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EMA/496744/2020
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/P46/132

Note

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

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1. Introduction

On 19th December 2019, the MAH submitted a completed paediatric study for *Infanrix Hexa*, in accordance with Article 46 of Regulation (EC) No1901/2006, 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 BOOSTRIX-049 (EudraCT number 2014-01120-30, GSK study report number 201334) 'A phase IV, open-label, non-randomised, multi-centre study to assess the immunogenicity and safety of a booster dose of *Infanrix hexa* in healthy infants born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery' is part of a clinical development program.

A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

Infanrix hexa is composed of: diphtheria (D), tetanus (T), pertussis (acellular, component) (Pa), hepatitis B (rDNA) (HBV), poliomyelitis (inactivated) (IPV) (DTPa-HBV-IPV) and Haemophilus influenzae type-b (Hib) conjugate vaccines. Hib vaccine is to be reconstituted before use with the liquid DTPa-HBV-IPV component.

Formulation of DTPa-HBV-IPV vaccine:

Diphtheria Toxoid (DT) >=30IU; Tetanus Toxoid (TT) >=40IU; Pertussis Toxoid (PT)=25µg; Filamentous Haemagglutinin (FHA)=25µg; Pertactin (PRN)=8µg; Hepatitis B surface antigen (HBsAg)=10µg; Inactivated Poliovirus type 1 (Mahoney strain)=40DU; Inactivated Poliovirus type 2 (MEF-1 strain)=8DU; Inactivated Poliovirus type 3 (Saukett strain)=32DU; Aluminium=700µg Al3+

Formulation of Hib vaccine:

Haemophilus influenzae type b polysaccharide (PRP)=10µg; TT (as carrier protein) ~=25µg; Aluminium as salts=0.12 mg.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- BOOSTRIX-049 (EudraCT number 2014-01120-30) : A phase IV, open-label, non-randomised, multi-centre study to assess the immunogenicity and safety of a booster dose of *Infanrix hexa* in healthy infants born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery.

2.3.2. Clinical study

BOOSTRIX-049, A phase IV, open-label, non-randomised, multi-centre study to assess the immunogenicity and safety of a booster dose of *Infanrix hexa* in healthy infants born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery.

Description

This was a phase IV, open-label, non-randomised, multi-centre, multi-country study with 2 parallel groups. The study was conducted to evaluate the immunogenicity and safety of booster dose of *Infanrix hexa* in infants who previously completed their primary vaccination series in study BOOSTRIX-048.

The study was initiated on September 19th 2016 and completed on March 19th 2019.

Methods

Objectives

1. Primary

- To assess the immunological response to *Infanrix hexa* in terms of seroprotection status for diphtheria, tetanus, hepatitis B, poliovirus and Hib antigens, and in terms of booster response for the pertussis antigens, 1 month after the booster dose in infants born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery.

2. Secondary

- To assess the persistence of antibodies to all vaccine antigens before the booster dose in infants born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery.
- To assess the immunological response to *Infanrix hexa* and *Prevenar 13* in terms of antibody concentrations or titres against all antigens, 1 month after the booster dose in infants born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery.
- To assess the immunological response to *Infanrix hexa* in terms of seropositivity rates against pertussis antigens, 1 month after the booster dose in infants born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery.
- To assess the safety and reactogenicity of *Infanrix hexa* and *Prevenar 13* in terms of solicited and unsolicited adverse events (AEs) and serious adverse events (SAEs).
- To assess the neurodevelopmental status of infants born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery, at 9 and 18 months of age.

A seroprotected subject was a subject whose antibody concentration/titre was greater than or equal to the level defining clinical protection.

The following seroprotection thresholds were applicable:

- ✓ *Anti-D antibody concentrations ≥ 0.1 IU/mL.*
- ✓ *Anti-T antibody concentrations ≥ 0.1 IU/mL.*
- ✓ *Anti-HBs antibody concentrations ≥ 10 mIU/mL.*

- ✓ *Anti-poliovirus types 1, 2 and 3 antibody titres ≥ 8 ED_{50}.*
- ✓ *Anti-PRP antibody concentrations ≥ 0.15 µg/mL.*
- ✓ *Anti-pneumococcal capsular polysaccharide antibody concentrations ≥ 0.35 µg/mL.*

*A seropositive subject was a subject whose antibody concentration/titre was greater than or equal to the assay cut-off defined in the study (*Table 1*).*

Table 1. Antibody determination

System	Component	Method	Kit/Manufacturer	Unit	Cut-off**	Laboratory*
SER	*Corynebacterium diphtheriae*. Diphtheria Toxoid Ab.IgG	ELI	NA	IU/mL	0.057	GSK
SER	*Clostridium tetani*. Tetanus Toxoid Ab.IgG	ELI	NA	IU/mL	0.043	GSK
SER	*Bordetella pertussis*. Filamentous Hemaglutinin Ab.IgG	ELI	NA	IU/mL	2.046	GSK
SER	*Bordetella pertussis*. Pertactin Ab.IgG	ELI	NA	IU/mL	2.187	GSK
SER	*Bordetella pertussis*. Pertussis Toxin Ab.IgG	ELI	NA	IU/mL	2.693	GSK
SER	Hepatitis B Virus.Surface Ab	CLIA	ADVIA Centaur anti-HBs2 (Siemens Healthcare)	mIU/mL	6.2	GSK
SER	Poliovirus Sabin Type 1 Ab	NEU	NA	ED_{50}	8	GSK
SER	Poliovirus Sabin Type 2 Ab	NEU	NA	ED_{50}	8	GSK
SER	Poliovirus Sabin Type 3 Ab	NEU	NA	ED_{50}	8	GSK
SER	*Haemophilus influenzae* type b. Polyribosyl Ribitol Phosphate Ab	ELI	NA	µg/mL	0.066	GSK
SER	*Streptococcus pneumoniae*. Polysaccharide 01 Ab.IgG	ECL	NA	µg/mL	0.080	GSK
SER	*Streptococcus pneumoniae*. Polysaccharide 03 Ab.IgG	ECL	NA	µg/mL	0.075	GSK
SER	*Streptococcus pneumoniae*. Polysaccharide 04 Ab.IgG	ECL	NA	µg/mL	0.061	GSK

System	Component	Method	Kit/Manufacturer	Unit	Cut-off**	Laboratory*
SER	*Streptococcus pneumoniae*. Polysaccharide 05 Ab.IgG	ECL	NA	µg/mL	0.198	GSK
SER	*Streptococcus pneumoniae*. Polysaccharide 06A Ab.IgG	ECL	NA	µg/mL	0.111	GSK
SER	*Streptococcus pneumoniae*. Polysaccharide 06B Ab.IgG	ECL	NA	µg/mL	0.102	GSK
SER	*Streptococcus pneumoniae*. Polysaccharide 07F Ab.IgG	ECL	NA	µg/mL	0.063	GSK
SER	*Streptococcus pneumoniae*. Polysaccharide 09V Ab.IgG	ECL	NA	µg/mL	0.066	GSK
SER	*Streptococcus pneumoniae*. Polysaccharide 14 Ab.IgG	ECL	NA	µg/mL	0.160	GSK
SER	*Streptococcus pneumoniae*. Polysaccharide 18C Ab.IgG	ECL	NA	µg/mL	0.111	GSK
SER	*Streptococcus pneumoniae*. Polysaccharide 19A Ab.IgG	ECL	NA	µg/mL	0.199	GSK
SER	*Streptococcus pneumoniae*. Polysaccharide 19F Ab.IgG	ECL	NA	µg/mL	0.163	GSK
SER	*Streptococcus pneumoniae*. Polysaccharide 23F Ab.IgG	ECL	NA	µg/mL	0.073	GSK

*GSK laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium.
** Assay cut-off and unit for few antigens were changed during the course of the study due to re-validation of all assays. Refer to Section 5.12 for more details.
SER=Serum
ECL=Electrochemiluminescence
ELI=Enzyme-linked immunosorbent assay (ELISA)
ELIF=22F Inhibition ELISA
NEU=Neutralisation assay
CLIA=ChemiLuminescence ImmunoAssay
IU/mL=International Units/millilitre
mIU/mL=milliInternational Units/millilitre
µg/mL=Micrograms/millilitre

Booster response to the pertussis toxin (PT), filamentous hemagglutinin (FHA) and pertactin (PRN) antigens, was defined as:

- *for subjects with pre-vaccination antibody concentration below the assay cut-off, postvaccination antibody concentration ≥ 4 times the assay cut-off,*
- *for subjects with pre-vaccination antibody concentration between the assay cut-off and < 4 times the assay cut-off, post-vaccination antibody concentration ≥ 4 times the pre-vaccination antibody concentration, and*
- *for subjects with pre-vaccination antibody concentration ≥ 4 times the assay cut-off, postvaccination antibody concentration ≥ 2 times the pre-vaccination antibody concentration.*

Study design

This was a phase IV, open-label, non-randomised, multi-centre, multi-country study with 2 parallel groups (figure 1).

