the study vaccine(s) was not suspected to have contributed to the AE.

YES: There was a reasonable possibility that the vaccine(s) contributed to the AE.

Concerning the previous paragraph on Safety/Reactogenicity, it is not clear how the causal relationship of fever >40°C to vaccination after the primo-vaccination was assessed. The MAH is requested to discuss this methodology concern. The Applicant should present and discuss the number of patients considered to develop fever causally related to vaccination versus the number of patients the fever non-causally related to vaccination. The causal factors for fever other than vaccination should be discussed for the latter patients.

2. *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.

Immunogenicity

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

1. *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.

2. *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[2].
   - 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[3]/antigen was displayed using tables and/or reverse cumulative distribution curves (RCCs).

Results

Safety results:

1. *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.

[2] 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.

[3] 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.

- The first primary confirmatory objective to demonstrate that the 10Pn-PD-DiT-dPly-PhtD 10 vaccine is non-inferior to the 10Pn-PD-DiT vaccine in terms of post-primary immunisation febrile reactions with fever > 40.0°C (rectal temperature) considered by the investigator to be causally related to vaccination was reached as the 1-sided p-value was below 5% (p-value = 0.003).
- The second primary confirmatory objective (sequential) was the same criterion as the first one but considering the 10Pn-PD-DiT-dPly-PhtD 30 vaccine compared to the 10Pn-PD-DiT vaccine. It was reached as the first primary objective was reached and the one sided p-value for the second primary objective was below 5% (p-value = 0.003).

Synopsis Table 3: Difference between 10vPP10 and 10Pn groups in % of subjects reporting fever > 40.0°C with causal relationship to vaccination after at least one primary dose (Epoch 001) (Total vaccinated cohort)

							Difference in percentage (10vPP10 minus 10Pn)			
	10vPP10			10Pn				95% CI		
Symptoms	N	n	%	N	n	%	%	LL	UL	P-value
Overall/subject										
Fever (Rectal) > 40.0 (°C) & Related	146	0	0.0	144	0	0.0	0.00	-2.61	2.57	0.003

10vPP10 = 10Pn-PD-DiT vaccine combined with the pneumococcal protein vaccine containing the pneumococcal proteins dPly and PhtD (10µg-10µg), co-administered with DTPa-HBV-IPV/Hib
10Pn = 10Pn-PD-DiT vaccine co-administered with DTPa-HBV-IPV/Hib
N = Number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting a specified symptom
95% CI = Standardized asymptotic 95% confidence interval , LL = Lower Limit, UL = Upper Limit
P-value = one-sided p-value computed using Kem Philips' approach for ruling out an increase in the percentage of subjects reporting fever with rectal temperature greater than 40.0°C with causal relationship to vaccination above the boundary expressed as 5%+0.5*rate in the control group

Synopsis Table 4: Difference between 10vPP30 and 10Pn groups in % of subjects reporting fever > 40.0°C with causal relationship to vaccination after at least one primary dose (Epoch 001) (Total vaccinated cohort)

							Difference in percentage (10vPP30 minus 10Pn)			
	10vPP30			10Pn				95% CI		
Symptoms	N	n	%	N	n	%	%	LL	UL	P-value
Overall/subject										
Fever (Rectal) > 40.0 (°C) & Related	142	0	0.0	144	0	0.0	0.00	-2.61	2.64	0.003

10vPP30 = 10Pn-PD-DiT vaccine combined with the pneumococcal protein vaccine containing the pneumococcal proteins dPly and PhtD (30µg-30µg), co-administered with DTPa-HBV-IPV/Hib
10Pn = 10Pn-PD-DiT vaccine co-administered with DTPa-HBV-IPV/Hib
N = Number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting a specified symptom
95% CI = Standardized asymptotic 95% confidence interval , LL = Lower Limit, UL = Upper Limit
P-value = one-sided p-value computed using Kem Philips' approach for ruling out an increase in the percentage of subjects reporting fever with rectal temperature greater than 40.0°C with causal relationship to vaccination above the boundary expressed as 5%+0.5*rate in the control group

2. *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).

