Amsterdam, 20 July 2023
EMA/361395/2023
Human Medicines 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/P46/135

Note

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

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1. Introduction

On 20 April 2023, the MAH submitted a completed paediatric study for GSK's Infanrix hexa (DTPa-HBV-IPV/Hib) vaccine, in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study DTPA-HBV-IPV-141 'A Phase IV, single-blind, randomised, controlled, multi-country study to evaluate the immunogenicity and safety of GSK's Infanrix Hexa (DTPa-HBV-IPV/Hib) vaccine versus MCM Vaccine BV's Vaxelis (DTaP5-HBV-IPVHib) vaccine, when administered intramuscularly according to a 2, 4, and 12 months schedule in healthy infants and toddlers' (protocol number 212645, trial registry number 2019-002988-10) is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

A list of investigational products used in this study are presented in Table 1.

Table 1. Treatments Administered (Source: Report Body Table 2)

Study Treatment	***Infanrix hexa***		***Vaxelis***	***Prevenar 13***
Vaccine/ Product	**DTPa-HBV-IPV**	**Hib**	***Vaxelis***	***Prevenar 13***
Presentation	Suspension for injection, Syringe	Powder for suspension for injection, Vial	Suspension for injection, Syringe	Suspension for injection, Syringe
Number of Doses	3		3	3
Dose Volume	~0.5 mL[a]		0.5 mL	0.5 mL
Route of Administration	IM injection, right thigh		IM injection, right thigh	IM injection, left thigh
Dosing Instructions	Refer to and follow the SmPC or directions for handling and administration.		Refer to and follow the SmPC or directions for handling and administration.	Refer to and follow the SmPC or directions for handling and administration.
Packaging and Labelling	Study treatment was provided in a carton, containing 1 vial and 1 prefilled syringe without needles. Each carton was clinically labeled as required per country requirement.		Study treatment was provided in a carton, 1 prefilled syringe without needles. Each carton was clinically labeled as required per country requirement.	Study treatment was provided in a carton, 1 prefilled syringe without needles. Each carton was clinically labeled as required per country requirement.
Manufacturer	GSK Biologicals		MCM Vaccine BV	Pfizer
QA Release for Study	GSK Biologicals		GSK Biologicals	GSK Biologicals

Study Treatment	*Infanrix hexa*		*Vaxelis*	*Prevenar 13*
Vaccine/ Product	**DTPa-HBV-IPV**	**Hib**	*Vaxelis*	*Prevenar 13*
Dosage Formulation	Diphtheria toxoid (≥30 I.U.) adsorbed on aluminium hydroxide; Tetanus toxoid (≥40 I.U.) adsorbed on aluminium hydroxide; Bordetella pertussis antigens-Pertussis toxoid (25 µg) adsorbed on aluminium hydroxide; Bordetella pertussis antigens-Filamentous Haemagglutinin (FHA) (25 µg) adsorbed on aluminium hydroxide; Bordetella pertussis antigens-Pertactin (PRN) (8 µg) adsorbed on aluminium hydroxide; Hepatitis B surface antigen (HBs) (10 µg) adsorbed on aluminium phosphate; Poliovirus (inactivated) (IPV) type 1 (Mahoney strain) (40 DAgU);	Haemophilus influenzae type b polysaccharide (polyribo-sylribitol phosphate, PRP) (10 µg) conjugated to tetanus toxoid (~25 µg) adsorbed on aluminium phosphate; Aluminium phosphate; Lactose	Diphtheria toxoid (not less than 20 I.U.) adsorbed on aluminium phosphate; Tetanus toxoid (not less than 40 µg I.U.) adsorbed on aluminium phosphate; Bordetella pertussis antigens - Pertussis toxin (20 µg) adsorbed on aluminium phosphate; Bordetella pertussis antigens - Filamentous haemagglutinin (20 µg) adsorbed on aluminium phosphate; Bordetella pertussis antigens - Pertactin (3 µg) adsorbed on aluminium phosphate; Bordetella pertussis antigens - Fimbriae type 2 and 3 (5 µg) adsorbed on aluminium phosphate; Hepatitis B surface antigen (10 µg) adsorbed on amorphous aluminium hydroxyphosphate sulfate; Poliovirus (Inactivated) Type 1 (Mahoney) (40 D antigen units); Poliovirus (Inactivated) Type 2 (MEF-1) (8 D antigen units); Poliovirus (Inactivated) Type 3 (Saukett) (32 D antigen units); Haemophilus influenzae type b polysaccharide (Polyribosylribitol Phosphate) (3 µg) conjugated to meningococcal protein (50 µg) adsorbed on amorphous aluminium hydroxyphosphate sulfate; Aluminium phosphate (0.17 mg	Pneumococcal polysaccharide serotype 1 (2.2 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Pneumococcal polysaccharide serotype 3 (2.2 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Pneumococcal polysaccharide serotype 4 (2.2 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Pneumococcal polysaccharide serotype 5 (2.2 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Pneumococcal polysaccharide serotype 6A (2.2 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Pneumococcal polysaccharide serotype 6B (4.4 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Pneumococcal polysaccharide serotype 7F (2.2 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Pneumococcal polysaccharide serotype 9V (2.2 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Pneumococcal polysaccharide serotype 14 (2.2 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Pneumococcal polysaccharide serotype 18C (2.2 µg) conjugated to

Study Treatment	*Infanrix hexa*		*Vaxelis*	*Prevenar 13*
Vaccine/ Product	**DTPa-HBV-IPV**	**Hib**	*Vaxelis*	*Prevenar 13*
	Poliovirus (inactivated) (IPV) type 2 (MEF-1 strain) (8 DAgU); Poliovirus (inactivated) (IPV) type 3 (Saukett strain) (32 DAgU); Aluminium hydroxide ($Al(OH)_3$)/Aluminium phosphate ($AlPO_4$) (0.7 mg Al^{3+}); Medium 199; Sodium chloride; Water for injections q.s. 0.5 mL		Al^{3+}); Amorphous aluminium hydroxyphosphate sulfate (0.15 mg Al^{3+}); Glutaraldehyde (Traces); Formaldehyde (Traces); Neomycin (Traces); Streptomycin (Traces); Polymyxin B (Traces); Sodium phosphate; Water for injections q.s. 0.5 mL	CRM_{197} carrier protein, adsorbed on aluminium phosphate; Pneumococcal polysaccharide serotype 19A (2.2 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Pneumococcal polysaccharide serotype 19F (2.2 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Pneumococcal polysaccharide serotype 23F (2.2 µg) conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate; Total CRM_{197} carrier protein (32 µg [EU]/34 µg [US]); Aluminium phosphate (0.125 mg Al^{3+}); Sodium chloride; Succinic acid; Polysorbate 80; Water for injections q.s. 0.5 mL

Abbreviations: CRM=cross reactive material; Hib=*Haemophilus influenzae* type b; IM=intramuscular; IPV=inactivated poliovirus vaccine; SmPC=summary of product characteristics.

Subjects were observed closely for at least 30 minutes after the administration of the vaccines. Appropriate medical treatment was readily available during the observation period in case of anaphylaxis and/or syncope.

Infanrix hexa and *Vaxelis* were administered IM to the right thigh; *Prevenar 13* was administered to the left thigh.

