3 September 2020
EMA/496743/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Infanrix hexa

Common name: diphtheria, tetanus, pertussis (acellular, component), hepatitis b (rdna), poliomyelitis (inact.) and haemophilus type b conjugate vaccine (adsorbed)

Procedure No. EMEA/H/C/000296/II/0275

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	11 May 2020	11 May 2020
☐	CHMP Rapporteur Assessment Report	15 June 2020	10 June 2020
☐	CHMP members comments	29 June 2020	29 June 2020
☐	Updated CHMP Rapporteur Assessment Report	02 July 2020	03 July 2020
☐	Start of written procedure	07 July 2020	07 July 2020
☐	Request for supplementary information	09 July 2020	09 July 2020
	Submission of responses	05 August 2020	05 August 2020
☐	Start of procedure	06 August 2020	06 August 2020
☐	CHMP Rapporteur Assessment Report	19 August 2020	13 August 2020
☐	CHMP members comments	24 August 2020	n/a
☐	Updated CHMP Rapporteur Assessment Report	27 August 2020	n/a
☐	Start of written procedure	02 Sept 2020	02 Sept 2020
☒	Opinion	03 Sept 2020	03 Sept 2020

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GlaxoSmithkline Biologicals SA submitted to the European Medicines Agency on 20 March 2020 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIB

Update of sections 4.8 and 5.1 of the SmPC in relation to the frequency of adverse reactions somnolence and fatigue and to update the safety and immunogenicity information in infants and toddlers born to mothers vaccinated with dTpa during pregnancy; based on data generated from DTPA-048 and DTPA-049; these are phase IV, open-label, non-randomised, multicentre studies aimed to provide immunological responses to Infanrix hexa in terms of seroprotection status for diphtheria (D), tetanus (T), HBs antigen, inactivated poliovirus (IPV) and Haemophilus influenzae type b (Hib) antigens (PRP) and in terms of vaccine or booster responses to the pertussis antigens, 1 month after the last dose of the primary vaccination or the booster dose.

The MAH took the opportunity to update the posology information in the package leaflet to align it with the SmPC.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to bring the PI in line with the latest QRD template version 10.1.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

2. Overall conclusion and impact on the benefit/risk balance

The purpose of the present variation was to submit the Final Clinical Study Report (CSR) of studies DTPA-047, DTPA-048 and DTPA-049. These 3 Phase IV studies were part of a Maternal immunisation (MI) clinical development programme initiated by the MAH in 2013-2014. Results of DTPA-048 study related to pertussis immune response and their interpretation were discussed with the Belgian and the German Regulatory Authorities during a Scientific-Technical Advice meeting in June 2019. CSR of studies DTPA-048 and DTPA-049 were already assessed under Article 46 procedure (EMA/H/C/000296/P46/0131 and EMA/H/C/000296/P46/0132). Results of study DTPA-048 were also discussed at VWP (December 2019). Based on the study findings and previous assessments, the MAH proposes updates of section 4.8 and 5.1 of the SmPC.

MI has proved its benefit in protecting neonates against (severe) pertussis disease during the first months of life. On the other hand, MI has been shown to interfere with immune responses of infants to their childhood vaccination. In consequence, the MAH has initiated a MI clinical development programme to gain further insights on the immunogenicity and safety of maternal vaccination with the dTpa vaccine Boostrix and the impact on infants'/toddlers' immune responses after their primary and booster vaccination with Infanrix hexa. The first study, DTPA-047, was a randomized, placebo-controlled, multicentre study that evaluated the immunogenicity and safety of Boostrix when administered to pregnant women aged 18–45 years during the third trimester of pregnancy. Both

other studies, DTPA-048 and DTPA-049, were non-randomised, open label, multicentre studies that evaluated the immunogenicity and safety of Infanrix hexa given in the primary vaccination schedule (DTPA-048) or as a booster dose (DTPA-049) to infants and toddlers born to mothers participating in study DTPA-047. In DTPA-048, Infanrix hexa was administered with Prevenar 13 in a 2- or 3- dose schedule according to the country of enrolment. In DTPA-049, Infanrix hexa was co-administered with Prevenar 13.

Immunogenicity assessment consisted in the measurement of specific antibodies (Ab). Only Ab specific to the 3 pertussis antigens (PT, FHA, PRN) were assessed in cord blood samples (DTPA-047), whereas anti-D and anti-T Ab were measured before and after primary or booster infant's vaccination in parallel to the pertussis-specific immune responses (DTPA-048 and DTPA-049). Humoral immune responses to all other components of the paediatric Infanrix hexa vaccine were assessed in infants and toddlers after the primary vaccination (DTPA-048) as well as before and after the booster vaccination (DTPA-049). The clinical protections against diphtheria, tetanus, hepatitis B, poliomyelitis, *Haemophilus influenzae* type b and *Streptococcus pneumoniae* infections were defined by their serological correlates of protection (CoP). The seroprotection thresholds were ≥0.1 IU/mL for anti-D and anti-T 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. Since there is no CoP established for *B. pertussis* infection, results expression in term of GMC was deemed the most relevant.

In line with the literature, MI was shown to interfere with the infants' immune responses to the Infanrix hexa primary and boost vaccination. The blunting effect was specific to certain homologous and heterologous antigens. Whereas no immune interferences were observed, at any timepoint tested, for tetanus, Hepatitis B, poliovirus type 1, 2 and 3 and *Haemophilus influenzae* type b infections, blunting of the immune responses specific to diphtheria, *Streptococcus pneumoniae* or *B. pertussis* were observed.

Lower GMC of Ab specific to diphtheria toxoid and to most of the serotypes of *Streptococcus pneumoniae* were observed post-primary and post-booster vaccination in the dTpa group when compared to the control group. However, the observed interference of MI on infant's Ab concentration post-vaccination is not likely to be clinically relevant in the short term since, one month after the booster vaccination, (i) all subjects were seroprotected against diphtheria and (ii) the percentages of subjects achieving the protective threshold of 0.35 µg/ml to the various serotypes of *Streptococcus pneumoniae* were generally high and comparable between groups, suggesting that the subjects of both groups are comparatively able to mount an anamnestic response.