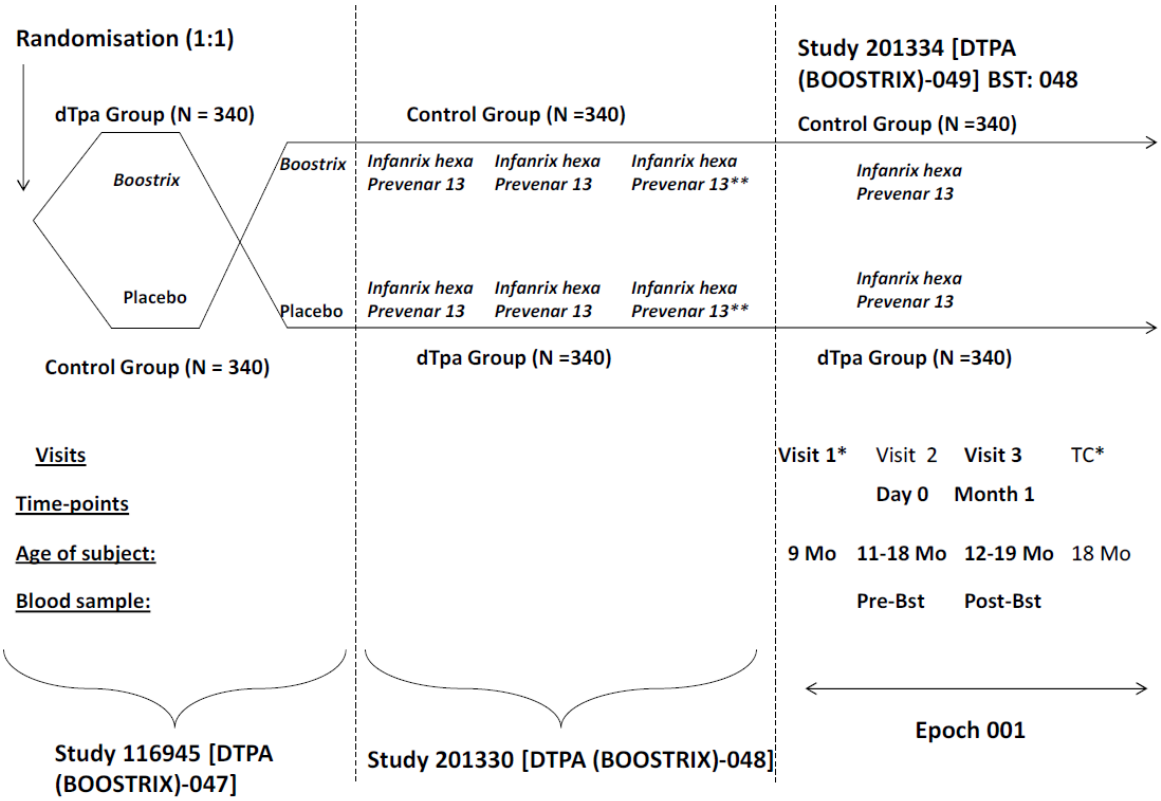
All subjects received a booster dose of *Infanrix hexa* coadministered with *Prevenar 13* between 11-18 months of age according to the routine national/local immunisation schedule or as specified in the study procedure manual (SPM).

Blood samples were to be drawn from all subjects before the booster dose administration and one month after the booster dose.

Data collection was done through an electronic case report form.

An IDMC (Independent data monitoring committee) was established to oversee the safety aspects including neurodevelopmental status of infants born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery in this clinical study.

The intended study duration was approximately 9-10 months, per subject.



N: Maximum Number of subjects planned to be enrolled; Mo: Age in Months
*The neurodevelopmental status was to be recorded when the subject was 9 months and 18 months of age. It was encouraged that subjects who were getting vaccinated at 18 months of age at Visit 2 or coming for Visit 3, complete their Ages and Stages Questionnaire-3 (ASQ-3) during their visit to the study centre. In case subjects completed Visit 3 before 18 months of age, the study staff contacted the parents/LAR(s) via phone and conducted an interview to complete the child's ASQ-3 at 18 months of age. For Czechia, the phone call at 18 months could be replaced by a clinic visit if deemed preferable by the study team. Refer to Section 5.9.4.4 for further details.
**Subjects received either 2 or 3-doses of *Infanrix hexa* and *Prevenar 13* during the course of the study 201330 [DTPA (BOOSTRIX)-048 PRI], depending on the national/local routine immunisation schedule.
Pre-Bst: Blood sample collected before the booster dose.
Post-Bst: Blood sample collected 1 month after the booster dose.

Figure 1. Study design

Study population /Sample size

Healthy male or female infants aged 9 months at the time of enrolment, born to mothers who were vaccinated in BOOSTRIX-047 study and who had completed their primary vaccination series as per protocol requirement in the study BOOSTRIX-048.

A maximum of 680 infants aged 9 months were planned to be enrolled in the study to receive the booster dose of *Infanrix hexa* and *Prevenar 13* at 11-18 months of age.

Infants were divided in 2 groups in the study as follows:

- dTpa Group: This group comprised infants, born to mothers belonging to the dTpa Group in BOOSTRIX-047 (i.e., mothers who had received a single dose of *Boostrix* during pregnancy and a dose of placebo immediately post-delivery).
- Control Group: This group comprised infants, born to mothers belonging to the Control Group in study BOOSTRIX-047 (i.e., mothers who had received a single dose of placebo during pregnancy and a dose of *Boostrix* immediately post-delivery).

Treatments

Formulation and characteristics of the study vaccine are presented in Table 2. The dosage and administration of study vaccine is given in Table 3.

Table 2. Study vaccines

Treatment name	Vaccines name	Formulation	Presentation	Volume to be administered*	Number of doses	Lot numbers
Infanrix hexa	DTPa-HBV-IPV	DT≥30 IU; TT≥40 IU; PT=25 µg; FHA=25 µg; PRN=8 µg; HBsAg=10 µg; Inactivated Poliovirus type 1 (Mahoney strain)=40 DU; Inactivated Poliovirus type 2 (MEF-1 strain)=8 DU; Inactivated Poliovirus type 3 (Saukett strain); Aluminium=700 µg Al3+	The DTPa-HBV-IPV component was presented as a turbid white suspension in a pre-filled syringe.	0.5 mL*	1	DTPa-HBV-IPV AC21B551A AC21B576C AC21B614A AC21B623A AC21B632C AC21B632C AC21B659A Hib AHIBD095B AHIBD095B AHIBD165C AHIBD184C AHIBD202B AHIBD214C AHIBD202B
	Hib	PRP=10 µg; TT ≅ 25 µg Aluminium as salts=0.12 mg	The lyophilised Hib component was presented as a white pellet in a glass vial; it had to be reconstituted before use			

Treatment name	Vaccines name	Formulation	Presentation	Volume to be administered*	Number of doses	Lot numbers
			with the liquid DTPa-HBV-IPV component.			
Prevenar 13	*Prevenar 13*	PS1=2.2 µg CRM197; PS3=2.2 µg CRM197; PS4=2.2 µg CRM197; PS5=2.2 µg CRM197; PS6A=2.2 µg CRM197; PS6B=4.4 µg CRM197; PS7F=2.2 µg CRM197; PS9V=2.2 µg CRM197; PS14=2.2 µg CRM197; PS18C=2.2 µg CRM197; PS19A=2.2 µg CRM197; PS19F=2.2 µg CRM197; PS23F=2.2 µg CRM197; $AlPO_4$=125 µg Al3+	Suspension for injection in a pre-filled syringe	0.5 mL	1	DEXTA539AZ DEXTA549AZ DEXTA553AZ DLOCA159A DLOCA168A

*After reconstitution
DT: Diphtheria toxoid, TT: Tetanus toxoid, PT: Pertussis toxoid, FHA: Filamentous haemagglutinin, PRN: Pertactin; PRP, polyribosyl-ribitol phosphate.

Table 3. Vaccination schedule/site

Type of contact and time point	Volume to be administered	Study group	Treatment name	Route	Site*	Side
Visit 2 (Day 0)	0.5 mL	dTpa Group and Control Group	*Infanrix hexa*	Intramuscular	Thigh or Deltoid	Right
			Prevenar 13			Left

*The vaccines had to be administered in the thigh or deltoid, according to the national recommendations/local practice.

Outcomes/endpoints

1. Primary
   - Immunogenicity with respect to components of *Infanrix hexa*
     - Anti-diphtheria (anti-D), anti-tetanus (anti-T), anti-HBs, anti-poliovirus type 1, 2, 3 and antipolyribosyl-ribitol phosphate (anti-PRP) seroprotection status, 1 month after the booster dose.
     - Booster response to PT, FHA and PRN antigens, 1 month after the booster dose.
2. Secondary
   - Immunogenicity with respect to components of *Infanrix hexa* and *Prevenar 13*

Before the booster dose:

- Anti-D, anti-T, anti-poliovirus type 1, 2, 3, anti-HBs and anti-PRP seroprotection status.
- Anti-PT, anti-FHA and anti-PRN and anti-pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) seropositivity rates.
- Anti-D, anti-T, anti-PT, anti-FHA, anti-PRN, anti-poliovirus type 1, 2, 3, anti-HBs and antipneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) and anti-PRP antibody concentrations or titres.

One month after the booster dose:

- Anti-D, anti-T, anti-poliovirus type 1, 2, 3, anti-HBs, anti-PRP, anti-PT, anti-FHA, anti-PRN and anti-pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) antibody concentrations or titres.
- Anti-PT, anti-FHA, anti-PRN antibody seropositivity rates.