[a] Full volume after reconstitution (approximately 0.5 mL) to be administered.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

Study 212645 -DTPA-HBV-IPV-141: "A Phase IV, single-blind, randomised, controlled, multi-country study to evaluate the immunogenicity and safety of GSK's Infanrix hexa (DTPa-HBV-IPV/Hib) vaccine versus MCM Vaccine BV's Vaxelis (DTaP5-HBV-IPV-Hib) vaccine, when administered intramuscularly according to a 2, 4, and 12 months schedule in healthy infants and toddlers."

2.3.2. Clinical study

Study 212645 -DTPA-HBV-IPV-141: "A Phase IV, single-blind, randomised, controlled, multi-country study to evaluate the immunogenicity and safety of GSK's Infanrix hexa (DTPa-HBV-IPV/Hib) vaccine versus MCM Vaccine BV's Vaxelis (DTaP5-HBV-IPV-Hib) vaccine, when administered intramuscularly according to a 2, 4, and 12 months schedule in healthy infants and toddlers."

Description

Infanrix hexa was registered in Europe in 2000 and is currently licensed for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and disease caused by *Haemophilus influenzae* type b (Hib) in more than 90 countries worldwide.

Barbour et al. (Emerg Infect Dis. 1996;2:176-182) reported that the acquisition of Hib or the prolonged Hib carriage in the nasopharynx may occur only below a threshold concentration of serum or mucosal anti-polyribosylribitol phosphate (PRP) antibodies. Other literature reports that high anti-PRP antibody concentrations above the established correlates of clinical protection (0.15 µg/mL for short-term and 1.0 µg/mL for long-term protection) may be needed to reduce Hib nasopharyngeal colonisation and carriage. Also, the protection against colonisation seems to be well correlated with anti-PRP antibody concentrations ≥ 5 μg/mL at 1-month following the third vaccine dose in infants. Comparative data on the proportion of subjects reaching the 5 µg/mL titre after Infanrix hexa or Vaxelis are not publicly available.

This phase IV, single-blind, randomised, controlled, multi-country study was intended to show both the non-inferiority of Infanrix hexa versus Vaxelis, as well as the superiority of Infanrix hexa versus Vaxelis in terms of anti-PRP geometric mean concentrations (GMCs) and proportion of subjects with antibody concentrations greater than or equal to a threshold of 5 µg/mL 1-month after the booster dose.

Methods

Study participants

Inclusion criteria:

- Subjects' parent(s)/ LAR(s) who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., return for follow-up visits)
- Written or witnessed/thumb printed informed consent obtained from the parent(s)/LAR(s) of the subject prior to performing any study specific procedure.
- A male or female child between and including 6 and 12 weeks of age (42 to 84 days) at the time of the first vaccination.

- Subject born after at least 37 weeks of gestation.
- Healthy subjects as established by the investigator based on medical history and the clinical examination before entering into the study.

Exclusion criteria:

Medical conditions

- Any clinical condition that, in the opinion of the investigator, might pose any risk to the subject due to participation in the study. As with other vaccines, administration of Infanrix hexa should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection is not a contraindication.
- Known history of diphtheria, tetanus, pertussis, HBV, poliomyelitis and Hib diseases since birth.
- History of any reaction or hypersensitivity likely to be caused or exacerbated by any excipient or active component of the vaccine(s).
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including malignancies, based on medical history and physical examination (no laboratory testing
- required).
- Family history of congenital or hereditary immunodeficiency.
- Major congenital defects, as assessed by the investigator.
- Acute or chronic clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined via medical history including physical examination.
- Medical history of neurological disorder, including seizures.

Prior/Concomitant Therapy

- Previous vaccination for diphtheria, tetanus, pertussis, HBV, poliomyelitis, Hib diseases and previous vaccination against pneumococcal infection with pneumococcal conjugate vaccine, with the exception of a birth dose of HBV vaccine, which may be given in accordance with local recommendations.
- Use of any investigational or nonregistered product (drug, vaccine, or medical device) other than the study vaccine(s) during the period starting 30 days before the first dose of study vaccine(s) (Day -29 to Day 1), or planned use during the study period.
- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before the first dose and ending 30 days after the last dose of vaccine(s) with the exception of administration of vaccines given as part of the national immunisation schedule and as part of routine vaccination practice, e.g., rotavirus vaccine, that are allowed at any time during the study period. In case emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is organised by public health authorities outside the routine immunisation programme, the time period described above can be reduced if necessary for that mass vaccination vaccine, provided this vaccine/product(s) is licensed and used according to its Product Information.
- Administration of long-acting immune-modifying drugs in the period starting 30 days before the first dose and at any time during the study period.

- Administration of immunoglobulins and/or any blood products or plasma derivatives from birth or planned administration during the study period.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 3 months prior to the first vaccine. For corticosteroids, this will mean prednisone ≥0.5 mg/kg/day (for paediatric subjects), or equivalent. Inhaled and topical steroids are allowed.

Prior/Concurrent Clinical Study Experience

- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (drug or medical device).

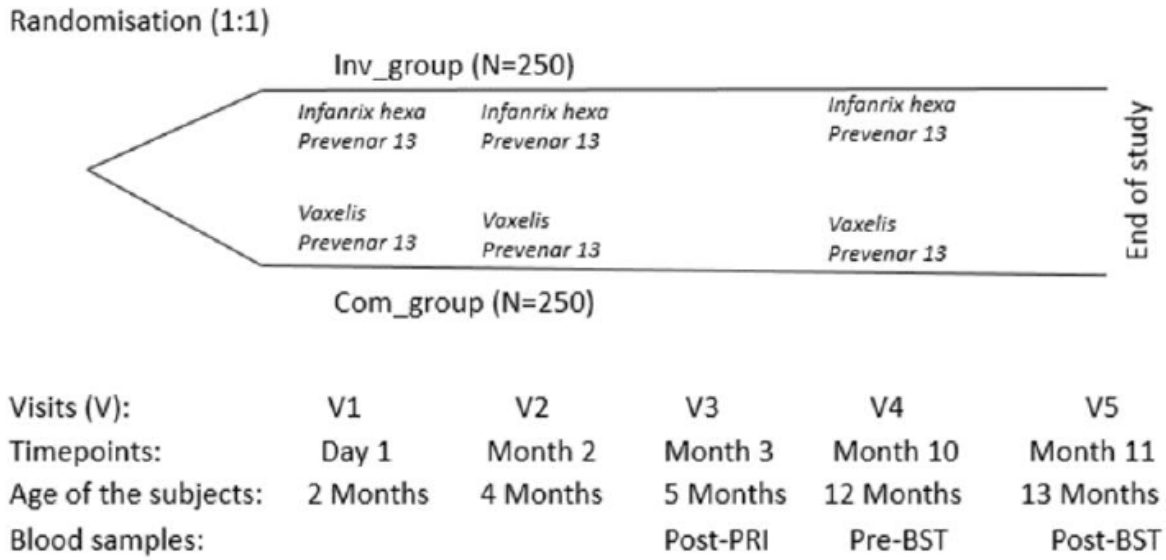
Other exclusions

- Child in care.

Treatments

The subjects were assigned to 1 of 2 parallel groups:

- Inv_group (Investigational group): All subjects in this group received 3 doses (2 primary doses+1 booster dose) of Infanrix hexa co-administered with 3 doses of Prevenar 13 at 2-, 4-, and 12- months.
- Com_group (Comparator group): All subjects in this group received 3 doses (2 primary doses+1 booster dose) of Vaxelis co-administered with 3 doses of Prevenar 13 at 2-, 4-, and 12- months.



Abbreviations: BST=booster; N=number of subjects in group; PRI=primary; V=visit.