Results and interpretation of immune responses to pertussis antigens are more difficult to interpret since there is currently no established and validated correlate of vaccine protection. Lower GMC were observed at one month post-primary vaccination for anti-PT, anti-FHA and anti-PRN Ab in the dTpa group when compared to the control group. One month post-boost, lower PT- and FHA- Ab responses were still observed in infants whose mothers did receive dTpa immunisation during pregnancy when compare to control infants. This is in line with the literature describing a blunting of pertussis-specific immune responses in different studies in which different vaccines were used for maternal and childhood immunisation. It therefore appears that the blunting effect is not product-specific. It also appears, based on the DTPA-049 post-boost response, that infants born to dTpa vaccinated mothers 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 in a longer term. Although current epidemiological data are reassuring regarding the absence of any clinical impact of the blunting of infants immune responses during and/or shortly after the primary vaccination, uncertainties yet remain for the long-term clinical protection.

Both Infanrix hexa and Prevenar 13 were well tolerated. The safety profile was similar in both groups, regardless of exposure/non-exposure of the mothers to Boostrix during pregnancy. The frequency of the reported solicited and unsolicited adverse events (AEs) were in line with the frequency described in the Infanrix hexa product information (PI).

The MAH has described the safety and immunogenicity in infants and toddlers born to mothers vaccinated with dTpa during pregnancy in sections 4.8 and 5.1. The MAH has also updated the frequency of adverse reactions (ARs) following the reclassification of frequency for "Fatigue" (from very common to uncommon) and "Somnolence" (from uncommon to very common), which is supported.

Based on the current epidemiological data following initiation of MI programs, the benefit-risk balance of Infanrix hexa remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIB

Update of sections 4.8 and 5.1 of the SmPC in relation to the frequency of adverse reactions somnolence (from uncommon to very common) and fatigue (from very common to uncommon) and to update the safety and immunogenicity information in infants and toddlers born to mothers vaccinated with dTpa during pregnancy; based on data generated from DTPA-048 and DTPA-049; these are phase IV, open-label, non-randomised, multicentre studies aimed to provide immunological responses to Infanrix hexa in terms of seroprotection status for diphtheria (D), tetanus (T), HBs antigen, inactivated poliovirus (IPV) and Haemophilus influenzae type b (Hib) antigens (PRP) and in terms of vaccine or booster responses to the pertussis antigens, 1 month after the last dose of the primary vaccination or the booster dose.

The MAH took the opportunity to update the posology information in the package leaflet to align it with the SmPC.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to bring the PI in line with the latest QRD template version 10.1.

☒ is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Maternal immunisation has proved its benefit in protecting neonates against (severe) pertussis disease during the first months of life.

Based on data generated from DTPA-048 and DTPA-049, post-primary and post-booster vaccination, immunological data did not show clinically relevant interference of maternal vaccination with diphtheria, tetanus, acellular pertussis (dTpa) on the infant's and toddler's responses to diphtheria, tetanus, hepatitis B, inactivated poliovirus, Haemophilus influenzae type b or pneumococcal antigens.

Lower antibody concentrations against pertussis antigens post-primary (PT, FHA and PRN) and post-booster (PT, FHA) vaccination were observed in infants and toddlers born to mothers vaccinated with dTpa during pregnancy. The fold-increases of anti-pertussis antibody concentrations from the pre-booster to the 1-month post-booster time point were in the same range for infants and toddlers born to mothers vaccinated with dTpa or with placebo, demonstrating effective priming of the immune system. In the absence of correlates of protection for pertussis, the clinical relevance of these observations remains to be fully understood. However, current epidemiological data on pertussis disease following the implementation of dTpa maternal immunisation do not suggest any clinical relevance of this immune interference.

The MAH also took the opportunity to update the frequency for "Fatigue" (from very common to uncommon) and "Somnolence" (from uncommon to very common) as a result of the reencoding "Drowsiness" under the MedDRA Preferred Term from "Fatigue" to "Somnolence".

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Medicinal product

Infanrix hexa is GSK's combination diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis and *Haemophilus influenzae* type b (Hib) conjugate vaccine (DTPa-HBV-IPV/Hib). Infanrix hexa was authorised in Europe in October 2000 and is currently licensed in more than 90 countries worldwide.

Infanrix hexa is indicated for primary and booster vaccination of infants and toddlers against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and Hib disease.

The primary vaccination schedule consists of 2 or 3 doses administered in the first year of life. The booster dose must be administered at least 6 months after the last dose of the primary vaccination and preferably between 11 and 13 months of age or before 18 months of age respectively after primary vaccination with 2 doses or 3 doses of Infanrix hexa.

Rationale of the proposed changes

In response to pertussis outbreaks that occurred in 2011–2013, several national health authorities worldwide issued recommendations for maternal immunisation (MI) with combined reduced-antigen content diphtheria-tetanus-acellular pertussis (dTpa) vaccines with the aim of passively protecting the neonate and young infants from pertussis disease. Effectiveness of maternal immunization against pertussis disease in the first 3 months of life has been demonstrated (Amirthalingam 2016, Baxter 2017, Bellido-Blasco 2017, Becker-Dreps 2018, Saul 2018). Consequently, vaccination during pregnancy is currently included in the therapeutic indication of dTpa vaccines. On the other hand, the MI with a dTpa vaccine results in immune interference with primary vaccination series in these infants, as compared with no dTpa vaccination during pregnancy.

To gain further insights on the immunogenicity and safety of maternal vaccination with its dTpa booster vaccine Boostrix and the impact on infants'/toddlers' immune responses after their primary and booster vaccination with Infanrix hexa, the MAH has initiated a MI clinical development programme, that included 3 Phase IV studies, i.e. studies DTPA-047, DTPA-048 and DTPA-049.

Results of DTPA-048 study related to pertussis immune response and their interpretation were discussed with the Belgian and the German Regulatory Authorities during a Scientific-Technical Advice meeting in June 2019. DTPA-048 and DTPA-049 study complete results were further assessed under Article 46 procedure (EMA/H/C/296/P46 131 and EMA/H/C/000296/P46 132). Results of study DTPA-048 were also discussed at VWP (December 2019) and recommendations on if and how data could be reflected in the PI were made.

The MAH proposes an update of the section 4.8 and section 5.1 of the SmPC based on the clinical data generated in these studies. The MAH also takes the opportunity to make editorial changes to the PI.