- Solicited local and general adverse events (AEs)
  - Occurrence of solicited local and general AEs during the 4-day (Days 0-3) follow-up period after booster vaccination.
- Unsolicited AEs
  - Occurrence of unsolicited AEs during the 31-day (Days 0-30) follow-up period after booster vaccination.
- Serious adverse events (SAEs)
  - Occurrence of reported SAEs from booster dose up to study end.
- Neurodevelopmental status was to be assessed at 9 and 18 months of age adjusted for prematurity
  - Proportion of infants with an Ages and Stages Questionnaire-3 (ASQ-3) score in the black zone in any domain.
  - Proportion of infants with an ASQ-3 score in the black zone for gross motor skills.
  - Proportion of infants with an ASQ-3 score in the black zone for fine motor skills.
  - Proportion of infants with an ASQ-3 score in the black zone for communication.
  - Proportion of infants with an ASQ-3 score in the black zone for problem solving skills.
  - Proportion of infants with an ASQ-3 score in the black zone for personal-social skills.
  - Proportion of infants referred for formal neurodevelopmental evaluation using Bayley Scale for Infant Development, Version III (BSID-III).
  - Proportion of infants with at least 1 of the indicators of neurodevelopmental impairment using BSID-III.

Statistical Methods

1. Analysis of immunogenicity

The primary analysis was based on the According-to-protocol (ATP) cohort for analysis of immunogenicity. As the percentage of enrolled subjects excluded from this ATP cohort was more than

5%, a second analysis based on the Total vaccinated cohort (TVC) was performed to complement the ATP analysis. All analyses were descriptive.

For each group, at each time point that a blood sample result was available:

- Seropositivity rates against PT, FHA and PRN antigens and pneumococcal antigens (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) with exact 95% confidence interval (CI) were calculated.
- Seroprotection rates against diphtheria toxoid, tetanus toxoid, HBs, PRP antigen and poliovirus types 1, 2, 3 antigens (with exact 95% CI) were calculated.
- Percentage of subjects with anti-pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) antibody concentrations ≥0.35 μg/mL (invasive pneumococcal disease threshold of protection for electrochemiluminescence GSK assay) was calculated along with its exact 95% CI.
- Percentage of subjects with anti-D and anti-T antibody concentrations ≥ 1.0 IU/mL was calculated along with its exact 95% CI.
- Percentage of subjects with anti-PRP antibody concentrations ≥ 1.0 µg/mL and anti-HBs antibody concentrations ≥ 100 mIU/mL was calculated along with its exact 95% CI.
- Geometric mean concentration/titre with 95% CI was tabulated for antibodies against each antigen.
- The booster response rates to PT, FHA and PRN (with exact 95% CI) 1 month after the booster dose were calculated.

The above summaries were also provided by primary vaccination schedule, by gestational age and age of the mother at dose 1 in the primary study.

- The distribution of antibody concentrations/titres for each antigen was displayed using reverse cumulative distribution curves.
- The immunogenicity analysis for the pertussis antigens was generated on the adapted ATP cohort taking in to account all the time points from 116945 [DTPA (BOOSTRIX)-047] up to the current study.

2. Analysis of safety

The primary analysis was based on the TVC. All analyses were descriptive.

- The percentage of subjects with at least 1 local AE (solicited or unsolicited), with at least 1 general AE (solicited or unsolicited) and with any AE (solicited or unsolicited) during the 4-day (Days 0-3) follow-up period was tabulated with exact 95% CI. The same calculations were done for AEs (solicited or unsolicited) rated as grade 3 in intensity, for AEs (solicited or unsolicited) leading to medical advice and for AEs (solicited or unsolicited) assessed as causally related to vaccination.
- The incidence of local AEs (solicited and unsolicited) was calculated at each injection site as well as overall (all sites considered) for each group.
- The percentage of subjects reporting each individual solicited local and general AE during the 4-day (Days 0-3) solicited follow-up period was tabulated after the vaccine dose, with exact 95% CI. The same calculations were done for each individual solicited AE rated as grade 3 in intensity and for each individual solicited AE assessed as causally related to vaccination. The

computations were also done for grade ≥2 (solicited AEs only) and grade 3 AEs, for AEs considered related to vaccination (general AEs only), for grade 3 AEs considered related to vaccination (general AEs only) and for AEs that resulted in a medically-attended visit.

- Occurrence of fever and related fever was reported per 0.5°C cumulative temperature increments as well as the occurrence of grade 3 fever (>39.0°C axillary temperature) with causal relationship to vaccination.
- The verbatim reports of unsolicited AEs were reviewed by a physician and the signs and symptoms were coded according to Medical Dictionary for Regulatory Authorities. Every verbatim term was matched with the appropriate Preferred Term. The percentage of subjects with unsolicited AEs occurring within 31-day (Days 0-30) follow-up period after any dose with its exact 95% CI was tabulated by group, and by preferred term. Similar tabulation was done for unsolicited AEs rated as grade 3, for unsolicited AEs with causal relationship to vaccination and AEs/SAEs leading to withdrawal from the study.
- The percentage of subjects who received concomitant medication and antipyretic medication during the 4-day (Days 0-3) follow-up period and during the entire study period was tabulated (with exact 95% CI) after the booster dose.
- Any large injection site reaction (defined as any local swelling with diameter >50 mm and/or any noticeable diffuse injection site swelling [diameter not measurable] and/or any noticeable increased circumference of the injected limb) reported during the 4-day (Days 0-3) follow-up period after the booster dose was described in detail.
- Subjects who experienced at least 1 SAE from booster vaccination up to study end were described.
- Subjects who reported at least 1 SAE after the end of primary study 201330 [DTPA (BOOSTRIX)-048 PRI] and before 201334 [DTPA (BOOSTRIX)-049 BST: 048] study were described.
- Withdrawals due to AEs and SAEs following vaccinations were described in detail.
- Neurodevelopmental status of the subjects was assessed depending on the ASQ-3 score. The proportion of subjects in the black zone for any domain, for gross motor skills, fine motor skills, communication, problem solving skills and personal-social skills was tabulated. The proportion of infants referred for formal neurodevelopmental evaluation using BSID-III and those with at least 1 indicator of neurodevelopmental impairment using BSID-III was also tabulated. In order to account for subjects who withdrew from the study after Visit 1 (after completion of ASQ-3 questionnaire but had not received booster vaccination), the analysis was to be performed on the Total enrolled cohort.
- The percentage of subjects with congenital anomalies reported across the 3 studies (116945 [DTPA (BOOSTRIX)-047], 201330 [DTPA (BOOSTRIX)-048 PRI] and 201334 [DTPA (BOOSTRIX)-049 BST: 048) with its exact 95% CI was tabulated by group, and preferred term.

Assessor's comment

Methods are overall acceptable.

Primary and secondary objectives and endpoints are relevant. The seroprotection thresholds proposed as associated with clinical protection against diphtheria, tetanus, hepatitis B, poliomyelitis, *Haemophilus influenzae type b* and *Streptococcus pneumoniae* infections are appropriate.
The definition of booster response to pertussis antigens is acceptable.

Results

Recruitment/ Number analysed

A total of 540 subjects were vaccinated, of which 4 subjects from the dTpa Group were withdrawn from the study (1 subject due to consent withdrawal and 3 subjects were lost to follow-up). Hence, 536 subjects completed the study.

For the ATP analysis, 6 subjects were excluded from safety analysis and further 55 subjects were excluded from immunogenicity analysis (Table 4). Therefore, 534 subjects comprised the ATP cohort for safety and 479 subjects comprised the ATP cohort for immunogenicity.

Table 4. Number of subjects enrolled into the study as well as excluded from ATP analysis

	Total			dTpa Group		Control Group	
Title	n	s	%	n	s	n	s
All enrolled subjects	551			270		281	
Study vaccine dose not administrated but subject number allocated (code 1030)	11	11		7	7	4	4
Total vaccinated cohort	**540**		**100**	**263**		**277**	
Administration of vaccine(s) forbidden in the protocol (code 1040)	2	3		1	1	1	2
Randomisation failure (code 1050)	1	1		0	0	1	1
Randomisation code broken at the investigator site (code 1060)	2	2		1	1	1	1
Vaccine temperature deviation (code 1080)	1	1		0	0	1	1
Expired vaccine administered (code 1090)	0	1		0	0	0	1
ATP cohort for safety	**534**		**98.9**	**261**		**273**	
Protocol violation (inclusion/exclusion criteria) (code 2010)	8	8		4	4	4	4
Non-compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	9	10		3	3	6	7
Non-compliance with blood sampling schedule (including wrong and unknown dates) (code 2090)	21	24		14	15	7	9
Essential serological data missing (code 2100)	17	29		11	19	6	10
ATP cohort for immunogenicity	**479**		**88.7**	**229**		**250**	

dTpa Group=Infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received dTpa during pregnancy.
Control Group=Infants born to mothers belonging to the Control Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received placebo during pregnancy.
All subjects in this study received *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Note: Subjects may have more than one elimination code assigned
n=number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s=number of subjects with the elimination code assigned
%=percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort
All eliminations from the study 201330 [DTPA(BOOSTRIX)-048 PRI] were carried forward for this follow up study except for the visit specific elimination codes (2090, 2100 and 2120).

Assessor's comment

Similar proportion of subjects were withdrawn from the ATP cohort for safety and for immunogenicity in both groups. ATP cohort for safety consists of 99.3 and 98.6% of the TVC for dTpa and control groups, respectively. ATP cohort for immunogenicity consists of 87.1 and 90.3% of the TVC for dTpa and control groups, respectively. This is acceptable.