Figure 1. Study Schema (Source: Report Body Figure 1)

CHMP comment

Participants were randomised in two groups (n=250 subjects/group). The investigational group received 3 doses (2 primary doses+1 booster dose) of Infanrix hexa and the comparator group received 3 doses (2 primary doses+1 booster dose) of Vaxelis, at 2-, 4-, and 12-months timepoints. All subjects in both groups received co-administration with 3 doses (2 primary doses+1 booster dose) of Prevenar 13. As stated in the SmPC, Infanrix hexa can be given concomitantly with pneumococcal conjugate vaccines (PCV7, PCV10 and PCV13).

Blood samples were taken post-primary vaccination (1 month post-dose 2), but not pre-primary vaccination. Blood samples were also taken pre- and post-booster (after 1 month) vaccination.

Objectives and Endpoints

Objectives and endpoints are presented in Table 2.

Table 2. Study Objectives and Endpoints (Source: Report Body Table 1)

Objectives	Endpoints
Co-primary	
Confirmatory 1.To demonstrate that the Hib response in Investigational group (Inv_group) is non-inferior to Comparator group (Com_group), 1-month post-booster vaccination in terms of: • GMCs ○ *Criterion: LL of the 2-sided 95% CI on group GMC ratio (Inv_group over Com_group) is above 0.5.* • Percentage of subjects with anti-PRP antibody concentrations ≥5 µg/mL. ○ *Criterion: First primary objective is met and the LL of the 2-sided 95% CI on group difference in the percentage (Inv_group minus Com_group) is more than -10%.* 2.To demonstrate that the Hib response in Inv_group is superior to Com_group, 1-month post-booster vaccination in terms of: • GMCs ○ *Criterion: All previous objectives are met and the LL of the 2-sided 95% CI on group GMC ratio (Inv_group over Com_group) is above 1.* • Percentage of subjects with anti-PRP antibody concentrations ≥5 µg/mL. ○ *Criterion: All previous objectives are met and the LL of the 2-sided 95% CI on group difference in the percentage (Inv_group minus Com_group) is above 0.* • Note: A hierarchical procedure was used to control the risk of concluding erroneously.	• Anti-PRP antibody concentrations at 1-month post-booster vaccination. • Anti-PRP antibody concentration ≥5 µg/mL at 1-month post-booster vaccination.

Objectives	Endpoints
Secondary	
Descriptive • To assess the immunogenicity of Hib-components in terms of percentage of subjects above the thresholds for short-term (≥0.15 µg/mL) and long-term (≥1.0 µg/mL) protection as well as in terms of GMCs (post-primary, pre- and post-booster vaccination).	• Anti-PRP antibody concentrations at 1-month post-primary vaccination, pre-booster, and 1-month post-booster vaccination.
• To assess the safety of *Infanrix hexa* and *Vaxelis* co-administered with *Prevenar 13* in terms of unsolicited AEs and SAEs.	• Occurrence of unsolicited AEs during the 31-day (Days 1-31) follow-up period after each vaccination. • Occurrence of SAEs after first dose up to study end.
Tertiary/Exploratory	
• If the co-primary objectives are met and the assay is available to assess the quality of the anti-PRP responses (post-booster vaccination).	• Avidity index of anti-PRP antibodies.

Abbreviations: AE=adverse event; CI=confidence interval; GMC=geometric mean concentration; Hib=*haemophilus influenzae* type b; LL=lower limit; PRP=polyribosylribitol phosphate; SAE=serious adverse event.

CHMP comment

The study has a co-primary immunogenicity objective, in order to assess non-inferiority and superiority of Infanrix hexa vs. Vaxelis, in terms of anti-PRP antibody concentrations at 1-month post-booster vaccination and anti-PRP antibody concentration ≥5 µg/mL at 1-month post-booster vaccination. A hierarchical approach is used.

The success criterion for NI demonstration in terms of GMCs is that the LL of the 2-sided 95% CI on group GMC ratio (Infanrix hexa/Vaxelis) is >0.5. The chosen margin could have been more stringent, i.e. 0.67.

In terms of percentages of subjects with anti-PRP Ab titers ≥5 µg/ml, the success criterion for NI demonstration is that the LL of the 2-sided 95% CI on group difference in the percentage (Infanrix hexa/Vaxelis) is >-10%, which is deemed appropriate.

Both superiority criteria are deemed adequate.

The confirmatory analyses of non-inferiority is based on the per-protocol set (PPS) while the confirmatory analyses of superiority is based on the Exposed set (ES) (see section 'Participant flow'). The reason for this difference is unclear.

The secondary immunogenicity objective is to assess immunogenicity of Hib-components in terms of percentage of subjects above the thresholds for short-term (≥0.15 µg/mL) and long-term (≥1.0 µg/mL) protection as well as in terms of GMCs (post-primary, pre-, and post-booster vaccination).

Anti-PRP IgG were measured by ELISA with a LLOQ of 0.066 µg/ml.

The secondary safety objective is to assess safety of Infanrix hexa and Vaxelis co-administered with Prevenar 13 in terms of unsolicited AEs during the 31-day follow-up period after each vaccination and

SAEs until the end of the study (approximately 11 months after first vaccination; 1 month after the booster). Safety data will be analysed on the ES population.

Sample size

The study will enrol approximately 500 subjects in a 1:1 ratio. Assuming that 20% of the subjects would not be evaluable, the power was computed for 400 evaluable subjects (i.e., 200 subjects each in the Inv_group and Com_group). Evaluable is defined as: meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, qualified for inclusion in the according-to-protocol analysis.

Randomisation and blinding (masking)

The subjects were randomised at a 1:1 ratio to Inv_group or Com_group using a minimisation algorithm with the study country and maternal immunisation status of the infants as minimisation factors. This was done at the study entry using an Interactive Web Response System (IWRS) randomisation.

The study is single-blinded. In a single-blind study, the investigator knows the identity of the treatment assigned while the subject's parent(s)/legally acceptable representatives(s) don't know.

The laboratory in charge of sample testing was blinded to the intervention assignment. The data management and biostatistics teams remained blinded to the study treatment until after the final database lock. No unblinded data summaries (presented by treatment) were available prior to the final database lock. An independent unblinded Biostatistician was identified to review potentially unblinding information ahead of the final database lock, e.g., randomisation specifications and schedule.

Statistical Methods

All analyses were based on the intervention as received at Dose 1.

Demographics and Other Baseline Characteristics: Baseline and demographic information were summarised using descriptive statistics for continuous and ordinal variables (e.g., age, weight, height [Day 1 only]), and counts and percentages for categorical variables (e.g., sex, race).

Immunogenicity Analyses: The confirmatory analyses of non-inferiority were based on the per protocol set (PPS) defined as all eligible and vaccinated subjects. Lab results were censored after DTPa-combination study vaccines deviating from protocol, after intercurrent conditions that may interfere with immunogenicity or after prohibited concomitant medication/vaccination. In addition, lab results from Visits 3 and 5 blood draws were censored for the visit when taken outside of allowed study intervals. The confirmatory analyses of superiority were based on the exposed set (ES).

Method for non-inferiority and superiority in anti-PRP antibody concentration at 1-month post-booster vaccination: The 2-sided 95% CI for group GMC ratio derived from an analysis of variance (ANOVA) model on log10 transformed concentration was used. The model included country, maternal immunisation, and group as fixed effects. Concentration below assay cut-off was replaced by half the assay cut-off.