Immunogenicity results:

Primary epoch

One month post-primary vaccination:

- *All subjects in all groups (except one in the 10vPP30 group) had anti-D antibody concentrations ≥0.1 IU/mL.*
- *All subjects in all groups had anti-T antibody concentrations ≥0.1 IU/mL.*
- *All subjects in all groups had anti-PT (except one in the Prev13 group), anti-FHA and anti-PRN antibody concentrations ≥ 5 EL.U/mL.*
- *98.3%, 96.3%, 100% and 96.7% of subjects in the 10vPP10, 10vPP30, 10Pn and Prev13 groups, respectively, had anti-PRP antibody concentrations ≥0.15 µg/mL.*
- *The adjusted percentage of seroprotected subjects against HBs was 98.0%, 95.3%, 100% and 97.9% in the 10vPP10, 10vPP30, 10Pn and Prev13 groups, respectively.*
- *For each of the 3 polio antigens, at least 95.6%, 100%, 95.3% and 100% of subjects in the 10vPP10, 10vPP30, 10Pn and Prev13 groups, respectively, had anti-polio titres ≥ 8.*

Booster epoch

One month post-booster vaccination:

- *All subjects in all groups had anti-D and anti-T antibody concentrations ⩾ 0.1 IU/mL.*
- *All subjects in all groups had anti-PT, anti-FHA and anti-PRN antibody concentrations ⩾ 5 EL.U/mL.*
- *All subjects in all groups (except one in the Prev13 group) had anti-PRP antibody concentrations ⩾ 0.15 µg/mL.*
- *All subjects in all groups (except one in each of the 10vPP10 and Prev13 groups) had anti-HBs antibody concentrations ≥10 mIU/mL.*
- *For each of the 3 polio antigens, all subjects in all groups (except one in the 10vPP30 group for anti-polio 1) had anti-polio titres ≥8.*

Discussion & Conclusion:

The sequential primary confirmatory objectives of this study were reached: Vaccine 10Pn-PD-DiT-dPly- PhtD 10 vaccine and 10Pn-PD-DiT-dPly-PhtD 30 vaccine given as 3-dose primary vaccination co-administered with DTPa-HBV-IPV/Hib vaccine did not induce more febrile reactions (fever > 40.0°C (rectal temperature)) with causal relationship to vaccination than in the control group receiving 10Pn-PD-DiT vaccine co-administered with DTPa-HBV-IPV/Hib vaccine, in terms of an increase above the boundary 5% + half the incidence in the control group. 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.

The secondary confirmatory objective was reached: superiority of the 10Pn-PD-DiT-dPly-PhtD 30 vaccine formulation to the 10Pn-PD-DiT-dPly-PhtD 10 vaccine formulation in terms of post-dose 3 immune responses to pneumococcal proteins Ply and PhtD in infants was demonstrated. The results showed that the 10Pn-PD-DiT-dPly-PhtD 10 and 10Pn-PD-DiT-dPly-PhtD 30 vaccines induced immune responses in infants to all vaccine antigens (i.e. Ply and PhtD pneumococcal proteins, pneumococcal serotype-specific capsular polysaccharides and protein D). The immune response to pneumococcal serotype-specific capsular polysaccharides and protein D did not seem to be altered by addition of pneumococcal proteins dPly and PhtD in the combined protein and conjugate vaccine recipients compared to 10Pn-PD-DiT vaccine recipients. Immunogenicity of the co-administered vaccine Infanrix hexa appeared unaffected and assessment of the safety and reactogenicity profile did not raise any concerns.

At least one non-fatal SAE was reported for 56 out of 575 subjects (12 in the 10vPP10 group, 9 in the 10vPP30 group, 21 in the 10Pn group and 14 in the Prev13 group) during the primary epoch and for 4 out of 564 subjects (one in the 10vPP10 group and 3 in the Prev13 group) during the booster epoch. One SAE (hypotonic-hyporesponsive episode in subject in the 10Pn group on the day of vaccination dose 1) was assessed by the investigator to be causally related to vaccination.

In conclusion, in this study SPNG-003 [EudraCT 2010-019730-27] , the 10Pn-PD-DiT-dPly-PhtD 10 and 10Pn-PD-DiT-dPly-PhtD 30 vaccine formulations were generally well-tolerated and immunogenic and was well tolerated with co-administration of Infanrix Hexa.