Baseline data

The demographic characteristics for the ATP cohort for immunogenicity is presented in Table 5. The demographic characteristics of the ATP cohort for immunogenicity were similar to the TVC.

Table 5. Summary of demographics characteristics

		dTpa Group N=229		Control Group N=250		Total N=479	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age [month] at vaccination dose: 1	Mean	15.0	-	14.8	-	14.9	-
	SD	2.5	-	2.5	-	2.5	-
	Q1	12.0	-	12.0	-	12.0	-
	Median	16.0	-	16.0	-	16.0	-
	Q3	17.0	-	17.0	-	17.0	-
Gender	Female	105	45.9	111	44.4	216	45.1
	Male	124	54.1	139	55.6	263	54.9
Geographic Ancestry	African Heritage/African American	4	1.7	7	2.8	11	2.3
	Asian-East Asian Heritage	1	0.4	0	0.0	1	0.2
	Asian-South East Asian Heritage	2	0.9	0	0.0	2	0.4
	White-Arabic/North African Heritage	1	0.4	2	0.8	3	0.6
	White-Caucasian/European Heritage	206	90.0	235	94.0	441	92.1
	Other	15	6.6	6	2.4	21	4.4
Primary vaccination schedule	2-dose schedule	22	9.6	32	12.8	54	11.3
	3-dose schedule	207	90.4	218	87.2	425	88.7
Country	Australia	10	4.4	8	3.2	18	3.8
	Canada	59	25.8	68	27.2	127	26.5
	Czechia	30	13.1	32	12.8	62	12.9
	Finland	17	7.4	26	10.4	43	9.0
	Italy	3	1.3	3	1.2	6	1.3
	Spain	110	48.0	113	45.2	223	46.6
Maternal age group	18-24Y	4	1.7	11	4.4	15	3.1
	25-34Y	140	61.1	156	62.4	296	61.8
	35-45Y	85	37.1	83	33.2	168	35.1
Gestational week of foetus at dose 1 of maternal vaccination	27-32W	135	59.0	149	59.6	284	59.3
	33-36W	94	41.0	101	40.4	195	40.7

dTpa Group=Infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received dTpa during pregnancy.
Control Group=Infants born to mothers belonging to the Control Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received placebo during pregnancy.
All subjects in this study received *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
N=total number of subjects; n(%)=number(percentage) of subjects in a given category
Value=value of the considered parameter
SD=standard deviation; Q1=Quartile 1; Q3=Quartile 3
2-dose schedule=subjects who received 2-dose of *Infanrix hexa* at 2,4 months of age or 3,5 months of age, co-administered with *Prevenar 13*.
3-dose schedule=subjects who received 3-dose of *Infanrix hexa* at 2,3,4 months of age or 2,4,6 months of age, co-administered with *Prevenar 13*.
Prevenar 13 could be administered as 2-doses or 3-doses primary vaccination schedule (according to the routine national immunisation schedule of the country)

Assessor's comment

Demographic characteristics are appropriately balanced between groups.

Efficacy results

1. Immune responses to Diphtheria and Tetanus toxoids (Table 6)

- Before the booster dose of *Infanrix hexa*, 81.2% and 90.2% of subjects were seroprotected against diphtheria respectively in dTpa group and control group (Secondary objective). The geometric mean concentration (GMC) value for anti-D was lower in dTpa group (0.207) when compared to control group (0.322).

  Similar proportion of subjects (96.4% and 95.1%) were seroprotected against tetanus respectively in dTpa group and control group (Secondary objective). No differences were observed in the GMCs between the 2 groups for anti-T.

- At 1 month after the booster dose of *Infanrix hexa*, the percentage of subjects seroprotected against diphtheria was 100% in both groups (Primary objective). Slightly lower anti-D GMC value was observed in the dTpa group (6.114) when compared to the control group (8.402).

  The percentage of subjects seroprotected against tetanus was 100% in both groups (Primary objective). There were no differences between the 2 groups in terms of anti-T GMCs.

Table 6. Overall percentage of subjects with anti-D and anti-T antibody concentration above or equal to 0.1 IU/mL and 1.0 IU/mL and geometric mean concentrations, before and 1 month after the booster dose (ATP cohort for immunogenicity)

				≥0.1 IU/mL				≥1 IU/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-D antibody	dTpa Group	Pre-Bst	223	181	81.2	75.4	86.1	10	4.5	2.2	8.1	0.207	0.184	0.234
		Post-Bst	221	221	100	98.3	100	219	99.1	96.8	99.9	6.114	5.577	6.703
	Control Group	Pre-Bst	244	220	90.2	85.7	93.6	27	11.1	7.4	15.7	0.322	0.285	0.363
		Post-Bst	247	247	100	98.5	100	247	100	98.5	100	8.402	7.694	9.174
anti-T antibody	dTpa Group	Pre-Bst	223	215	96.4	93.1	98.4	87	39.0	32.6	45.8	0.753	0.646	0.878
		Post-Bst	221	221	100	98.3	100	220	99.5	97.5	100	8.200	7.324	9.180
	Control Group	Pre-Bst	244	232	95.1	91.6	97.4	73	29.9	24.2	36.1	0.578	0.506	0.659
		Post-Bst	247	247	100	98.5	100	243	98.4	95.9	99.6	6.758	6.143	7.433

dTpa Group=Infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received dTpa during pregnancy.
Control Group=Infants born to mothers belonging to the Control Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received placebo during pregnancy.
All subjects in this study received *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
GMC=geometric mean antibody concentration calculated on all subjects; N=number of subjects with available results
n/%=number/percentage of subjects with concentration equal to or above specified value
95% CI=95% confidence interval; LL=Lower Limit, UL=Upper Limit
Pre-Bst=blood sample collected before the booster dose in infants
Post-Bst=blood sample collected 1 month after the booster dose in infants

Assessor's comment

As expected, the percentage of seroprotected (cut-off of 0.1 IU/ml) subjects against diphtheria before the boost was lower for dTpa group. Around 20%, instead of 10%, of the infants born from mothers vaccinated during pregnancy would be susceptible to diphtheria infection during a certain laps of time between post-primary and booster vaccination.

All subjects were seroprotected against diphtheria and tetanus 1 month after the booster vaccination with *Infanrix hexa*, independently of the time of vaccination of the mother, maternal age and dose schedule of infant's vaccination. Most of the dTpa and control subjects achieved the threshold of 1.0 IU/ml associated with long term protection, even if lower anti-D GMC value was observed in the dTpa group. Conversely, a trend for a lower anti-T GMC value was observed in the control group compared to the dTpa group. These data suggest that the primary vaccination induced adequate immune memory in both group, i.e. independently of maternal immunisation (MI).

2. Immune response to HBs antigen (

Table 7)

- Before the booster dose of *Infanrix hexa*, 94.1% and 94.2% of subjects were seroprotected against hepatitis B respectively in dTpa group and control group (Secondary objective). No differences were observed in the GMCs between the 2 groups for anti-HBs.
- At 1 month after the booster dose of *Infanrix hexa*, 99.5% and 99.2% of subjects were seroprotected against hepatitis B respectively in dTpa group and control group (Primary objective). There were no differences between the 2 groups in terms of anti-HBs GMCs.

Table 7. Overall percentage of subjects with anti-HBs Ab concentration ≥10 mIU/ml, ≥100 mIU/ml, and GMC, before and 1 month after the booster dose (ATP cohort for immunogenicity)

				≥10 mIU/mL				≥100 mIU/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-HBs antibody	dTpa Group	Pre-Bst	219	206	94.1	90.1	96.8	147	67.1	60.5	73.3	158.7	129.9	194.0
		Post-Bst	216	215	99.5	97.4	100	211	97.7	94.7	99.2	4858.3	3918.4	6023.7
	Control Group	Pre-Bst	243	229	94.2	90.5	96.8	171	70.4	64.2	76.0	193.4	158.4	236.1
		Post-Bst	241	239	99.2	97.0	99.9	233	96.7	93.6	98.6	5031.2	4072.7	6215.4

dTpa Group=Infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received dTpa during pregnancy.
Control Group=Infants born to mothers belonging to the Control Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received placebo during pregnancy.
All subjects in this study received *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
GMC=geometric mean antibody concentration calculated on all subjects
N=number of subjects with available results
n/%=number/percentage of subjects with concentration equal to or above specified value
95% CI=95% confidence interval; LL=Lower Limit, UL=Upper Limit
Pre-Bst=blood sample collected before the booster dose in infants
Post-Bst=blood sample collected 1 month after the booster dose in infants

Assessor's comment

Percentages of infants that were seroprotected (cut-off of 10 mIU/ml) against Hepatitis B before and 1 month after the boost with *Infanrix hexa* were high, independent of the time of vaccination of the mother, the mother's maternal age and the dose schedule of infant's vaccination. Percentages of subjects mounting an Ab response ≥ 100 mIU/ml and GMT were similar between groups suggesting that maternal immunization does not interfere with the infant's vaccine induced-protection against Hepatitis B.

3. Immune responses to poliovirus types 1, 2 and 3 (Table 8)

- Before the booster dose of *Infanrix hexa*, 88.3-91.7% and 89.5-95.1% of subjects were seroprotected against poliovirus types 1, 2 and 3 respectively in dTpa group and control group (Secondary objective). No differences were observed in the GMCs between the 2 groups for anti-poliovirus Ab.
- At 1 month after the booster dose of *Infanrix hexa*, 100% of subjects were seroprotected against poliovirus types 1, 2 and 3 in both groups (Primary objective). There were no differences between the 2 groups in terms of anti-poliovirus GMCs.