Method for non-inferiority and superiority in the percentage of subjects with anti-PRP antibody concentration ≥5.0 μg/mL at 1-month post-booster vaccination: The 2-sided 95% CI on group difference in seroconversion rate (Inv_group minus Com_group) was computed based on Miettinen and Nurminen method.

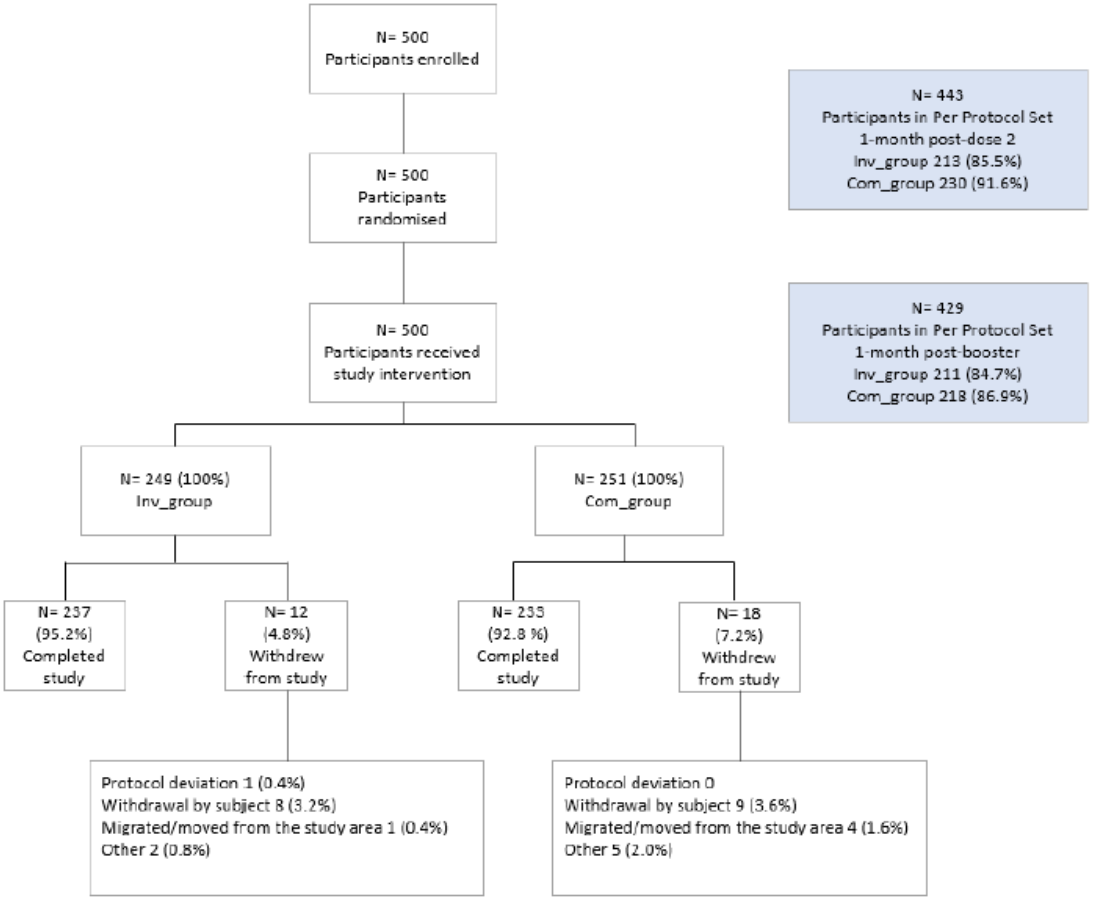
Descriptive analysis for each study group was provided by country and maternal immunization status for anti-PRP antibody concentrations and for the percentage of subjects with anti-PRP antibody concentration ≥0.15, 1, and 5.0 μg/mL at 1-month post-primary vaccination, pre-booster and 1-month post-booster vaccination.

Safety Analyses: Safety data was analysed on the ES population. Descriptive analyses for the AEs and SAEs were provided by study group. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA). For each study treatment, number of AEs and percentage of subjects with AE within 31 days post-vaccination was tabulated by preferred term and system organ class. The same summary was provided for related AE within 31 days post-vaccination, by maximal severity and for SAE after vaccination up to study end.

Results

Participant flow

Table 3. Disposition of Subjects (Source: Report Body Figure 2)



Abbreviations: Com_group=comparator group; Inv_group=investigative group; N=number of subjects in Enrolled Set.

Source: Table 14.1-1.1.1

Table 4. Analysis Sets (Source: Protocol Table 7)

Analysis Set	Description
Enrolled set	All subjects with a study intervention (either randomised or vaccinated or with a blood draw).
Exposed set (ES)	All vaccinated subjects. Subjects will be analysed according to the intervention they received at Dose 1.
Per protocol set (PPS)	All eligible subjects who received all DTPa-combination study vaccines as per protocol, who had anti-PRP results post-vaccination, who complied with vaccination/blood draw intervals (Table 8), without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination. Subjects will be analysed according to the intervention they received at Dose 1.

CHMP comment

In total, 500 subjects were enrolled, randomised and received study intervention. The investigational group which received Infanrix hexa includes 249 subjects and the comparator group with Vaxelis 251 subjects. These subjects represent the Enrolled set and Exposed set (ES).

The Per-Protocol Set (PPS) includes all subjects who received all study vaccines as per protocol, who had anti-PRP results post-vaccination, who complied with vaccination/blood draw intervals, without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination. In total 429 subjects are part of the PPS, of which 211 in the Infanrix hexa group and 218 in the Vaxelis group.

In total, 30 subjects withdrew from the study, of which 12 in the Infanrix hexa group and 18 in the Vaxelis group. The main cause was withdrawal by the subject.

Recruitment

The first subject was enrolled on 17 February 2021 and the last subject complete on 25 July 2022.

Baseline data

Subject demographics and other baseline characteristics are presented in Table 5.

Table 5. Summary of Demographics and Baseline Characteristics (Exposed Set) (Source: Report Body Table 9)

Characteristic	Statistic	*Infanrix hexa* (N=249)	*Vaxelis* (N=251)	Total (N=500)
Gestational Age (Weeks)	n	249	251	500
	Mean (SD)	39.2 (1.16)	39.2 (1.19)	39.2 (1.17)
	Median	39.0	39.0	39.0
	Min - Max	37 - 42	37 - 42	37 - 42
Age at Dose 1 (Weeks)	n	249	251	500
	Mean (SD)	8.6 (1.17)	8.6 (1.24)	8.6 (1.20)
	Median	9.0	9.0	9.0
	Min - Max	6 - 11	6 - 12	6 - 12
Sex				
Male	n (%)	144 (57.8)	116 (46.2)	260 (52.0)
Female	n (%)	105 (42.2)	135 (53.8)	240 (48.0)
Race				
Black or African American	n (%)	1 (0.4)	2 (0.8)	3 (0.6)
American Indian or Alaska Native	n (%)	1 (0.4)	2 (0.8)	3 (0.6)
Asian - Central / South Asian Heritage	n (%)	0	1 (0.4)	1 (0.2)
Asian - East Asian Heritage	n (%)	1 (0.4)	0	1 (0.2)
Asian - Japanese Heritage	n (%)	0	0	0
Asian - South East Asian Heritage	n (%)	0	1 (0.4)	1 (0.2)
Native Hawaiian or Other Pacific Islander	n (%)	0	0	0
White - Arabic / North African Heritage	n (%)	5 (2.0)	4 (1.6)	9 (1.8)
White - Caucasian / European Heritage	n (%)	236 (94.8)	235 (93.6)	471 (94.2)
Other	n (%)	5 (2.0)	6 (2.4)	11 (2.2)
Height at Day 1 (cm)	n	249	251	500
	Mean (SD)	57.8 (2.39)	57.6 (2.49)	57.7 (2.44)
	Median	57	57	57
	Min - Max	51 - 65	51 - 66	51 - 66
Weight at Day 1 (kg)	n	249	251	500
	Mean (SD)	5.272 (0.7011)	5.206 (0.6541)	5.239 (0.6781)
	Median	5.20	5.20	5.20
	Min - Max	3.57 - 7.90	3.29 - 6.86	3.29 - 7.90
DTPa mother Vaccination during pregnancy				
Yes	n (%)	191 (76.7)	188 (74.9)	379 (75.8)
No	n (%)	54 (21.7)	55 (21.9)	109 (21.8)
Unknown	n (%)	4 (1.6)	8 (3.2)	12 (2.4)