6. Clinical Efficacy aspects

Three studies were included in the MI clinical development programme:

- ✓ DTPA[BOOSTRIX]-047 (DTPA-047): randomized, placebo-controlled, multicentre study that evaluated the immunogenicity and safety of Boostrix when administered to pregnant women aged 18–45 years.
  This study provides data on the quantification of maternal pertussis antibodies transferred to the neonate as measured in the cord blood at birth.
- ✓ DTPA [BOOSTRIX]-048 PRI (DTPA-048): non-randomised, open label, multicentre study that

evaluated the immunogenicity and safety of Infanrix hexa given in the primary vaccination schedule to infants born to mothers participating in study DTPA-047.

- ✓ DTPA [BOOSTRIX]-049 BST 048 (DTPA-049): non-randomised, open label, multicentre study that evaluated the immunogenicity and safety of Infanrix hexa given as a booster dose to infants/toddlers born to mothers participating in study DTPA-047 and who completed their primary vaccination in study DTPA-048.

Results of these studies that are relevant for the proposed changes are discussed below.

6.1. Methods – analysis of data submitted

An overview of the 3 clinical studies supporting the application is presented in the Table below.

Table 1. overview of the clinical studies supporting the application

Study ID	Study countries	Study Design Objectives	Population (age) Schedule of vaccination	Study groups	Number of subjects	
					ATP cohort for immunogenicity	TVC cohort
DTPA-047 (116945)	Australia, Canada, Czechia, Finland, Italy, Spain	Phase IV, observer-blind, randomised 1:1, placebo-controlled, multi-country, multicentre study with 2 cross-over groups Primary objective: ○ To demonstrate that the maternally transferred antibodies against pertussis in the dTpa Group were superior to that in the Control Group in terms of geometric mean concentrations (GMCs) for the pertussis antibodies, in the cord blood sample. Secondary objectives*: ○ To assess the immunogenicity of a single dose of *Boostrix* administered during pregnancy in terms of seropositivity status for antibodies against pertussis, in the cord blood sample.	Healthy pregnant woman between, and including, 18-45 years of age at the time of screening and at $27^{0/7}$-$36^{6/7}$ weeks (completed 27 weeks but not 37 weeks) of gestation at the time of vaccination (Visit 1) Single dose of *Boostrix* or placebo at Visit 1, followed by 1 dose of placebo or *Boostrix* post-delivery (Visit 3) (see "Study groups" column)	dTpa Group Pregnancy dose: *Boostrix* Post-delivery dose: placebo Control Group Pregnancy dose: placebo Post-delivery dose: *Boostrix*	291 292 Total: 583	341 346 Total: 687
DTPA-048 (201330)	Australia, Canada, Czechia, Finland, Italy, Spain	Phase IV, open-label, non-randomised, multi-country, multicentre study with 2 parallel groups Primary objective: ○ 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 vaccine response to the pertussis antigens, 1 month after the last dose of the primary vaccination in infants born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery. Secondary objectives: ○ To assess the persistence of antibodies against diphtheria, tetanus and pertussis antigens, before the first dose of	Healthy infants, between and including $6^{0/7}$-$14^{6/7}$ weeks of age at the time of the first vaccination, born to mothers enrolled in DTPA-047 study 3 doses of *Infanrix hexa* co-administered with *Prevenar 13* at 2, 4 and 6 months or 2, 3 and 4 months, OR 2 doses of *Infanrix hexa* co-administered with	dTpa Group Infants born to mothers receiving *Boostrix* during pregnancy and placebo post-delivery in study DTPA-047 (dTpa Group) Control Group Infants born to mothers receiving placebo during	268 274	296 305

Study ID	Study countries	Study Design Objectives	Population (age) Schedule of vaccination	Study groups	Number of subjects	
					ATP cohort for immunogenicity	TVC cohort
		Infanrix hexa 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 last dose of the primary vaccination 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 last dose of the primary vaccination 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 AEs and SAEs.	*Prevenar 13* at 3 and 5 months or 2 and 4 months	pregnancy and *Boostrix* post-delivery in study DTPA-047 (Control Group)	Total: 542	Total: 601
DTPA-049 (201334)	Australia, Canada, Czechia, Finland, Italy, Spain	Phase IV, open-label, non-randomised, multi-country, multicentre study with 2 parallel groups Primary objective: ○ 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 to the pertussis antigens, 1 month after the booster dose in infants born to mothers vaccinated with *Boostrix* during pregnancy or immediately post-delivery. Secondary objectives: ○ 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.	Healthy infants, 9 months of age at enrolment, born to mothers enrolled in study DTPA-047 and who received full primary vaccination course in study DTPA-048 One dose of *Infanrix hexa* co-administered with *Prevenar 13* from 11 to 18 months	dTpa Group Infants born to mothers receiving *Boostrix* during pregnancy and placebo post-delivery in study DTPA-047 (dTpa Group) Control Group Infants born to mothers receiving placebo during pregnancy and *Boostrix* post-	229 250	263 277

Study ID	Study countries	Study Design Objectives	Population (age) Schedule of vaccination	Study groups	Number of subjects	
					ATP cohort for immunogenicity	TVC cohort
		○ 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 AEs and 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.		delivery in study DTPA-047 (Control Group)	Total: 479	Total: 540

AE=adverse event; ATP=according-to-protocol; GMC=geometric mean concentration; SAE=serious adverse event; TVC=total vaccinated cohort; $6^{0/7}$-$14^{6/7}$ weeks of age = Infants who were between 6 and 14 weeks of age (including 6 weeks and up to and including 14 weeks and 6 days of age); $27^{0/7}$-$36^{6/7}$ weeks = Pregnant women who completed 27 weeks but not 37 weeks of gestation at the time of vaccination.

*For study DTPA-047, only the secondary objective relevant for the current submission is presented in this table. Please refer to Module 2.7.3 Summary of Clinical Efficacy for the full list of study objectives.

**In some countries/regions with an *Infanrix hexa* 3-dose vaccination schedule, *Prevenar 13* could be administered as 2-dose or 3-dose primary vaccination schedule (according to the routine national immunisation schedule). In such an instance, the evaluation was performed 1 month after the last *Infanrix hexa* dose regardless of *Prevenar 13* vaccination. In the countries/regions with an *Infanrix hexa* 2-dose schedule, *Prevenar 13* was co-administered at the same time as *Infanrix hexa*.