Assessor's comments

The MAH has reviewed the immunogenicity and safety results of the study SPNG003.

The immunogenicity data were in line with the current PI for Infanrix hexa.

For the incidences of pain, redness and swelling related to the Infanrix hexa injection site after primo or booster immunization, they were in line with the currently PI wherein they are listed as "very common".

For the incidences of general solicited adverse events (i.e irritability, loss of appetite and fever (>38°C)) related to the Infanrix hexa injection after primo or booster immunization, they were in line with the currently PI wherein they are listed as "very common". Furthermore, the MAH considered that the incidence of "drowsiness" was in line with the incidence "very common" listed in the PI of Synflorix and higher than the incidence of "drowsiness" listed in the PI of Infanrix hexa.

The MAH should explain to which adverse events it is referring as the term "drowsiness" is not listed in the current PI of Infanrix hexa (see below) and to which general solicited adverse event(s) the term drowsiness could be related to the listed adverse events listed in the current SmPC section 4.8.

In conclusion, in this study SPNG-003 [EudraCT 2010-019730-27] , the 10Pn-PD-DiT-dPly-PhtD 10 and 10Pn-PD-DiT-dPly-PhtD 30 vaccine formulations were generally well-tolerated and immunogenic and was well tolerated with co-administration of Infanrix Hexa. Immunogenicity of the co-administered vaccine Infanrix hexa appeared unaffected and assessment of the safety and reactogenicity profile did

not raise any new safety concerns. The Company concluded that currently no changes to the Product Information of Infanrix hexa were needed as the benefit/risk remained favourable, which is acceptable.

The following drug-related adverse reactions were reported in clinical studies (data from more than 16,000 subjects) and during post-marketing surveillance.

System Organ Class	Frequency	Adverse events
Infections and infestations	Uncommon	Upper respiratory tract infection
Blood and lymphatic system disorders	Rare	Lymphadenopathy[2], thrombocytopenia[2]
Immune system disorders	Rare	Anaphylactic reactions[2], anaphylactoid reactions (including urticaria)[2] Allergic reactions (including pruritus)[2]
Metabolism and nutrition disorders	Very common	Appetite lost
Psychiatric disorders	Very common	Crying abnormal, irritability, restlessness
	Common	Nervousness
Nervous system disorders	Uncommon	Somnolence
	Rare	Collapse or shock-like state (hypotonic-hyporesponsive episode)[2]
	Very rare	Convulsions (with or without fever)
Respiratory, thoracic and mediastinal disorders	Uncommon	Cough
	Rare	Bronchitis, apnoea[2] [see section 4.4 for apnoea in very premature infants (≤ 28 weeks of gestation)]
Gastrointestinal disorders	Common	Diarrhoea, vomiting
Skin and subcutaneous tissue disorders	Rare	Rash, Angioedema[2]
	Very rare	Dermatitis
General disorders and administration site conditions	Very common	Fever ≥ 38°C, local swelling at the injection site (≤ 50 mm), fatigue, pain, redness
	Common	Fever >39.5°C, injection site reactions, including induration, local swelling at the injection site (> 50 mm)[1]
	Uncommon	Diffuse swelling of the injected limb, sometimes involving the adjacent joint[1]
	Rare	Swelling of the entire injected limb[1, 2], extensive swelling reactions[2], injection site mass[2], injection site vesicles[2]

[1] Children primed with acellular pertussis vaccines are more likely to experience swelling reactions after booster administration in comparison with children primed with whole cell vaccines. These reactions resolve over an average of 4 days.
[2] Adverse reactions from spontaneous reporting.

- Experience in co-administration:

Analysis of postmarketing 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.

3. Rapporteur's overall conclusion

The Rapporteur agrees and endorses the discussion and conclusion of the MAH to the RSI..