Characteristic	Statistic	*Infanrix hexa* (N=249)	*Vaxelis* (N=251)	Total (N=500)
Source: Table 14.1-4.1 Abbreviations: N=number of PPS subjects in treatment group; n(%)=number/percentage of subjects in that treatment group with characteristic; SD=standard deviation. Percentages are based on Per Protocol Set - Post Booster.				

CHMP comments

In both groups, the majority of the subjects were of White Caucasian/European heritage (94.2%), had a median age of 9.0 weeks at Dose 1 study intervention administration and were born after a median

gestational age of 39.0 weeks. Overall 52% of the subjects were male, with some imbalance between groups: 57.8% of males in the Infanrix hexa group and 46.2% of males in the Vaxelis group.

In total, 379 (75.8%) of the subject's mothers received DTPa vaccine during pregnancy, 109 (21.8%) mothers did not, and for 12 (2.4%) subjects it was unknown for the mother to have received DTPa vaccination during pregnancy. DTPa vaccination characteristics are balanced between both groups.

Immunogenicity results

Co-primary endpoints

Table 6 presents the statistics of the first co-primary efficacy endpoint: Anti-PRP antibody concentrations at 1-month post-booster vaccination.

Table 7 presents the statistics of the second co-primary endpoint: Anti-PRP antibody concentration ≥5 μg/mL at 1-month post-booster vaccination.

Table 6. Ratio of GMCs for Anti-PRP between Groups (Infanrix hexa divided by Vaxelis), 1-Month Post-Booster Vaccination (Per Protocol Set – Post Booster) (Source: Report Body Table 11)

					Adjusted GMC Ratio		
					(*Infanrix Hexa/ Vaxelis*)		
	Infanrix hexa		*Vaxelis*		95% CI		
Antibody	N	Adjusted GMC	N	Adjusted GMC	Value	LL	UL
anti-PRP	211	11.61	218	12.66	0.917	0.710	1.185

Abbreviations: 95% CI=95% confidence interval for the adjusted GMC ratio; LL=lower limit; N=number of subjects with available results; UL=upper limit.
Adjusted GMC=geometric mean antibody concentration adjusted for DTPa vaccination of the mother.
Infanrix hexa=Subjects who received 3 doses (2 primary doses+1 booster dose) of *Infanrix hexa* co-administered with 3 doses of Prevenar 13 at 2-, 4-, and 12-months.
Vaxelis=Subjects who received 3 doses (2 primary doses+1 booster dose) of *Vaxelis* co-administered with 3 doses of Prevenar 13 at 2-, 4-, and 12-months.
The analysis is based on ANOVA model with log10 transformed concentration values as response variable and country, maternal immunisation, and treatment group as fixed effects.
Source: Table 14.2-1.1

Table 7. Difference Between Groups in Percentage of Subjects with Anti-PRP Antibody Concentrations Equal to or Above 5.0 µg/mL at 1-month Post-Booster Vaccination (Per Protocol Set Post-Booster) (Source: Report Body Table 12)

								Difference in Percentage above 5 µg/mL		
		Infanrix hexa			*Vaxelis*				95% CI	
Antibody	**Timepoint**	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
anti-PRP	POST-BST	211	159	75.4	218	178	81.7	-6.30	-14.10	1.49

Abbreviations: %=Percentage of subjects who seroconverted (i.e., anti-PRP antibody concentration ≥5.0 µg/mL) at Post-booster; 95% CI=95% confidence interval; LL=lower limit; N=number of subjects with available results; POST-BST=1-month Post-booster vaccination (Month 11 Visit 5); UL=upper limit.

95% CI=95% CI computed based on Miettinen and Nurminen method

Infanrix hexa=Subjects who received 3 doses (2 primary doses+1 booster dose) of *Infanrix hexa* co-administered with 3 doses of Prevenar 13 at 2-, 4-, and 12-months.

Vaxelis=Subjects who received 3 doses (2 primary doses+1 booster dose) of *Vaxelis* co-administered with 3 doses of Prevenar 13 at 2-, 4-, and 12-months.

Source: Table 14.2-1.2

CHMP Comments

The adjusted ratio of anti-PRP GMCs (95% CI) induced by Infanrix hexa vs. Vaxelis one month post-booster was 0.917 (0.710; 1.185). As the LL of the 95% CI of the GMC ratio was above 0.5, the first criterion of the first co-primary objective in relation to GMCs was met.

The percentage of subjects with anti-PRP antibody concentrations equal to or above 5.0 µg/mL at 1-month Post-Booster was 75.4% in the Infanrix hexa group and 81.7% in the Vaxelis group, resulting in a difference (95% CI) of -6.30% (-14.10; 1.49). As the LL of the 2-sided 95% CI on group difference in the percentage was not more than -10%, the second criterion of the first co-primary objective in relation to percentage of subjects with anti-PRP antibody concentrations ≥5 µg/mL was not met.

As a result, the co-primary objectives of the study demonstrate that the Hib response induced at 1-month post-vaccination with Infanrix hexa was non-inferior to vaccination with Vaxelis in terms of anti-PRP GMC, though not in terms of the percentage of subjects with anti-PRP Ab concentrations ⩾5.0 µg/mL.

Consequentially, the condition for meeting the second co-primary objective on superiority of Infanrix hexa vs. Vaxelis at 1-month post-booster vaccination is also not satisfied.

Anti-PRP Antibody Concentrations (Secondary objective)

Table 8. Number and Percentage of Subjects with Anti-PRP Antibody Concentrations Equal to or Above 0.15 µg/mL, 1.0 µg/mL, and 5.0 µg/mL and GMCs at 1-Month Post-Primary Vaccination, Pre-Booster and 1-Month Post-Booster Vaccination (Per Protocol Set) (Source: Report Body Table 13)

				>=0.15 µg/mL				>=1.0 µg/mL				>=5.0 µg/mL				GMC		
						95% CI				95% CI				95% CI			95% CI	
Antibody	Visit	Group	N	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
anti-PRP	POST-PRI	*Infanrix hexa*	213	170	79.8	73.79	84.99	65	30.5	24.41	37.18	13	6.1	3.29	10.21	0.5	0.41	0.62
		Vaxelis	230	230	100.0	98.41	100.00	212	92.2	87.91	95.30	171	74.3	68.19	79.86	11.3	9.35	13.60
	PRE-BST	*Infanrix hexa*	206	126	61.2	54.14	67.86	27	13.1	8.82	18.49	3	1.5	0.30	4.20	0.2	0.19	0.28
		Vaxelis	216	204	94.4	90.50	97.10	149	69.0	62.35	75.08	59	27.3	21.49	33.77	1.9	1.56	2.26
	POST-BST	*Infanrix hexa*	211	210	99.5	97.39	99.99	205	97.2	93.91	98.95	159	75.4	68.97	81.01	12.0	9.96	14.34
		Vaxelis	218	217	99.5	97.47	99.99	206	94.5	90.58	97.12	178	81.7	75.86	86.56	12.9	10.75	15.55

Abbreviations: 95% CI=95% confidence interval; GMC=geometric mean antibody concentration calculated on all subjects; LL=lower limit; N=number of subjects with available results; n/%=number/percentage of subjects with concentration equal to or above specified value; POST-BST=1-month Post-booster vaccination (Month 11 Visit 5); POST-PRI=1-month Post-primary vaccination (Month 3 Visit 3); PRE-BST=Pre-booster vaccination (Month 10 Visit 4); UL=upper limit.