Data source: DTPA (BOOSTRIX)-047 (116945) Report Amendment 2 Main (05-Jul-2019) Sections 2, 4, 5 and Table 19; DTPA (BOOSTRIX)-048 PRI (201330) Report Amendment 1 Main (23-Sep-2019) Sections 2, 4, 5 and Table 23; DTPA (BOOSTRIX)-049 BST 048 (201334) Report (31-Oct-2019) Sections 2, 4, 5 and Table 14

6.1.1. Design features

Study designs of studies DTPA -047, -048 and -049 are summarized in Figures 1, 2, 3 and 4.

6.1.1.1. Study DTPA-047 (pregnant women)

Experimental design: Phase IV, observer-blind, randomised, placebo-controlled, multi-country, multicentre study with 2 cross-over groups. The study was conducted in Australia, Canada, Czechia, Finland, Italy and Spain.

Population: Healthy pregnant women between, and including, 18-45 years of age at the time of screening and $27^{0/7}$-$36^{6/7}$ weeks of gestation at the time of vaccination.

Blinding: Data were collected in an observer-blind manner, meaning that the vaccine recipient and those responsible for the evaluation of any study endpoint were unaware of which vaccine was administered. Therefore, vaccine preparation and administration was done by authorised medical personnel who did not participate in any of the study clinical evaluation assays. GSK staff and other study staff, i.e., laboratory in charge of the laboratory testing, were also blinded to the treatment.

Randomization: The randomisation of supplies within blocks was performed at GSK, using MATerial EXcellence (MATEX), a programme developed for use in Statistical Analysis System (SAS) [Cary, NC, United States] by GSK.

Vaccination schedule: At Visit 1, all subjects received a single dose of Boostrix or placebo. Subjects who received Boostrix at Visit 1 received a dose of placebo postdelivery (Visit 3), while those who received placebo at Visit 1 received Boostrix post-delivery (Visit 3).

Control vaccine: The placebo received by the Control Group during pregnancy and by the dTpa Group post-delivery consisted of 0.5 mL of 150 mM saline water supplied as pre-filled syringes.

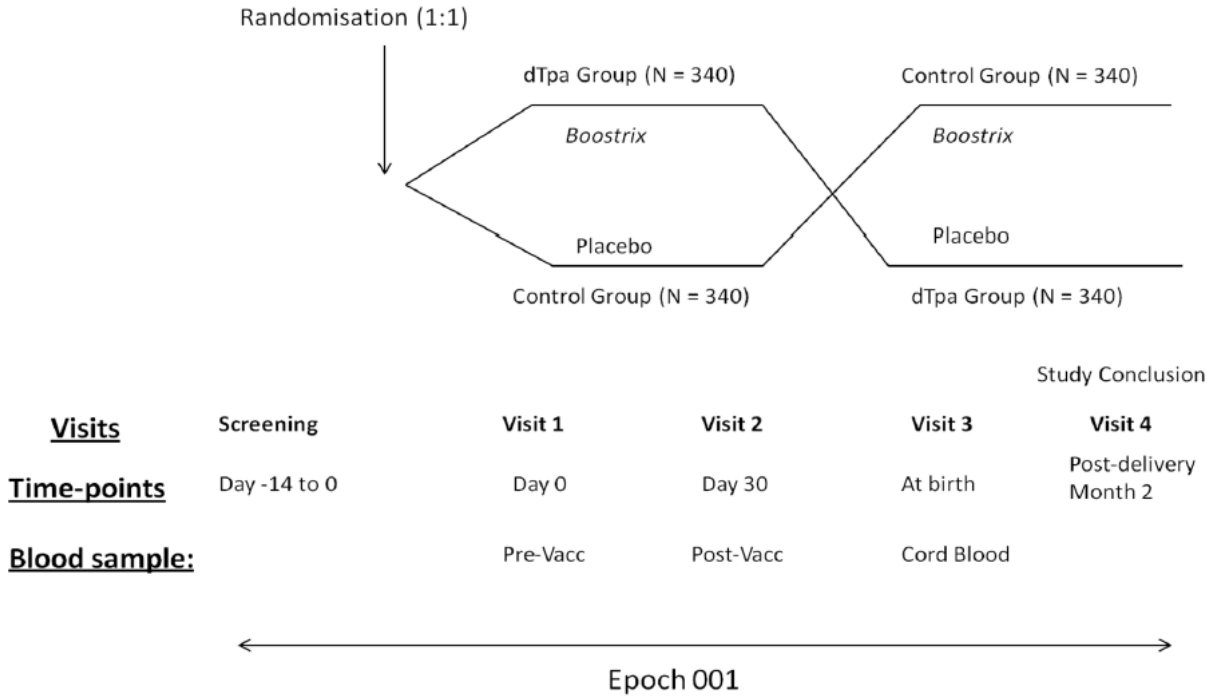
Treatment allocation: The subjects were randomly assigned to 2 groups in a 1:1 ratio. The randomisation algorithm used a minimisation procedure accounting for centre, age (≥18-<25 years, ≥25-<35 years and ≥35-≤45 years), gestational age (27-32 weeks and 33-36 weeks) and country.

Study duration: It was approximately 5 months for each subject, starting at the Screening Visit (Days -14–0) and ending at Visit 4 (post-delivery Month 2).

Immunological assessment: Comprised a blood sample prior to and 1 month after vaccination for determination of antibodies to all vaccine antigens. Additionally, an umbilical cord blood sample was collected from all subjects at delivery for determination of antibodies to the pertussis antigens. Methods and results expression are described in section 6.1.2 Immunogenicity.

Safety assessment: Detail safety assessments performed in the study are provided in section 7. Clinical safety aspects.

Data collection: Data were collected electronically and recorded in the individual subject Case Report Forms (eCRF).



N = Number of subjects planned for enrolment
Pre-vacc = Blood sample collected before the dose of the booster vaccination in pregnant women (Visit 1).
Post-vacc = Blood sample collected 1-month after the booster vaccination in pregnant women (Visit 2).
Data source: DTPA (BOOSTRIX)-047 (116945) Report Amendment 2 Main (05-Jul-2019), Figure 1

Figure 1. Study DTPA-047 design

6.1.1.2. Studies DTPA -048 and -049 (infants and toddlers)

Experimental design: Phase IV, open-label, non-randomised, multi-country, multicentre study with 2 parallel groups. The study was conducted in the same countries as study DTPA-47, i.e., Australia, Canada, Czechia, Finland, Italy and Spain.