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

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

RSI:

1. ***it is not clear how the causal relationship of fever >40°C to vaccination after the primo-vaccination was assessed. The MAH is requested to discuss this methodology concern. The Applicant should present and discuss the number of patients considered to develop fever causally related to vaccination versus the number of patients the fever non-causally related to vaccination. The causal factors for fever other than vaccination should be discussed for the latter patients.***
2. *For the incidences of general solicited adverse events (i.e irritability, loss of appetite and fever (>38°C)) related to the Infanrix hexa injection after primo or booster immunization, they were in line with the currently PI wherein they are listed as "very common". Furthermore, the MAH considered that the incidence of "drowsiness" was in line with the incidence "very common" listed in the PI of Synflorix and higher than the incidence of "drowsiness" listed in the PI of Infanrix hexa.*

   The MAH should explain to which adverse events it is referring as the term "drowsiness" is not listed in the current PI of Infanrix hexa and to which general solicited adverse event(s) the term "drowsiness" could be referred to in the adverse events listed in the current SmPC section 4.8.

<u>Assessment of the responses to the RSI :</u>

1. ***it is not clear how the causal relationship of fever >40°C to vaccination after the primo-vaccination was assessed. The MAH is requested to discuss this methodology concern. The Applicant should present and discuss the number of patients considered to develop fever causally related to vaccination versus the number of patients the fever non-causally related to vaccination. The causal factors for fever other than vaccination should be discussed for the latter patients.***

A causality assessment is usually required for adverse event cases in clinical trials. In study SPNG-003, it was the investigator's responsibility to assess the causality of any adverse event to the investigational product, as detailed in the clinical trial protocol. Moreover, the investigator was also

instructed to consult the Investigator Brochure and/or PI for marketed products in the determination of the causality assessment.

Extract of the protocol:

"*The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator will use clinical judgement to determine the relationship. Alternative plausible causes, based on natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator will also consult the Investigator Brochure and/or Product Information for marketed products, in the determination of his/her assessment.*

…

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of general AEs to the individual vaccines administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines.

…

All solicited local (injection site) reactions will be considered causally related to vaccination. Causality of all other AEs should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE may have been caused by the investigational product?

NO : The AE is not causally related to administration of the study vaccine(s). There are other, more likely causes and administration of the study vaccine(s) is not suspected to have contributed to the AE.

YES : There is a reasonable possibility that the vaccine(s) contributed to the AE. "

The number of patients considered to develop fever causally related to vaccination versus the number of patients for whom the fever was considered non-causally related to vaccination, following each dose, overall/dose and overall/subject reported during the 7- day post-vaccination period are detailed in Table 25 of the MAH responses to the RSI ; and the incidence of fever (and other solicited general AEs) following each dose, overall/dose and overall/subject reported during the 4-day post-vaccination period are detailed in Table 7.25 in the Clinical Study Report.

As expected, the majority of fever cases (>72% of reported fever cases following each dose and overall) was assessed by the investigator as 'related' to either vaccine or vaccination.

According to the protocol, the investigator had to consider underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product; however, the investigator was not requested to provide the more likely cause of fever in case the fever was assessed as 'not related' to study vaccine or vaccination. Therefore the Company cannot comment on other plausible causal factors of fever being assessed as not related to the vaccine/vaccination.

Assessor's comment

The methodology is acceptable and the issue is considered resolved.

2. ***The MAH should explain to which adverse events it is referring as the term "drowsiness" is not listed in the current PI of Infanrix hexa and to which general solicited adverse event(s) the term "drowsiness" could be referred to in the adverse events listed in the current SmPC section 4.8.***

The Company acknowledges that the term DROWSINESS is not listed in the PI of *Infanrix hexa*. However, the PI of *Infanrix hexa* lists the MedDRA Preferred Term (PT) SOMNOLENCE with a frequency 'uncommon', as observed in clinical trials with *Infanrix hexa*.

It is to be noted that the PT SOMNOLENCE comprises several Lower Level Terms (LLTs) amongst which DROWSINESS. In the SPNG-003 study the event DROWSINESS is a solicited general adverse event. Any possible term of SOMNOLENCE (e.g. SLEEPY) would therefore be reported under the solicited event DROWSINESS.

In its conclusions, the Company therefore considered that the incidence of DROWSINESS as observed in clinical trial SPNG-003 was in line with the incidence 'very common' as listed in the PI of *Synflorix* and was higher than the incidence of SOMNOLENCE (which includes SOMNOLENCE and DROWNSINESS) as listed in the PI of *Infanrix hexa*.

Assessor's comment

The issue is considered resolved.

The Rapporteur agrees and endorses the discussion and conclusion of the MAH on the RSI. The PAM is considered fulfilled.

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

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