Infanrix hexa=Subjects who received 3 doses (2 primary doses+1 booster dose) of *Infanrix hexa* co-administered with 3 doses of Prevenar 13 at 2-, 4-, and 12-months.

Vaxelis=Subjects who received 3 doses (2 primary doses+1 booster dose) of *Vaxelis* co-administered with 3 doses of Prevenar 13 at 2-, 4-, and 12-months.

Source: Table 14.2-1.3

CHMP Comments

Anti-PRP antibody concentrations were measured at 1-month post-primary vaccination, pre-booster, and at 1-month post-booster.

The Infanrix hexa group showed that 79.8% of subjects had short-term protection (anti-PRP ≥0.15 µg/mL), and 30.5% of the subjects had long-term protection (protection (anti-PRP ≥1.0 µg/mL) at one month post-primary vaccination, while in the Vaxelis group, 100% of subjects had short-term protection and 92.2% of subjects had long-term protection.

At the pre-boost timepoint, seven months later, a decrease in antibody concentrations is noted in both groups, with sustained short-term protective levels in 61.2% of the Infanrix hexa vaccinated subjects and 94.4% of the Vaxelis vaccinated subjects; and long-term protective levels in 13.1% of the Infanrix hexa vaccinated subjects and 69.0% of the Vaxelis vaccinated subjects.

At one month post-boost, both groups showed an increase in the proportion of subjects with protective anti-PRP titers, with in the Infanrix hexa group 99.5% of the subjects with short-term protective levels and 97.2% of the subjects with long-term protective levels; and in the Vaxelis group 99.5% of the subjects with short-term protective levels and 94.5% of the subjects with long-term protective levels.

At the one month post-primary and pre-boost timepoint, anti-PRP GMCs [95%CI] were significantly lower in the Infanrix hexa group vs. the Vaxelis group (0.5 [0.41-0.62] vs. 11.3 [9.35-13.60] and 0.2 [0.19-0.28] vs. 1.9 [1.56-2.26], respectively). At one month post-boost, the anti-PRP GMC [95% CI] are similar in both groups (12.0 [9.96-14.34] vs. 12.9 [10.75-15.55]).

Avidity Index of Anti-PRP Antibodies (Tertiary objective)

Table 9. Avidity Index (AI%) of Anti-PRP and Geometric Mean Concentrations (GMC) at 1-Month Post-Booster Vaccination by Treatment Group (Per Protocol Set – Post Booster) (Source: Report Body Table 15)

				>= assay cut-off				GMC		
						95% CI			95% CI	
	Visit	Group	N	n	%	LL	UL	Value	LL	UL
Avidity Index (AI%)	POST-BST	*Infanrix hexa*	209	204	97.6	94.51	99.22	25.7	23.88	27.68
		Vaxelis	215	212	98.6	95.98	99.71	23.2	21.63	24.88

Abbreviations: 95% CI=95% confidence interval; GMC=geometric mean antibody concentration; LL=lower limit; N=number of subjects with available results; n/%=number/percentage of subjects with concentration equal to or above specified value; POST-BST=post-booster vaccination (Month 11 Visit 5); UL=upper limit.

GMC=geometric mean antibody concentration calculated on all subjects

Infanrix hexa=Subjects who received 3 doses (2 primary doses+1 booster dose) of *Infanrix hexa* co-administered with 3 doses of Prevenar 13 at 2-, 4-, and 12-months.

Vaxelis=Subjects who received 3 doses (2 primary doses+1 booster dose) of *Vaxelis* co-administered with 3 doses of Prevenar 13 at 2-, 4-, and 12-months.

Source: Table 14.2-4.1

CHMP Comments

A tertiary objective aimed to evaluate potential differences in anti-PRP antibody avidity for the 2 vaccines. This was evaluated at the post-boost timepoint. The avidity index (95% CI) was similar in the Infanrix hexa group (25.7 [23.88; 27.68]) and in the Vaxelis group (23.2 [21.63; 24.88]).

Safety results

Unsolicited Adverse events

Table 10. Incidence of Unsolicited Adverse Events Occurring in ⩾2.0% of Subjects in Either or Both Treatment Groups (Exposed Set)

		Infanrix hexa N=249				*Vaxelis* N=251			
				95% CI				95% CI	
Primary System Organ Class	**Preferred Term**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom		178	71.5	65.4	77.0	199	79.3	73.7	84.1
Gastrointestinal disorders	Abdominal pain	6	2.4	0.9	5.2	4	1.6	0.4	4.0
	Constipation	3	1.2	0.2	3.5	9	3.6	1.7	6.7
	Diarrhoea	15	6.0	3.4	9.7	16	6.4	3.7	10.1
	Vomiting	8	3.2	1.4	6.2	5	2.0	0.6	4.6
General disorders and administration site conditions	Crying	5	2.0	0.7	4.6	7	2.8	1.1	5.7
	Injection site erythema	6	2.4	0.9	5.2	8	3.2	1.4	6.2
	Injection site pain	6	2.4	0.9	5.2	8	3.2	1.4	6.2
	Injection site swelling	7	2.8	1.1	5.7	8	3.2	1.4	6.2
	Pyrexia	103	41.4	35.2	47.8	132	52.6	46.2	58.9
Infections and infestations	Bronchitis	6	2.4	0.9	5.2	5	2.0	0.6	4.6
	Conjunctivitis	14	5.6	3.1	9.3	14	5.6	3.1	9.2
	COVID-19	14	5.6	3.1	9.3	9	3.6	1.7	6.7
	Gastroenteritis	9	3.6	1.7	6.8	10	4.0	1.9	7.2
	Laryngitis	5	2.0	0.7	4.6	4	1.6	0.4	4.0
	Nasopharyngitis	6	2.4	0.9	5.2	14	5.6	3.1	9.2
	Otitis media	1	0.4	0.0	2.2	0	0	0.0	1.5
	Otitis media acute	5	2.0	0.7	4.6	6	2.4	0.9	5.1
	Respiratory tract infection	2	0.8	0.1	2.9	6	2.4	0.9	5.1
	Upper respiratory tract	18	7.2	4.3	11.2	20	8.0	4.9	12.0
	Viral upper respiratory tract	5	2.0	0.7	4.6	6	2.4	0.9	5.1
Investigations	Body temperature increased	3	1.2	0.2	3.5	5	2.0	0.6	4.6
Metabolism and nutrition disorders	Decreased appetite	4	1.6	0.4	4.1	5	2.0	0.6	4.6
Nervous system disorders	Somnolence	4	1.6	0.4	4.1	5	2.0	0.6	4.6
Psychiatric disorders	Irritability	31	12.4	8.6	17.2	37	14.7	10.6	19.7
	Restlessness	8	3.2	1.4	6.2	13	5.2	2.8	8.7
Respiratory, thoracic and mediastinal disorders	Cough	7	2.8	1.1	5.7	5	2.0	0.6	4.6
Skin and subcutaneous tissue	Dermatitis	7	2.8	1.1	5.7	4	1.6	0.4	4.0
	Dermatitis diaper	6	2.4	0.9	5.2	6	2.4	0.9	5.1
	Eczema	6	2.4	0.9	5.2	5	2.0	0.6	4.6
	Rash	5	2.0	0.7	4.6	3	1.2	0.2	3.5

Source: Table 14.3.1-1.1

Abbreviations: 95% CI=exact 95% confidence interval; COVID-19=coronavirus disease 2019; LL=Lower Limit; N=number of subjects with at least one administered dose; n/%=number/percentage of subjects reporting the symptom at least once; UL=Upper Limit.