Population:

Study DTPA-048: Healthy infants 6 to 14 weeks of age (including 6 weeks and up to and including 14 weeks and 6 days of age) born to mothers vaccinated in the DTPA-047 study.

Study DTPA-049:Healthy infants 9 months of age at enrolment (Visit 1), born to mothers vaccinated with Boostrix during pregnancy or post-delivery in study DTPA-047 and who completed their primary vaccination course with Infanrix hexa and Prevenar 13 in study DTPA-048.

Blinding: The study was conducted in an open-label manner as the treatment was similar between the 2 groups. However, the study personnel operating SBIR and the site staff remained blinded towards the treatment allocation of subjects in study DTPA-047.

Randomization: There was no randomisation of subjects into groups in this study. The enrolled infants were allocated to the same groups and retained the same subject numbers as their mothers in study DTPA-047.

Vaccination schedule:

Study DTPA-048: All subjects received either 3 doses of Infanrix hexa coadministered with Prevenar 13 at 2, 4 and 6 months or 2, 3 and 4 months, or 2 doses of Infanrix hexa co-administered with Prevenar 13 at 3 and 5 months or 2 and 4 months, depending on the immunisation schedule of the country. In some countries/regions with an Infanrix hexa 3-dose routine national immunisation schedule, Prevenar 13 could be administered either as a 2-dose or 3-dose primary vaccination schedule (according to the routine national immunisation schedule).

Study DTPA-049: 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 immunization schedule.

Treatment allocation: As there was no randomisation, treatment numbers were allocated by dose.

Study duration:

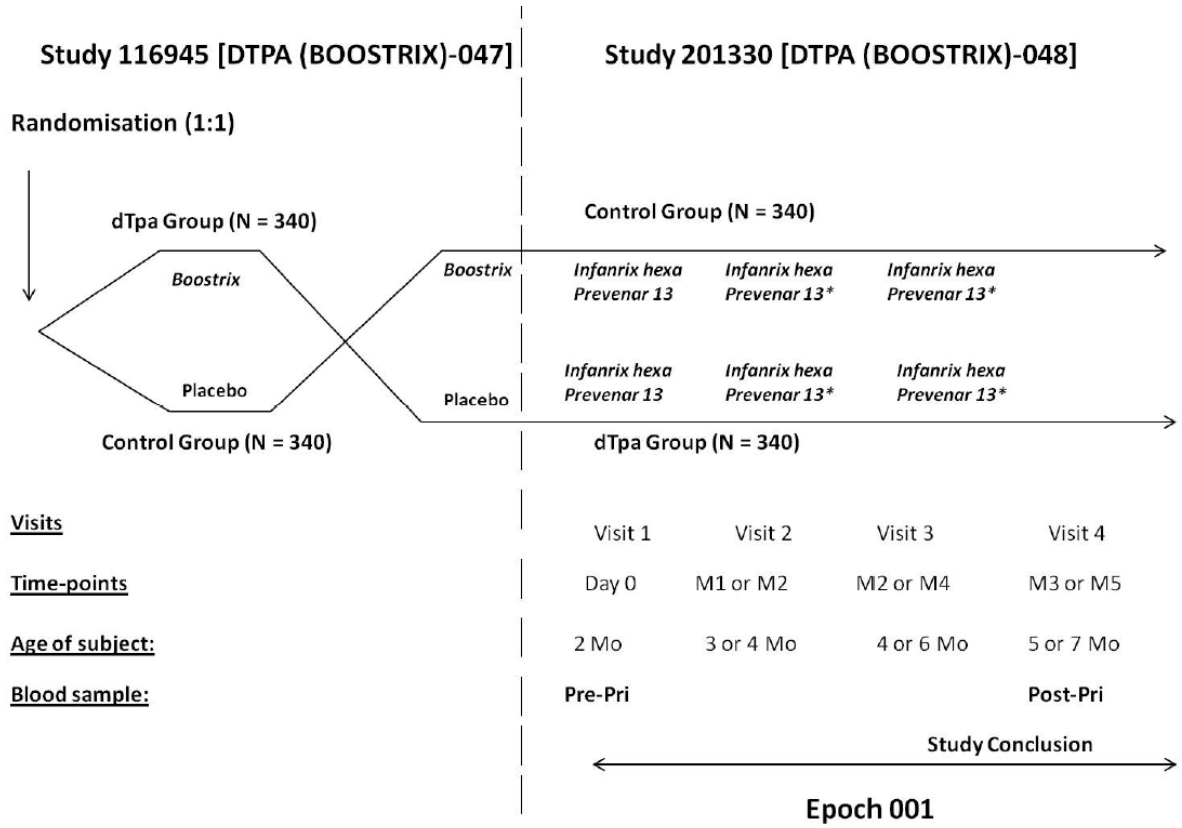
Study DTPA-048: Approximately 3 months, for subjects vaccinated according to the 2-dose schedules (at 2 and 4 months, or at 3 and 5 months), or the 2, 3 and 4-month schedule, and approximately 5 months for those vaccinated according to 2, 4 and 6-month schedule.

Study DTPA-049: Approximately 9 to 10 months, starting with Visit 1 (9 months of age) and ending at telephone contact or at Visit 3 (18 or 19 months of age), depending on the time of vaccination.

Immunological assessment: Comprised a blood sample prior to the first and 1 month after the last dose of the primary vaccination course (Study DTPA-048) or of the booster dose (Study DTPA-049) for determination of antibodies to vaccine antigens. Methods and results expression are described in section 6.1.2 Immunogenicity.