Table 8. Overall percentage of subjects with anti-poliovirus type 1, 2 and 3 Ab titer ≥ 8 and GMC titre, before and 1 month after the booster dose (ATP cohort for immunogenicity)

				≥8 ED_{50}				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
anti-polio 1 antibody	dTpa Group	Pre-Bst	213	188	88.3	83.2	92.3	64.9	52.0	80.9
		Post-Bst	204	204	100	98.2	100	1611.7	1381.2	1880.6
	Control Group	Pre-Bst	237	212	89.5	84.8	93.1	83.3	67.7	102.5
		Post-Bst	228	228	100	98.4	100	1532.1	1322.2	1775.3
anti-polio 2 antibody	dTpa Group	Pre-Bst	210	188	89.5	84.6	93.3	71.7	57.6	89.4
		Post-Bst	201	201	100	98.2	100	2232.4	1931.2	2580.5
	Control Group	Pre-Bst	236	215	91.1	86.7	94.4	79.2	64.4	97.5
		Post-Bst	227	227	100	98.4	100	2371.2	2097.9	2680.1
anti-polio 3 antibody	dTpa Group	Pre-Bst	205	188	91.7	87.1	95.1	106.0	84.1	133.4
		Post-Bst	188	188	100	98.1	100	2944.6	2529.4	3427.9
	Control Group	Pre-Bst	226	215	95.1	91.5	97.5	118.4	97.0	144.5
		Post-Bst	210	210	100	98.3	100	2891.8	2496.2	3350.2

dTpa Group=Infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received dTpa during pregnancy.

Control Group=Infants born to mothers belonging to the Control Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received placebo during pregnancy.

Assessor's comment

All the children were seroprotected (cut-off of 8 ED_{50}) against poliovirus types 1, 2 and 3 one month after the booster dose with *Infanrix hexa*, independent of the time of vaccination of the mother, the mother's maternal age and the dose schedule of infant's primary vaccination.

4. Immune responses to *Haemophilus influenzae type b* PRP (Table 9)

- Before the booster dose of *Infanrix hexa*, 72.5% and 68.0% of subjects were seroprotected against Hib respectively in dTpa group and control group (Secondary objective). A trend for slightly lower anti-PRP GMC values were observed in the control group compared to the dTpa group.
- At 1 month after the booster dose of *Infanrix hexa*, 100% and 99.6% of subjects were seroprotected against Hib respectively in dTpa group and control group (Primary objective). A trend for lower anti-PRP GMC values were observed in the control group compared to the dTpa group.

Table 9. Overall percentage of subjects with anti-PRP Ab concentration ≥ 0.15 µg/ml, 1.0 µg/ml and GMC, before and 1 month after the booster dose (ATP cohort for immunogenicity)

				≥0.15 µg/mL				≥1 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-PRP antibody	dTpa Group	Pre-Bst	222	161	72.5	66.1	78.3	50	22.5	17.2	28.6	0.371	0.303	0.453
		Post-Bst	221	221	100	98.3	100	220	99.5	97.5	100	26.186	22.610	30.327
	Control Group	Pre-Bst	244	166	68.0	61.8	73.8	43	17.6	13.1	23.0	0.292	0.244	0.349
		Post-Bst	247	246	99.6	97.8	100	241	97.6	94.8	99.1	19.714	16.891	23.010

dTpa Group=Infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received dTpa during pregnancy.
Control Group=Infants born to mothers belonging to the Control Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received placebo during pregnancy.
All subjects in this study received *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
GMC=geometric mean antibody concentration calculated on all subjects; N=number of subjects with available results
n/%=number/percentage of subjects with concentration equal to or above specified value
95% CI=95% confidence interval; LL=Lower Limit, UL=Upper Limit
Pre-Bst=blood sample collected before the booster dose in infants
Post-Bst=blood sample collected 1 month after the booster dose in infants

Assessor's comment

Percentages of infants that were seroprotected (cut-off of 0.15 µg/ml) against *Haemophilus influenzae type b* 1 month after the booster dose with *Infanrix hexa* were high, independent of the time of vaccination of the mother, the mother's maternal age and the dose schedule of infant's primary vaccination. Most of the subjects of both groups achieved the Ab threshold associated with long-term protection (1.0 µg/ml).

5. Immune responses to *Bordetella pertussis* antigens (PT, FHA, PRN) (Table 10)

- Before the booster dose of *Infanrix hexa*, 68.6-96.4% and 82.4-98.8% of subjects were seropositive (antibody concentration ≥ assay cut-off) against pertussis antigens respectively in dTpa group and control group (Secondary objective). The GMCs for the anti-pertussis antibodies were slightly lower in the dTpa group (anti-PT: 4.4; anti-FHA: 11.2; anti-PRN: 6.9) when compared to control group (anti-PT: 6.3; anti-FHA: 16.5; anti-PRN: 9.6).
- At 1 month after the booster dose of *Infanrix hexa*, the booster response rates against pertussis antigens was 92.1-98.1 % in dTpa group and 96.7-99.6 % in control group (Primary objective). All subjects in both groups were seropositive (antibody concentration ≥ assay cut-off) against pertussis antigens, except for 1 subject in the dTpa group who did not reach seropositive antibody level for anti-PT.
- Lower GMCs values were observed in the dTpa group for anti-PT (52.4) and anti-FHA (152.5) when compared to the control group (anti-PT: 80.3; anti-FHA: 187.2). However, lower GMC value in the dTpa group compared to the control group was not observed for anti-PRN (dTpa group: 333.9; control group: 262.3). Large fold increases of the GMCs from the pre-booster to the 1-month after booster was observed in dTpa group (anti-PT: 11.9-fold, anti-FHA: 13.6-fold, anti-PRN: 48.4-fold), and this in similar ranges as observed in the control group (anti-PT: 12.7-fold, anti-FHA: 11.3-fold, anti-PRN: 27.3-fold).

- At 1 month after the booster dose of *Infanrix hexa*, the difference of GMC values observed between the dTpa and the control groups was more pronounced for infants that received the study vaccines as a 2-dose schedule when compared to the infants that received the study vaccines as a 3-dose schedule. A difference in anti-PRN GMC was also observed between 2-dose schedule dTpa and control groups.

- At 1 month after the booster dose of *Infanrix hexa*, differences of anti-PT and anti-FHA GMC values observed between the dTpa and the control groups were more pronounced for infants that were born from younger women (25-34Y).

Table 10. Overall percentage of subjects with anti-PT, anti-FHA and anti-PRN Ab concentration ≥ to the assay cut-off, and GMC across all time points (adapted ATP cohort for immunogenicity)

				≥Assay cut-off*				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
anti-PT antibody	dTpa Group	PRE	288	167	58.0	52.1	63.8	4.0	3.5	4.5
		PI(D30)	289	285	98.6	96.5	99.6	45.6	40.4	51.5
		PI(CORD)	290	286	98.6	96.5	99.6	46.9	41.2	53.3
		Pre-Pri	242	218	90.1	85.6	93.5	11.9	10.3	13.6
		Post-Pri	266	266	100	98.6	100	32.7	30.2	35.3
		Pre-Bst	223	153	68.6	62.1	74.6	4.4	3.8	5.0
		Post-Bst	221	220	99.5	97.5	100	52.4	46.9	58.4
	Control Group	PRE	291	184	63.2	57.4	68.8	4.3	3.8	4.8
		PI(D30)	292	179	61.3	55.5	66.9	4.1	3.6	4.6
		PI(CORD)	292	201	68.8	63.2	74.1	5.5	4.8	6.3
		Pre-Pri	253	88	34.8	28.9	41.0	2.2	2.0	2.5
		Post-Pri	271	271	100	98.6	100	54.7	51.0	58.6
		Pre-Bst	244	201	82.4	77.0	86.9	6.3	5.5	7.1
		Post-Bst	247	247	100	98.5	100	80.3	73.3	88.1
anti-FHA antibody	dTpa Group	PRE	289	273	94.5	91.2	96.8	13.7	11.8	15.8
		PI(D30)	290	290	100	98.7	100	317.5	285.0	353.8
		PI(CORD)	291	291	100	98.7	100	366.1	329.0	407.3
		Pre-Pri	242	242	100	98.5	100	88.3	77.7	100.4
		Post-Pri	266	266	100	98.6	100	68.5	63.5	73.9
		Pre-Bst	223	215	96.4	93.1	98.4	11.2	9.6	13.1
		Post-Bst	221	221	100	98.3	100	152.5	136.3	170.6
	Control Group	PRE	291	275	94.5	91.2	96.8	15.7	13.6	18.0
		PI(D30)	291	275	94.5	91.2	96.8	15.0	13.1	17.2
		PI(CORD)	292	282	96.6	93.8	98.3	22.7	19.7	26.2
		Pre-Pri	253	210	83.0	77.8	87.4	6.6	5.7	7.7
		Post-Pri	271	271	100	98.6	100	103.5	95.6	112.1
		Pre-Bst	244	241	98.8	96.4	99.7	16.5	14.4	18.8
		Post-Bst	247	247	100	98.5	100	187.2	172.7	202.9
anti-PRN antibody	dTpa Group	PRE	289	244	84.4	79.7	88.4	11.1	9.1	13.4
		PI(D30)	290	290	100	98.7	100	283.6	237.1	339.1
		PI(CORD)	290	289	99.7	98.1	100	301.8	250.9	362.9
		Pre-Pri	242	231	95.5	92.0	97.7	70.5	56.1	88.5
		Post-Pri	266	266	100	98.6	100	60.5	54.2	67.6
		Pre-Bst	223	187	83.9	78.4	88.4	6.9	5.8	8.2
		Post-Bst	220	220	100	98.3	100	333.9	285.4	390.7
	Control Group	PRE	290	247	85.2	80.6	89.1	11.3	9.4	13.6
		PI(D30)	291	246	84.5	79.9	88.5	10.5	8.7	12.5
		PI(CORD)	291	256	88.0	83.7	91.5	14.6	12.1	17.7
		Pre-Pri	253	151	59.7	53.4	65.8	4.5	3.7	5.4
		Post-Pri	270	269	99.6	98.0	100	92.0	81.6	103.6
		Pre-Bst	244	213	87.3	82.5	91.2	9.6	8.3	11.2
		Post-Bst	247	247	100	98.5	100	262.3	230.9	298.1

dTpa Group=Infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received dTpa during pregnancy.