Adverse event terms were coded using MedDRA version 25.0.

At least one symptom=at least one symptom experienced (regardless of the MedDRA Preferred Term).

Infanrix hexa=Subjects who received 3 doses (2 primary doses+1 booster dose) of *Infanrix hexa* co-administered with 3 doses of Prevenar 13 at 2-, 4-, and 12-months.

Vaxelis=Subjects who received 3 doses (2 primary doses+1 booster dose) of *Vaxelis* co-administered with 3 doses of Prevenar 13 at 2-, 4-, and 12-months.

CHMP Comments

Adverse events were classified according to the Medical Dictionary of Regulatory Activities (MedDRA) version 25.0.

A total of 178 (71.5%) subjects in the Infanrix hexa group and 199 (79.3%) subjects in the Vaxelis group experienced at least one symptom of unsolicited AE within the 31 days follow-up period after each vaccination. The highest incidence of AE by preferred term (PT) was pyrexia (103 [41.4%] subjects in the Infanrix hexa group and 132 [52.6%] subjects in the Vaxelis group), followed by irritability (31 [12.4%] subjects in the Infanrix hexa group and 37 [14.7%] subjects in the Vaxelis group), and upper respiratory tract infection (18 [7.2%] subjects in the Infanrix hexa group and 20 [8.0%] subjects in the Vaxelis group). While pyrexia and irritability are known as AEs with a very common frequency following vaccination with Infanrix hexa and Vaxelis, upper respiratory tract infection is only included in the SmPC of Infanrix hexa with uncommon frequency. For Vaxelis, upper respiratory tract infection is not known as an AE reported following vaccination, while Rhinitis is a known AE with uncommon frequency. In addition, upper respiratory tract infection or any related AE has not been reported upon vaccination with Prevenar 13. The very common occurrence of upper respiratory tract infection in this study is thus unexpected.

No relevant imbalances in unsolicited AEs reported withing one month after vaccination are observed between both groups.

Most of the unsolicited AEs were mild (144 [57.8%] subjects in the Infanrix hexa group and 156 [62.2%] subjects in the Vaxelis group) or moderate (30 [12.0%] subjects in the Infanrix hexa group and 38 [15.1%] subjects in the Vaxelis group) in severity. There were similar number of subjects in both groups (4 [1.6%] in the Infanrix hexa group and 5 [2.0%] in the Vaxelis group) with severe symptoms. The unsolicited AEs with the highest reported severity were irritability (1 [0.4%] subjects in the Infanrix hexa group and 2 [0.8%] subjects in the Vaxelis group), restlessness (1 [0.4%] subjects in the Infanrix hexa group and 2 [0.8%] subjects in the Vaxelis group), eczema and injection site swelling (1 [0.4%] report of each in the Infanrix hexa group and no severe symptoms in the Vaxelis group), pyrexia (no severe symptoms in the Infanrix hexa group and 1 [0.4%] in the Vaxelis group), and respiratory syncytial virus bronchiolitis (no severe symptoms in the Infanrix hexa group and 1 [0.4%] in the Vaxelis group).

A total of 113 (45.4%) subjects in the Infanrix hexa group and 142 (56.6%) subjects in the Vaxelis group experienced at least one unsolicited AE considered by the Investigator to be related to the study intervention. Most unsolicited AEs assessed as possibly related to study intervention were mild in severity and resolved. The most frequently reported AE considered to be related to study intervention, in both treatment groups was pyrexia (88 [35.3%] subjects in the Infanrix hexa group and 118 [47.0%] subjects in the Vaxelis group). The next most frequently reported AEs considered to be related to study intervention were irritability (29 [11.6%] subjects in the Infanrix hexa group and 33 [13.1%] subjects in the Vaxelis group), restlessness (8 [3.2%] subjects in the Infanrix hexa group and 13 [5.2%] subjects in the Vaxelis group), injection site erythema (6 [2.4%] subjects in the Infanrix hexa group and 8 [3.2%] subjects in the Vaxelis group), injection site pain (6 [2.4%] subjects in the Infanrix hexa group and 8 [3.2%] subjects in the Vaxelis group), and injection site swelling (7 [2.8%] subjects in the Infanrix hexa group and 8 [3.2%] subjects in the Vaxelis group). All AEs considered to be related to the study intervention are known AEs reported after vaccination with Infanrix hexa, Vaxelis or Prevenar 13. None of the upper respiratory tract infections was considered by the Investigator to be related to the study intervention.

There was 1 SAE of seizure considered to be related to study intervention (refer to section 'Deaths and other Serious Adverse events' below).

There were no AEs leading to discontinuation of subjects for this study.

Deaths and other Serious Adverse events

Table 11. Number and Percentage of Subjects with Serious Adverse Events by System Organ Class and Preferred Term During the Study Period (Exposed Set)

		Infanrix Hexa N=249				*Vaxelis* N=251			
				95% CI				95% CI	
Primary System Organ Class	**Preferred Term**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom		14	5.6	3.1	9.3	10	4.0	1.9	7.2
Congenital, familial and genetic disorders	Hydrocele	1	0.4	0.0	2.2	0	0	0.0	1.5
Gastrointestinal disorders	Diarrhoea	1	0.4	0.0	2.2	0	0	0.0	1.5
	Vomiting	1	0.4	0.0	2.2	0	0	0.0	1.5
General disorders and administration site conditions	Pyrexia	2	0.8	0.1	2.9	0	0	0.0	1.5
Infections and infestations	Abscess neck	1	0.4	0.0	2.2	0	0	0.0	1.5
	Adenovirus infection	1	0.4	0.0	2.2	0	0	0.0	1.5
	Bronchiolitis	2	0.8	0.1	2.9	3	1.2	0.2	3.5
	Bronchitis	1	0.4	0.0	2.2	0	0	0.0	1.5
	Gastroenteritis	0	0	0.0	1.5	1	0.4	0.0	2.2
	Gastroenteritis norovirus	1	0.4	0.0	2.2	0	0	0.0	1.5
	Parainfluenzae virus infection	1	0.4	0.0	2.2	0	0	0.0	1.5
	Perirectal abscess	1	0.4	0.0	2.2	0	0	0.0	1.5
	Pneumonia	1	0.4	0.0	2.2	0	0	0.0	1.5
	Pyelonephritis acute	0	0	0.0	1.5	2	0.8	0.1	2.8
	Respiratory syncytial virus	1	0.4	0.0	2.2	3	1.2	0.2	3.5
	Rhinovirus infection	1	0.4	0.0	2.2	0	0	0.0	1.5
	Urinary tract infection	2	0.8	0.1	2.9	0	0	0.0	1.5
Investigations	Enterovirus test positive	1	0.4	0.0	2.2	0	0	0.0	1.5
Metabolism and nutrition	Hypophagia	1	0.4	0.0	2.2	0	0	0.0	1.5
Nervous system disorders	Febrile convulsion	1	0.4	0.0	2.2	1	0.4	0.0	2.2
	Seizure	2	0.8	0.1	2.9	0	0	0.0	1.5
Reproductive system and breast disorders	Testicular torsion	1	0.4	0.0	2.2	0	0	0.0	1.5
Respiratory, thoracic and mediastinal disorders	Respiratory failure	1	0.4	0.0	2.2	0	0	0.0	1.5

Abbreviations: 95% CI=exact 95% confidence interval; LL=Lower Limit; N=number of subjects with at least one administered dose; n/%=number/percentage of subjects reporting the symptom at least once; UL=Upper Limit.