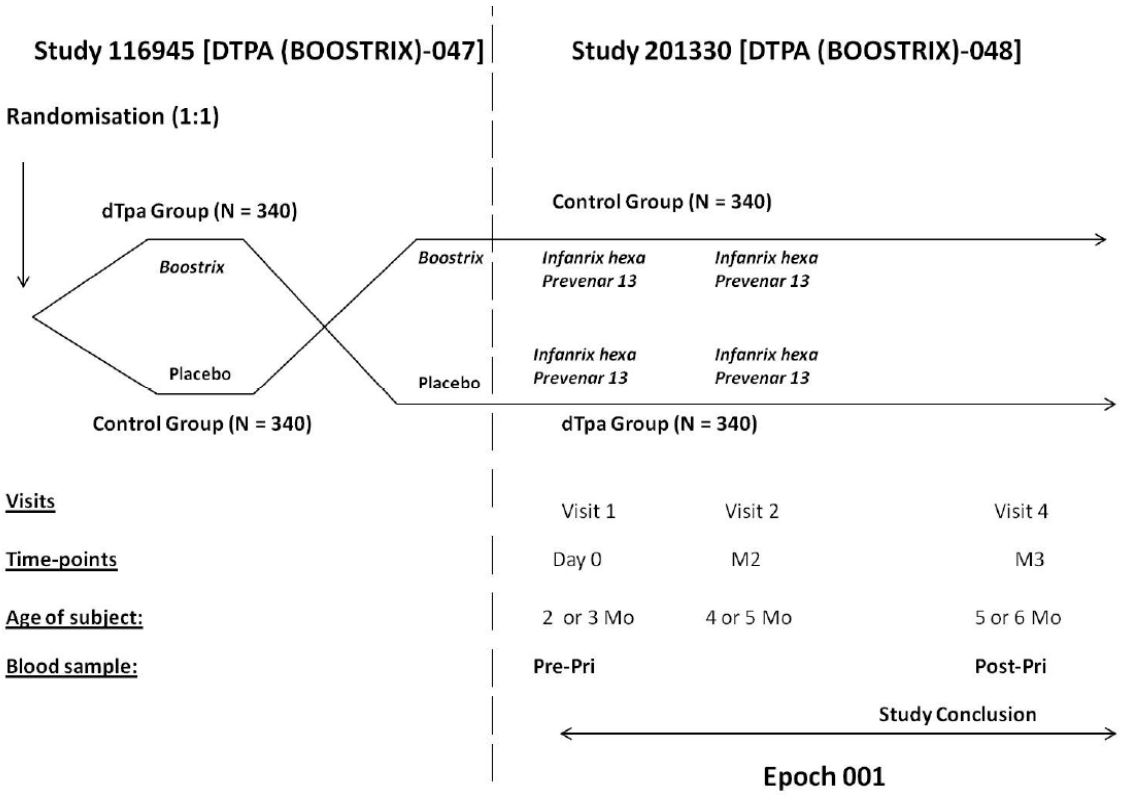
Safety assessment: Detailed safety assessments performed in each study are provided in section 7. Clinical safety aspects.

Data collection: Data were collected electronically and recorded in the individual subject eCRFs.



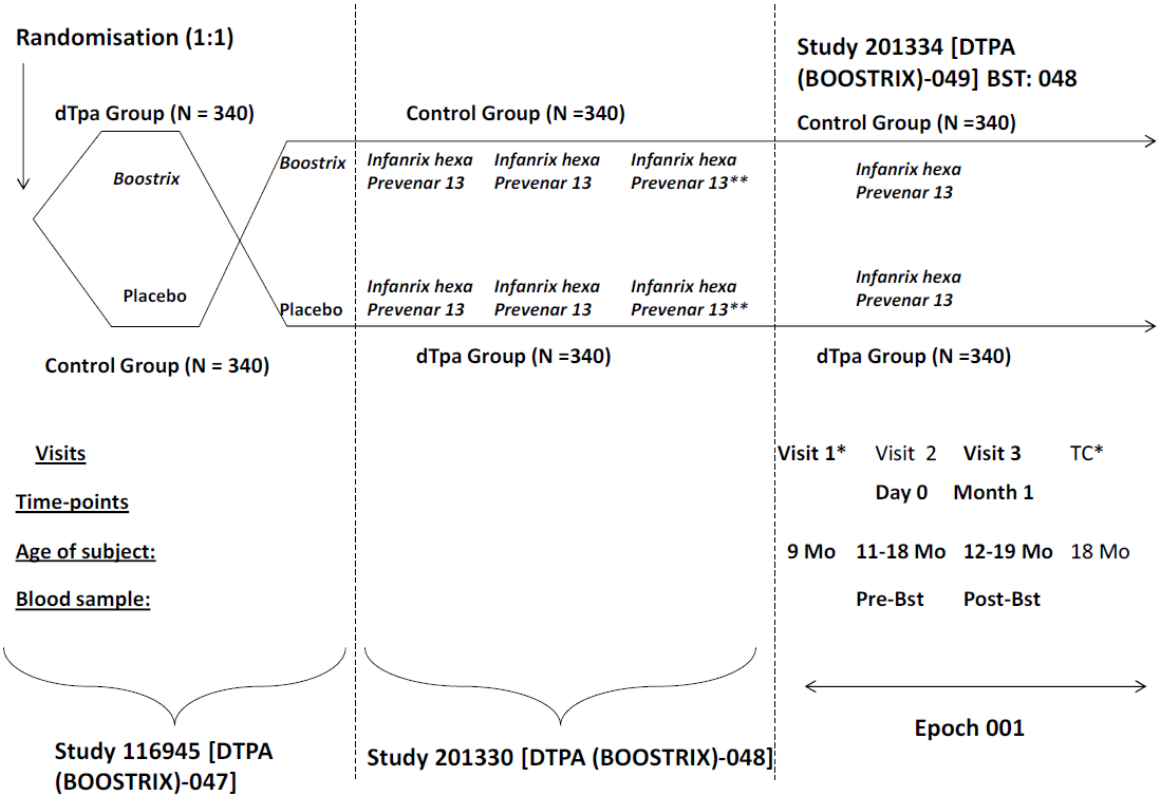
N=Maximum number of subjects that were planned to be enrolled.
M=Month, Mo=age in months
Timepoints were numbered based on the different vaccination schedules. D0, M1, M2 and M3 timepoints reflected for subjects who were to be vaccinated according to the 2, 3 and 4 month schedule while D0, M2, M4 and M5 timepoints reflected for subjects who were to be vaccinated according to the 2, 4 and 6 month schedule.
* In some countries/regions with an *Infanrix hexa* 3-dose schedule, *Prevenar 13* was given as a 2-dose schedule at 2 and 4 months of age as a part of the routine immunisation programme.
Pre-Pri=Blood sample was to be collected before the first dose of the primary vaccination course.
Post-Pri=Blood sample was to be collected 1 month after the last dose of the primary vaccination course.

Figure 2. Study DTPA-048 design diagram for infants receiving a 3-dose schedule of Infanrix hexa



N=Maximum number of subjects that were to be enrolled.
M=Month, Mo=age in months
Pre-Pri=Blood sample was to be collected before the first dose of the primary vaccination course.
Post-Pri=Blood sample was to be collected 1 month after the last dose of the primary vaccination course.
Subjects were to be vaccinated either at 2 and 4 months of age or 3 and 5 months of age, according to the routine national immunisation schedule.