Control Group=Infants born to mothers belonging to the Control Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received placebo during pregnancy.

All subjects in this study received *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.

GMC=geometric mean antibody concentration calculated on all subjects
N=number of subjects with available results
n/%=number/percentage of subjects with concentration equal to or above specified value
95% CI=95% confidence interval; LL=Lower Limit, UL=Upper Limit
PRE=pre-booster vaccination (pregnancy dose) blood sampling time-point in mothers
PI(D30)=post-booster vaccination (pregnancy dose) blood sampling time-point, 1 month after booster dose in mothers
PI(CORD)=cord blood sample at delivery post-pregnancy booster dose
Pre-Pri=blood sample collected before the first dose of the primary vaccination course in infants
Post-Pri=blood sample collected 1 month after the last dose of the primary vaccination course in infants
Pre-Bst=blood sample collected before the booster dose in infants
Post-Bst=blood sample collected 1 month after the booster dose in infants
*Assay cut-off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, 2.187 IU/mL for anti-PRN

Assessor's comment

Since there is no correlate of protection (CoP) regarding the *B. pertussis* infection, it is considered that the most appropriate way to study a potential effect of maternal immunization (MI) on infant's vaccination is to compare the GMC induced by the infant's vaccination in the dTpa and in the control groups. Seropositive rates and booster responses were not considered.

The concentrations of circulating Ab before the boost were comparable (only slightly lower values were observed in the control group compare to the dTpa group) between dTpa and control groups and in the same range than the titers observed in cord blood of infants born from non-vaccinated mothers.
A blunting of the PT- and FHA- Ab responses are however still observed at 1 month post-boost. 95% CI were not overlapping. Conversely, anti-PRN titers were higher for the dTpa group when compared to the control group.

Large fold increases of the GMCs from the pre-booster to the 1-month after booster was observed in both dTpa and control groups, suggesting that infants of both groups developed an immune memory against *B. pertussis*.

Although the analysis is not powered to generate statistically significant results, it is to be noted that the difference of anti-PT and anti-FHA GMC values observed between the dTpa and the control groups was more pronounced for infants that received the study vaccines as a 2-dose schedule when compared to the infants that received the study vaccines as a 3-dose schedule. A difference in anti-PRN GMC was also observed between 2-dose schedule dTpa and control groups (176.1 vs 233.4 IU/ml).

Nevertheless, in the absence of CoP, the observed blunting of the pertussis response is difficult to interpret in term of clinical relevance.

6. Immune responses to *Prevenar 13* (Table 11)

- Before the booster dose of *Prevenar 13*, 57.8-99.5% and 63.4-100% of subjects were seropositive against pneumococcal antigens respectively in dTpa group and control group. Slightly lower seroprotection rates for 2 serotypes (4 and 18C) were observed in dTpa group when compared to control group. No differences were observed in the GMCs between the 2 groups for anti-pneumococcal Ab except for both serotypes 4 and 18C for which slightly lower GMCs were observed in dTpa group when compared to control group.

- At 1 month after the booster dose of *Prevenar13*, in both groups for anti-pneumococcal Ab serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, >98% of subjects presented antibodies ≥ the assay cut-off and >79% of subjects presented Ab ≥ 0.35 µg/mL. There were no differences between the 2 groups in terms of anti-pneumococcal Ab GMCs.

Table 11. Overall percentage of subjects with anti-pneumococcal serotypes An concentration ≥ to the assay cut-off, 0.35 µg/mL and GMC, before and 1 month after the booster dose (ATP cohort for immunogenicity)

				≥Assay cut-off*				≥0.35 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-PnPS 1 antibody (ECL)	dTpa Group	Pre-Bst	211	196	92.9	88.5	96.0	61	28.9	22.9	35.5	0.22	0.19	0.24
		Post-Bst	208	208	100	98.2	100	208	100	98.2	100	3.22	2.88	3.60
	Control Group	Pre-Bst	232	214	92.2	88.0	95.3	91	39.2	32.9	45.8	0.27	0.24	0.30
		Post-Bst	236	236	100	98.4	100	236	100	98.4	100	3.64	3.28	4.04
anti-PnPS 3 antibody (ECL)	dTpa Group	Pre-Bst	211	122	57.8	50.8	64.6	8	3.8	1.7	7.3	0.08	0.07	0.09
		Post-Bst	208	208	100	98.2	100	165	79.3	73.2	84.6	0.59	0.53	0.65
	Control Group	Pre-Bst	232	147	63.4	56.8	69.6	12	5.2	2.7	8.9	0.10	0.09	0.11
		Post-Bst	235	235	100	98.4	100	187	79.6	73.8	84.5	0.62	0.57	0.69
anti-PnPS 4 antibody (ECL)	dTpa Group	Pre-Bst	209	189	90.4	85.6	94.1	28	13.4	9.1	18.8	0.15	0.13	0.16
		Post-Bst	208	208	100	98.2	100	207	99.5	97.4	100	2.91	2.54	3.33
	Control Group	Pre-Bst	232	215	92.7	88.5	95.7	63	27.2	21.5	33.4	0.19	0.17	0.22
		Post-Bst	234	234	100	98.4	100	232	99.1	96.9	99.9	3.28	2.89	3.72
anti-PnPS 5 antibody (ECL)	dTpa Group	Pre-Bst	211	163	77.3	71.0	82.7	100	47.4	40.5	54.4	0.33	0.29	0.37
		Post-Bst	204	204	100	98.2	100	204	100	98.2	100	2.66	2.39	2.97
	Control Group	Pre-Bst	229	182	79.5	73.7	84.5	124	54.1	47.5	60.7	0.34	0.31	0.38
		Post-Bst	229	228	99.6	97.6	100	227	99.1	96.9	99.9	2.81	2.52	3.14
anti-PnPS 6A antibody (ECL)	dTpa Group	Pre-Bst	211	196	92.9	88.5	96.0	112	53.1	46.1	60.0	0.38	0.33	0.43
		Post-Bst	208	208	100	98.2	100	208	100	98.2	100	9.07	8.05	10.22
	Control Group	Pre-Bst	232	219	94.4	90.6	97.0	146	62.9	56.4	69.2	0.44	0.39	0.50
		Post-Bst	236	236	100	98.4	100	236	100	98.4	100	9.49	8.45	10.67
anti-PnPS 6B antibody (ECL)	dTpa Group	Pre-Bst	211	175	82.9	77.2	87.8	96	45.5	38.6	52.5	0.29	0.25	0.33
		Post-Bst	208	208	100	98.2	100	208	100	98.2	100	7.83	6.82	8.98
	Control Group	Pre-Bst	232	205	88.4	83.5	92.2	115	49.6	43.0	56.2	0.33	0.29	0.38
		Post-Bst	236	236	100	98.4	100	235	99.6	97.7	100	8.00	7.06	9.06
anti-PnPS 7F antibody (ECL)	dTpa Group	Pre-Bst	211	210	99.5	97.4	100	147	69.7	63.0	75.8	0.49	0.44	0.54
		Post-Bst	208	208	100	98.2	100	208	100	98.2	100	5.00	4.55	5.50
	Control Group	Pre-Bst	232	232	100	98.4	100	175	75.4	69.4	80.8	0.56	0.51	0.61
		Post-Bst	235	235	100	98.4	100	235	100	98.4	100	4.96	4.50	5.48
anti-PnPS 9V antibody (ECL)	dTpa Group	Pre-Bst	211	203	96.2	92.7	98.3	71	33.6	27.3	40.5	0.26	0.23	0.29
		Post-Bst	208	208	100	98.2	100	208	100	98.2	100	3.74	3.35	4.16
	Control Group	Pre-Bst	232	225	97.0	93.9	98.8	106	45.7	39.2	52.3	0.32	0.28	0.36
		Post-Bst	235	235	100	98.4	100	235	100	98.4	100	3.91	3.52	4.35