Adverse event terms were coded using MedDRA version 25.0.

At least one symptom=at least one symptom experienced (regardless of the MedDRA Preferred Term)

Infanrix hexa=Subjects who received 3 doses (2 primary doses+1 booster dose) of *Infanrix hexa* co-administered with 3 doses of Prevenar 13 at 2-, 4-, and 12-months.

Vaxelis=Subjects who received 3 doses (2 primary doses+1 booster dose) of *Vaxelis* co-administered with 3 doses of Prevenar 13 at 2-, 4-, and 12-months.

Subjects experiencing multiple events within the same SOC and PT are counted only once under those categories.

Source: Table 14.3.1-2.1

CHMP Comments

There was no case of death in the study.

A total of 14 (5.6%) subjects in the Infanrix hexa group and 10 (4.0%) subjects in the Vaxelis group experienced at least 1 SAE during the study.

The most common SAEs in the Infanrix hexa group were pyrexia, bronchiolitis, urinary tract infection, and seizure, each reported by 2 (0.8%) subjects. Among these SAEs, 1 report of seizure in a 38 week-old female subject at enrolment, was considered related to study treatment. The participant received the first primary dose, second primary dose and booster dose of Infanrix hexa + Prevenar 13 on Study day 1 , Study day 58 and Study day 286 respectively. On Study day 1, 6 hours after receiving the first primary dose of Infanrix hexa + Prevenar 13, the participant developed an adverse event of seizure (afebrile presumptive convulsive event) of moderate intensity [CTCAE grade 2]. The participant experienced 5 to 6 episodes of afebrile convulsive event with cyanotic lips without fever. The participant was taken to emergency room (ER) and was subsequently hospitalized. The event was serious as it required hospitalization. The participant was hospitalized for 36 hours. A brain ultrasound scan result showed no pathological signs on Study day 1 and on Study day 6. On Study day 45, the electroencephalogram showed no marker for a convulsive event or manifestation of epilepsy. The participant did not receive any treatment for the event of seizure. On Study day 45, the event of seizure was resolved. The duration of the event of seizure was 44 days. The participant did not experience additional adverse events during the study, which was completed on Study day 315.

The most common SAEs reported in the Vaxelis group were bronchiolitis and respiratory syncytial virus bronchiolitis, each reported by 3 (1.2%) subjects and acute pyelonephritis, reported by 2 (0.8%) subjects in this group. None of these reports were considered related to study treatment.

2.3.3. Discussion on clinical aspects

Infanrix hexa is registered in Europe since 2000 and is licensed for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and disease caused by *Haemophilus influenzae* type b (Hib).

This phase IV, single-blind, randomised, controlled, multi-country study was intended to show both the non-inferiority of Infanrix hexa versus Vaxelis, as well as the superiority of Infanrix hexa versus Vaxelis in terms of anti-PRP geometric mean concentrations (GMCs) and proportion of subjects with antibody (Ab) concentrations greater than or equal to a threshold of 5 µg/mL 1-month after the booster dose.

Whereas serum anti-PRP Ab levels greater than 0.15 µg/mL are associated with short-term protection and 1 µg/mL with long-term protection, the anti-PRP Ab level required for protection against carriage is greater than 5 µg/mL. Thus, the level needed for protection against colonization is much higher than those needed to protect against invasive disease.

In total, 500 subjects were enrolled, of which 249 subjects in the Infanrix hexa group and 251 subjects in the Vaxelis group. Subjects received 3 doses of either Infanrix hexa or Vaxelis, co-administered with Prevenar 13, at 2-, 4- and 12 months (= booster dose).

The main demographic and baseline characteristics were overall similar between groups.

The co-primary objectives of the study to demonstrate that the Hib response induced at 1-month post-vaccination with Infanrix hexa was non-inferior to vaccination with Vaxelis was met in terms of anti-PRP GMC, but not in terms of the percentage of subjects with anti-PRP Ab concentrations ≥5.0 µg/mL. In addition, the condition for meeting the second co-primary objective on superiority at 1-month post-booster vaccination was not satisfied.

Regarding the secondary objectives, post-primary short-term seroprotection was observed in 79.8% of the subjects following vaccination with Infanrix hexa and in 100% following Vaxelis. At Pre-booster, a decrease in antibody concentrations is observed in both groups resulting in 61.2% of participants showing short-term seroprotection following vaccination with Infanrix hexa and in 94.4% following Vaxelis. Long-term seroprotection at one-month post-primary vaccination was reached in 30.5% of Infanrix hexa vaccinated subjects as compared to 92.2% of subjects vaccinated with Vaxelis.'

'Altogether, the submitted descriptive anti-PRP data suggest that a 2-doses primary vaccination with Vaxelis may have an added value over Infanrix hexa in terms of humoral immune responses up to the booster. Following administration of a booster dose, both vaccines achieve comparable short-term and long-term seroprotection rates.'

In total 71.5% of the subjects in the Infanrix hexa group and 79.3% of the subjects in the Vaxelis group experienced at least one symptom of unsolicited AE within the 31 days follow-up period after each vaccination, with the highest incidence of pyrexia, irritability and upper respiratory tract infection. A total of 45.4% of the subjects in the Infanrix hexa group and 56.6% of the subjects in the Vaxelis group experienced at least one unsolicited AE considered by the Investigator to be related to the study intervention. Most frequently reported AE considered related are pyrexia, irritability, restlessness, injection site erythema, injection site pain and injection site swelling.

These are all known AEs reported with a very common/common frequency after vaccination with Infanrix hexa, with the exception of upper respiratory tract infection. Of note, despite the very common occurrence in this study, none of the upper respiratory tract infections was considered by the Investigator to be related to the study intervention.
No relevant imbalances in unsolicited AEs reported within one month after vaccination are observed between both groups. Severe symptoms were reported in 1.6% of subjects in the Infanrix hexa group and 2.0% in the Vaxelis group, which include irritability, restlessness, eczema, injection site swelling, pyrexia and RSV bronchiolitis.
One SAE of seizure (afebrile presumptive convulsive event of moderate intensity) was considered related to the first dose of study vaccination (Infanrix hexa + Prevenar 13). The subject was hospitalized for 36 hours and the event was considered resolved after 44 days without complications. The participant continued in the study and did not experience additional adverse events. In addition, there were 23 SAEs considered not related to study intervention. There were no cases of death in the study.

There is no need to update of the SmPC of Infanrix hexa based data of this study.

3. CHMP overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.