Figure 3. Study DTPA-048 design diagram for infants receiving a 2-dose schedule of Infanrix hexa



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 4. Study DTPA-049 design

6.1.2. Immunogenicity

6.1.2.1. Laboratory assays

For all 3 studies, all serology tests were determined in GSK laboratories using standardised and validated procedures with adequate controls.

Table 2. Laboratory assays

Component	Assay method	Test kit/ Manufacturer	Assay unit	Assay cut-off*
Studies DTPA-047, DTPA-048 and DTPA-049				
Corynebacterium diphtheriae. Diphtheria Toxoid Ab. IgG	ELISA	In-house	IU/mL	0.057
Clostridium tetani. Tetanus Toxoid Ab. IgG	ELISA	In-house	IU/mL	0.043
Bordetella pertussis. Pertussis Toxin Ab. IgG	ELISA	In-house	IU/mL	2.693
Bordetella pertussis. Filamentous Hemaglutinin Ab. IgG	ELISA	In-house	IU/mL	2.046
Bordetella pertussis. Pertactin Ab. IgG	ELISA	In-house	IU/mL	2.187
Studies DTPA-048 and DTPA-049				
Hepatitis B Virus.Surface Ab	CLIA	ADVIA Centaur anti-HBs2 (Siemens Healthcare)	mIU/mL	6.2
Poliovirus Sabin Type 1 Ab Poliovirus Sabin Type 2 Ab Poliovirus Sabin Type 3 Ab	NEU	NA	ED_{50}	8
Haemophilus influenzae type b. Polyribosyl Ribitol Phosphate Ab	ELISA	NA	µg/mL	0.066

Component	Assay method	Test kit/ Manufacturer	Assay unit	Assay cut-off*
Streptococcus pneumoniae	ECL	NA	µg/mL	
PS 1 Ab.IgG				0.080
PS 3 Ab.IgG				0.075
PS 4 Ab.IgG				0.061
PS 5 Ab.IgG				0.198
PS 6A Ab.IgG				0.111
PS 6B Ab.IgG				0.102
PS 7F Ab.IgG				0.063
PS 9V Ab.IgG				0.066
PS 14 Ab.IgG				0.160
PS 18C Ab.IgG				0.111
PS 19A Ab.IgG				0.199
PS 19F Ab.IgG				0.163
PS 23F Ab.IgG				0.073

Ab=antibodies; CLIA=ChemiLuminescence ImmunoAssay; ECL=Electrochemiluminescence; ELISA=Enzyme-linked immunosorbent assay; IgG=Immunoglobulin G; IU/mL=International units/millilitre; NEU=Neutralisation assay; PS= polysaccharide.

*The new assay cut-offs were updated as per the new re-validated assay. Assays for diphtheria, tetanus and pertussis were re-developed and re-validated as per most recent Centre for Biologics Evaluation and Research (CBER) recommendations (Guidance for Industry "Bioanalytical Method Validation" from September 2013)

Data source: DTPA (BOOSTRIX)-047 (116945) Report Amendment 2 Main (05-Jul-2019) Table 10; DTPA (BOOSTRIX)-048 (201330) Report Amendment 1 Main (23-Sep-2019) Table 12; DTPA (BOOSTRIX)-049 BST 048 (201334) Report (31-Oct-2019) Table 8

6.1.2.2. Results expression

Response to the vaccines' antigens was assessed in term of percentage of seroprotected or seropositive subjects. Vaccine responses to *B. pertussis* antigens were further defined by using arbitrary criteria. Results were also presented in term of Ab GMT.

A seropositive (or seroresponder) subject was a subject whose antibody titre was greater than or equal to the assay cut-off defined in the study (Table 2).

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 ED50.
- ✓ Anti-PRP antibody concentrations ≥0.15 µg/mL.
- ✓ Anti-pneumococcal capsular polysaccharide antibody concentrations ≥0.35 µg/mL.

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

- ✓ Studies DTPA-047 and DTPA-049:

- for subjects with pre-vaccination antibody concentration below the assay cut-off, post-vaccination 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, post-vaccination antibody concentration ≥2 times the pre-vaccination antibody concentration.

- ✓ Study DTPA-048:

- for subjects with pre-vaccination antibody concentration below the assay cut-off, post-vaccination antibody concentration equal or above the assay cut-off;

- for subjects with pre-vaccination antibody concentration equal or above the assay cut-off, post-vaccination antibody concentration equal or above the pre-vaccination antibody concentration.

6.1.3. Study objectives and endpoints

6.1.3.1. Study DTPA-047

The primary objective of the DTPA-047 study was confirmatory: to demonstrate that the maternally transferred antibodies against pertussis in the dTpa Group were superior to those in the Control Group in terms of geometric mean concentrations (GMCs) for the pertussis antibodies, in the cord blood sample. The primary endpoint related to this objective was the assessment of anti-PT, anti-FHA and anti-PRN antibody concentrations at delivery (in the cord blood sample).

Key secondary objectives of the study were about further evaluation of the immune responses to Boostrix, through the following endpoints:

- ✓ Anti-D, anti-T, anti-PT, anti-FHA and anti-PRN seroprotection/seropositivity status and antibody concentrations, 1-month post-vaccination.
- ✓ Vaccine response to anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibodies, 1-month post vaccination.
- ✓ Anti-PT, anti-FHA and anti-PRN seropositivity status, in the cord blood sample.

6.1.3.2. Studies DTPA -048 and -049

The primary objective of the DTPA-048 study was descriptive: to assess the immunological response to all vaccine antigen components of Infanrix hexa 1 month after the last dose of the primary vaccination in infants born to mothers vaccinated with Boostrix during pregnancy or immediately post-delivery. The primary endpoint related to this objective included immunogenicity with respect to the antigen components of Infanrix hexa:

- ✓ Anti-D, anti-T, anti-HBs, anti-poliovirus types 1, 2, and 3 and anti-polyribosyl-ribitol phosphate (anti-PRP) seroprotection status, 1 month after the last dose of primary vaccination.
- ✓ Vaccine response to PT, FHA and PRN antigens, 1 month after the last dose of primary vaccination.