				≥Assay cut-off*				≥0.35 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-PnPS 14 antibody (ECL)	dTpa Group	Pre-Bst	211	201	95.3	91.5	97.7	184	87.2	81.9	91.4	0.97	0.85	1.11
		Post-Bst	208	208	100	98.2	100	208	100	98.2	100	10.36	9.22	11.64
	Control Group	Pre-Bst	232	223	96.1	92.8	98.2	206	88.8	84.0	92.5	1.19	1.04	1.37
		Post-Bst	236	236	100	98.4	100	236	100	98.4	100	11.62	10.34	13.06
anti-PnPS 18C antibody (ECL)	dTpa Group	Pre-Bst	211	168	79.6	73.5	84.8	42	19.9	14.7	25.9	0.19	0.17	0.21
		Post-Bst	208	208	100	98.2	100	207	99.5	97.4	100	3.23	2.86	3.65
	Control Group	Pre-Bst	232	190	81.9	76.3	86.6	79	34.1	28.0	40.5	0.23	0.21	0.26
		Post-Bst	236	236	100	98.4	100	236	100	98.4	100	3.57	3.21	3.98
anti-PnPS 19A antibody (ECL)	dTpa Group	Pre-Bst	211	148	70.1	63.5	76.2	86	40.8	34.1	47.7	0.32	0.27	0.37
		Post-Bst	208	208	100	98.2	100	208	100	98.2	100	7.90	7.06	8.83
	Control Group	Pre-Bst	232	172	74.1	68.0	79.6	118	50.9	44.2	57.5	0.37	0.32	0.43
		Post-Bst	236	236	100	98.4	100	236	100	98.4	100	8.68	7.82	9.63
anti-PnPS 19F antibody (ECL)	dTpa Group	Pre-Bst	211	183	86.7	81.4	91.0	104	49.3	42.4	56.2	0.37	0.32	0.43
		Post-Bst	208	208	100	98.2	100	208	100	98.2	100	7.66	6.84	8.57
	Control Group	Pre-Bst	232	202	87.1	82.1	91.1	143	61.6	55.0	67.9	0.47	0.41	0.55
		Post-Bst	236	236	100	98.4	100	236	100	98.4	100	8.63	7.75	9.62
anti-PnPS 23F antibody (ECL)	dTpa Group	Pre-Bst	210	160	76.2	69.8	81.8	33	15.7	11.1	21.4	0.14	0.12	0.16
		Post-Bst	207	206	99.5	97.3	100	203	98.1	95.1	99.5	2.07	1.83	2.34
	Control Group	Pre-Bst	229	191	83.4	77.9	88.0	58	25.3	19.8	31.5	0.19	0.16	0.22
		Post-Bst	235	235	100	98.4	100	232	98.7	96.3	99.7	2.38	2.10	2.69

dTpa Group=Infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received dTpa during pregnancy.

Control Group=Infants born to mothers belonging to the Control Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received placebo during pregnancy.

All subjects in this study received *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.

GMC=geometric mean antibody concentration calculated on all subjects

N=number of subjects with available results

n/%=number/percentage of subjects with concentration equal to or above specified value

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

Pre-Bst=blood sample collected before the booster dose in infants

Post-Bst=blood sample collected 1 month after the booster dose in infants

*Assay cut-off is 0.080 µg/mL for anti-pneumococcal serotypes 1, 0.075 µg/mL for anti-pneumococcal serotypes 3, 0.061 µg/mL for anti-pneumococcal serotypes 4, 0.198 µg/mL for anti-pneumococcal serotypes 5, 0.111 µg/mL for anti-pneumococcal serotypes 6A, 0.102 µg/mL for anti-pneumococcal serotypes 6B, 0.063 µg/mL for anti-pneumococcal serotypes 7F, 0.66 µg/mL for anti-pneumococcal serotypes 9V, 0.160 µg/mL for anti-pneumococcal serotypes 14, 0.111 µg/mL for anti-pneumococcal serotypes 18C, 0.199 µg/mL for anti-pneumococcal serotypes 19A, 0.163 µg/mL for anti-pneumococcal serotypes 19F, 0.073 µg/mL for anti-pneumococcal serotypes 23F

Assessor's comment

Lower *Streptococcus pneumoniae* immunogenicity at pre-booster timepoint was observed for serotypes 4 (13.4 vs 27.2%) and 18C (19.9 vs 34.2%) in dTpa subjects as compared to the control group. Around twofold of the infants born from mothers vaccinated during pregnancy would therefore be susceptible to *Streptococcus pneumoniae* infection due to serotypes 4 and 18C during a certain (unknown) laps of time between post-primary and booster vaccination.

One month post-boost, similar proportion of infants achieved the threshold associated with protection (0.35 µg/ml) between groups, independently of the time of vaccination of the mother, the mother's maternal age and the dose schedule of infant's primary vaccination.

GMCs were in general slightly lower for infants in dTpa group when compared to infants in control group but CI 95% were always overlapping.

Safety results

1. During the 4-day follow-up period post-booster dose of *Infanrix hexa* and *Prevenar 13*:
    - Any AE: At least 1 AE (solicited/unsolicited) was reported for 84.0% and 89.5% of subjects in dTpa group and control group, respectively.
    - Solicited local AE:
        - *Infanrix hexa* injection site: Redness was the most frequent solicited local AE reported for 49.0% and 53.5% of subjects in dTpa group and control group, respectively. A large injection site reaction was reported for 2 subjects in the dTpa group and 3 subjects in the control group.
        - *Prevenar 13* injection site: Redness was the most frequent solicited local AE reported for 46.7% and 48.2% of subjects in dTpa group and control group, respectively. A large injection site reaction was reported for 1 subject in the dTpa group and 1 subject in the control group.
    - Grade 3 solicited local AE:
        - *Infanrix hexa* injection site: Redness was also the most frequent grade 3 solicited local AE reported for 8.2% and 8.7% of subjects in dTpa group and control group, respectively.
        - *Prevenar 13* injection site: Redness (5.4%) and pain (5.8%) were the most frequently reported grade 3 solicited local AE in dTpa group and in control group, respectively.
    - Solicited general AE: Irritability was the most frequent solicited general AE reported for 63.2% and 68.4% of subjects in dTpa group and control group, respectively.
    - Grade 3 solicited general AE: Irritability was also the most frequent solicited general grade 3 AE reported for 5.0% and 10.2% of subjects in dTpa group and control group, respectively.
2. During the 31-day follow-up period post-booster dose of *Infanrix hexa* and *Prevenar 13*:
    - Unsolicited AEs: At least 1 unsolicited AE was reported for 35.7% and 40.1% of subjects in dTpa group and control group, respectively. Of which, most frequent AEs reported per group were pyrexia and nasopharyngitis (4.6%) in dTpa group and pyrexia (7.9%) in control group.
    - Grade 3 unsolicited AEs: At least 1 grade 3 unsolicited AE was reported for 7.2% and 5.8% of subjects in dTpa group and control group, respectively. Of which, most frequent AE reported per group was ear infection (2.3%) in dTpa group and pyrexia (1.4%) in control group.
    - Causally related unsolicited AEs: At least 1 causally related unsolicited AE was reported for 3.8% and 3.6% of subjects in dTpa group and control group, respectively. Of which, most frequent AE reported per group was vomiting (1.5%) in dTpa group and injection site mass (0.7%) in control group.

- Grade 3 causally related unsolicited AEs: There were no grade 3 causally related unsolicited AEs reported during the study period.
- Unsolicited AEs with medically attended visits: At least 1 unsolicited AE with medically attended visit was reported for 22.8% and 25.6% of subjects in dTpa group and control group, respectively. Of which, the most frequent AE reported was ear infection in both groups (3.4% in dTpa group and 4.0% in control group).

3. Throughout the study period:

- SAEs: One case with fatal outcome was reported in the dTpa group before the administration of booster dose. Post-booster dose of *Infanrix hexa* and *Prevenar 13*, 3 SAEs were reported in 3 subjects in the control group and none were assessed by the investigator as causally related to the vaccination. There were no SAEs reported in the dTpa group.
- Withdrawals due to AEs/SAEs: In the dTpa group, the same subject with a fatal outcome was withdrawn from the study after Visit 1. This fatal case was not considered by the investigator as related to the primary vaccination received in BOOSTRIX-048 study and this case occurred before the booster dose administration in the current study.

4. Congenital Anomalies:

   During the 3 clinical studies, at least 1 congenital anomaly in infants was reported for 10.4% and 12.9% of subjects in dTpa group and control group, respectively. Of which, atrial septal defect was the most frequent congenital anomaly reported in both groups (1.5% in dTpa group and 2.3% in control group).

5. Neurodevelopmental status:

   - At 9 or 18 months of age, 11.5% and 11.0% of subjects in the dTpa group and the control group, respectively, reported a score in the black zone for at least 1 domain of ASQ-3.
   - At 9 or 18 months of age, 4.61% and 5.84% of subjects in the dTpa group and the control group, respectively, had at least 1 indicator of neurodevelopmental delay.

Assessor's comment

Infanrix hexa and *Prevenar 13* were generally well tolerated. The safety profile of the *Infanrix hexa* and *Prevenar 13* co-administration is acceptable and similar between groups.

2.3.3. Discussion on clinical aspects

The study BOOSTRIX-049 was a phase IV, open-label, non-randomised, multi-centre study to assess the immunogenicity and safety of a booster dose of *Infanrix hexa* in healthy infants born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery.

The study is part of a clinical data generation plan consisting of 3 studies that document the maternal vaccination during the third trimester of pregnancy with Boostrix (BOOSTRIX-047), and the impact thereof on the response to the infant primary vaccination (BOOSTRIX-048) and toddler booster vaccination (BOOSTRIX-049).

Clinical protection against diphtheria, tetanus, hepatitis B, poliomyelitis, *Haemophilus influenzae type b* and *Streptococcus pneumoniae* infections were defined by their serological correlates of protection. The seroprotection thresholds were ≥0.1 IU/mL for anti-D and anti-T antibody (Ab) concentrations, ≥10 mIU/mL for anti-HBs Ab concentrations, ≥8 ED50 for anti-poliovirus types 1, 2 and 3 Ab titres, ≥0.15 µg/mL for anti-PRP Ab concentrations and ≥ 0.35 µg/mL for anti-PnPS Ab concentrations.

The percentage of seroprotected subjects against diphtheria before the boost was lower for dTpa group (81.2%) when compare to the control group (90.2%). Similarly, lower *Streptococcus pneumoniae* immunogenicity at pre-booster timepoint was observed for serotypes 4 (13.4 vs 27.2%) and 18C (19.9 vs 34.2%) in dTpa subjects as compared to the control group. Around twofold of the infants born from mothers vaccinated during pregnancy would therefore be susceptible to diphtheria and *Streptococcus pneumoniae* infection due to serotypes 4 and 18C during a certain (unknown) laps of time between post-primary and booster vaccination. Only few data are currently available in the literature. Lower anti-D (Maertens 2016, Zimmermann 2019) and lower anti-Pn specific to several serotypes, including 4 and 18C, (Zimmermann 2019) were also observed before the booster dose in infants born from mothers vaccinated during pregnancy compared to infants whose mothers did not receive dTpa immunisation during pregnancy. Conversely, no difference in pre-boost anti-D titers were observed between similar groups in Munoz 2014. The MAH is invited to discuss the clinical and epidemiological relevance of these observations in the Variation II dossier that will be submitted in March 2020. Changes in the SmPC reflecting these observations would be needed, unless adequately justified by the MAH.

At 1 month after the booster vaccination with *Infanrix hexa*, all subjects were seroprotected against diphtheria, tetanus, and poliovirus type 1, 2 and 3, >94% against hepatitis B, and >99% against *Haemophilus influenzae type b* infections, independently of the time of vaccination of the mother, maternal age and dose schedule of infant's vaccination.

In addition most the dTpa and control subjects achieved Ab thresholds associated with long term protection or robust immune responses against tetanus (1.0 IU/ml), hepatitis B (100 mIU/ml), and *Haemophilus influenzae type b* infections (1.0 µg/ml). For diphtheria, most of the subjects of both groups also achieved the threshold of 1.0 IU/ml, even if lower anti-D GMC value was observed in the dTpa group. Overall, these data suggest that the primary vaccination induced adequate immune memory in both group, i.e. independently of maternal immunisation (MI).

A trend for lower GMCs of Ab specific to most of the serotypes of *Streptococcus pneumoniae* was observed for the dTpa group compared to the control group post-boost. However 95% CI were always overlapping and the percentages of subjects achieving the protective threshold of 0.35 µg/ml to the various serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) of *Streptococcus pneumoniae* were generally high (ranging from 79 to 100%) and comparable between groups, suggesting that the subjects of both groups are comparatively able to mount an anamnestic response. Thus, the observed (slight) interference of MI on infant's Ab concentration post-booster vaccination is not likely to be clinically relevant in the short term.

One month post-boost, lower PT- and FHA- Ab responses were observed in infants whose mothers did receive dTpa immunisation during pregnancy when compare to control infants. 95% CI were not overlapping. Conversely, anti-PRN titers were higher for the dTpa group when compared to the control group. The observed results are in line with those found in the literature; Lower/trend for lower Ab responses to pertussis antigens were also observed post-boost in Hardy-Fairbanks 2013, Maertens 2016a, Maertens 2016b, Halperin 2018. Nevertheless, comparable fold increases of the anti-pertussis antigens GMCs from the pre-booster to the 1-month after booster were observed in both dTpa and control groups, suggesting that infants of both groups developed an immune memory against *B. pertussis*. Yet, even if data of BOOSTRIX-049 study suggest that an immune memory was induced by

the vaccination, it is not known for which duration and if the quality of the recall responses would be unaffected.
Although the analysis is not powered to generate statistically significant results, it is to be noted that the difference of anti-PT and anti-FHA GMC values observed between the dTpa and the control groups was more pronounced for infants that received the primary vaccination as a 2-dose schedule when compared to the infants that received the study vaccines as a 3-dose schedule. A difference in anti-PRN GMC was also observed between 2-dose schedule dTpa and control groups (176.1 vs 233.4 IU/ml).

Nevertheless, in the absence of correlate of protection (CoP), the observed blunting of the pertussis response is difficult to interpret in term of clinical relevance and the 'real' (long-term) impact of MI for the infants. As already discussed in the BOOSTRIX-048 AR, the VWP considered that it could be appropriate to add a subsection in section 5.1 of the SmPC for *Infanrix hexa* under a heading of *Infant immune responses following maternal immunisation* (or similar). The section could shortly describe the observed effect on infant GMCs for pertussis antigens.

Finally, both vaccines were generally well tolerated. The safety profile was similar whatever the time of mother's vaccination (during or post-pregnancy). An update of the section 4.8 would be proposed by the MAH as part of a variation in March 2020.

3. CHMP overall conclusion and recommendation

In the present study, infants born from mother either vaccinated during pregnancy (dTpa group) or post-delivery (control group) and having completed their primary vaccination with *Infanrix hexa* and *Prevenar 13* (according to a 2- or 3-dose schedule) were boosted with *Infanrix hexa* and *Prevenar 13* around 15 months of age.

Lower immunogenicity at pre-booster timepoint was observed for diphtheria and *Streptococcus pneumoniae* serotypes 4 and 18C in dTpa subjects as compared to the control group. The MAH is invited to discuss the clinical and epidemiological relevance of these observations in the Variation II dossier that will be submitted in March 2020. Changes in the SmPC reflecting these observations would be needed, unless adequately justified by the MAH.

Immunogenicity results at post-boost timepoint demonstrated that maternal immunization (MI) does not interfere with vaccine-induced seroprotection against diphtheria, tetanus, Hepatitis B, poliovirus type 1, 2 and 3, *Haemophilus influenzae type b* and, *Streptococcus pneumoniae*.
A slight blunting effect was however observed for diphtheria and *Streptococcus pneumoniae* induced-immune responses (in terms of GMT). Nevertheless, 1 month after the booster dose, >99% of the subjects of dTpa group achieved the anti-D Ab threshold associated with long-term protection and comparable percentage of subjects had anti-PnPs Ab titers ≥ 0.35 µg/ml in both groups. It is thus unlikely that the observed interference is clinically relevant in the short term.

Anamnestic responses to pertussis antigens were observed after the boost, suggesting that infants of both groups developed an immune memory against *B. pertussis*. It is however not known for which duration and if the quality of the recall responses would be unaffected. Indeed, in line with the literature, a blunting effect of the MI on infant vaccine-induced pertussis antibody responses was observed post-boost (in terms of GMT). In the absence of CoP, it is difficult to estimate the clinical relevance of this blunting of pertussis responses and the 'real' (long-term) impact of MI for the infants. As already discussed in the BOOSTRIX-048 assessment report, the VWP considered that it could be appropriate to add the results of the studies in section 5.1 of the SmPC for *Infanrix hexa.*

Both vaccines were generally well tolerated. The safety profile was similar whatever the time of mother's vaccination (during or post-pregnancy). An update of the section 4.8 of the SmPC would also be proposed.

The MAH committed to submit a variation in March 2020 in which the outcome of the three maternal vaccination studies dTpa-047, -048 and -049 will be discussed. An update of the product information will be proposed as part of this variation.

☒ Fulfilled:

In view of the available data from BOOSTRIX-049 and BOOSTRIX-048 (assessed as part of EMEA/H/C/000296/P46/131) and BOOSTRX-047 (not yet submitted but part of the same programme development), the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided by 31st March 2020.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: Infanrix hexa

Active substance: Diphtheria (D), tetanus (T), pertussis (acellular, component) (Pa), hepatitis B (rDNA) (HBV), poliomyelitis (inactivated) (IPV) and *Haemophilus* type b (Hib) conjugate vaccine (adsorbed)

Study title	Study number	Date of completion	Date of submission of final study report
A Phase IV, observer-blind, randomised, cross-over, placebo-controlled, multicentre study to assess the immunogenicity and safety of a single dose of *Boostrix* in pregnant women.	BOOSTRIX-047 (EudraCT number: 2014-001119-38)	24 October 2017	March 2020 (submission as part of variation)
A phase IV, open-label, non-randomised, multicentre study to assess the immunogenicity and safety of *Infanrix hexa* administered as primary vaccination in healthy infants born to mothers given *Boostrix* during pregnancy or post-delivery in 116945 [DTPA (BOOSTRIX)-047].	BOOSTRIX-048 (EudraCT number: 2014-001117-41)	07 March 2018	July 2019 (submission Art. 46)
A phase IV, open-label, non-randomised, multi-centre study to assess the immunogenicity and safety of a booster dose of *Infanrix hexa* in healthy infants born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery.	BOOSTRIX-049 BST: 048 (EudraCT number: 2014-001120-30)	19 March 2019	January 2020 (submission Art. 46)