The primary objective of the DTPA-049 study was descriptive: to assess the immunological response to all vaccine antigen components of Infanrix hexa 1 month after the booster dose in infants born to mothers vaccinated with Boostrix during pregnancy or immediately post-delivery. The primary endpoint related to this objective included immunogenicity with respect to the antigen components of Infanrix hexa:

- ✓ Anti-D, anti-T, anti-HBs, anti-poliovirus types 1, 2, and 3 and anti-PRP seroprotection status, 1 month after the booster dose.
- ✓ Booster response to PT, FHA, and PRN antigens, 1 month after the booster dose.

Key secondary objectives of the 2 studies were about further evaluation of the immune responses to each of the study vaccines. The secondary endpoints related to these objectives included:

- ✓ Evaluation of the persistence of antibodies before the first dose of Infanrix hexa (study DTPA-048) in infants born to mothers vaccinated with Boostrix during pregnancy or post-delivery in study DTPA-047:
  - (i) Anti-D, anti-T, anti-PT, anti-FHA and anti-PRN seroprotection/seropositivity status and antibody concentrations.
- ✓ Evaluation of the immune response to Infanrix hexa (studies DTPA-048 and DTPA-049) at the post-primary, pre-booster and post-booster dose timepoints:
  - (i) Anti-D, anti-T, anti-poliovirus types 1, 2, and 3, anti-HBs, and anti-PRP antibody concentrations or titres, 1 month after the last dose of primary vaccination in study DTPA-048, before booster vaccination and 1 month after booster vaccination in study DTPA-049. In addition, seroprotection status to all the above-mentioned antigens were assessed before booster vaccination in study DTPA-049.
  - (ii) Anti-PT, anti-FHA and anti-PRN antibody concentrations and seropositivity status, 1 month after the last dose of primary vaccination in study DTPA-048, before and 1 month after booster vaccination in study DTPA-049.

- ✓ Evaluation of the immune response to Prevenar 13 (studies DTPA-048 and DTPA-049) at the post-primary, pre-booster and post-booster dose timepoints:

    (i) Anti-pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) antibody concentrations, 1 month after the last dose of primary vaccination in study DTPA-048, before booster vaccination and 1 month after the booster vaccination in study DTPA-049. In addition, seropositivity rates to all the above-mentioned antigens were also evaluated in study DTPA-049 before the administration of the booster dose.

6.1.4. Statistical evaluation

6.1.4.1. Study cohorts

The According-to-protocol (ATP) cohort for immunogenicity was used for the analyses of immune response to Boostrix in study DTPA-047 and to Infanrix hexa and Prevenar 13 in studies DTPA-048 and DTPA-049. The ATP cohort for immunogenicity in each study included all eligible subjects who complied with all protocol-defined procedures and intervals, had not received a vaccine not specified or forbidden in the protocol and had data available for at least 1 study vaccine component after vaccination with Boostrix or Infanrix hexa and Prevenar 13.

Besides these, an additional criterion for the ATP cohort for immunogenicity in study DTPA-047 was cord blood collection. Additional criteria for the ATP cohort for immunogenicity in study DTPA-048 were full term birth (defined as ≥37 weeks of gestation) and no presentation with a medical condition leading to exclusion from an ATP analysis. An additional criterion for the ATP cohort for immunogenicity in study DTPA-049 was the receipt of all vaccine doses in study DTPA-048. The Adapted ATP cohort was used whenever different timepoints from the 3 studies are presented together, to denote that for each timepoint the corresponding ATP cohort for immunogenicity has been used.

Since more than 5% of the subjects with available immunogenicity data were eliminated from analysis for the ATP cohort for immunogenicity, an analysis based on the TVC was performed to complement the ATP analysis. The Total Vaccinated Cohort (TVC) for each study included all vaccinated subjects for whom data were available.

6.1.4.2. Statistical methods

Between group assessment (Study DTPA-047): The criterion to demonstrate superiority of the immune response in the dTpa group to that in the control group for the pertussis antigens, in the cord blood sample in study DTPA-047, was that the lower limit (LL) of the 95% confidence interval (CI) of the GMC ratio (dTpa group divided by control group) for anti-PT, anti-FHA and anti-PRN antibodies was ≥1.5. The CI of the group GMC ratios was computed using a 2-sample t-test assuming heterogeneity of variance.

Within groups assessment (all studies): Percentages of subjects with antibody titres/concentrations above threshold values with exact 95% CIs; GMCs/geometric mean titres (GMTs) with exact 95% CIs; and anti-D, anti-T, anti-PT, anti FHA and anti-PRN vaccine response or booster response, with exact 95% CIs, were calculated, as applicable for each study.

GMC/GMT calculations were performed by taking the anti-log of the mean of the log10 titre/concentration transformations. Antibody titres/concentrations below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMT/GMC calculation.

Results expression is detailed in section 6.1.2.2.

The descriptive analyses of the immune responses to Boostrix were also performed by sub-group of gestational age (27-32, 33-36 weeks of gestation of foetus) and age of the mother (18-24, 25-34, 35-45 years), at dose 1. In studies DTPA-048 and DTPA-049, the descriptive analysis of the immune response elicited by the study vaccine was also performed by dose schedule (2-dose versus 3-dose schedule, depending on the country recommendations). Whereas the gestational age at vaccination does not seem to influence the magnitude of infant's immune responses to their vaccination, 3 doses versus 2 doses seem better for limiting the blunting effect. These analyses are however to be interpreted with caution since they were not powered to generate statistically significant results. The limited sample size, particularly for the 2-dose schedule and the 18-24y age of the mother sub-group, does not allow to draw meaningful conclusions. Consequently, the data are not discussed in this report. Data were discussed in the previous PAM/FUM (EMA/H/C/296/P46 131 and 132).

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.
Since there is no established correlate of vaccine protection for *B. pertussis*, vaccine responses to pertussis antigens were arbitrary defined. Although the definition of vaccine response used in study DTPA-048 is less stringent than the one used in both other studies, vaccine seroresponse rate could be underestimated for infants born from dTpa vaccinated mothers compared to the group of infants born from unvaccinated mothers. A more appropriate way (than seroresponse rate) to study a potential effect of maternal immunization (MI) on infant's vaccination is to compare the GMC induced by the primary and booster vaccination in the dTpa and in the control groups. Accordingly, only results expressed in term of GMC are presented in this AR to describe the pertussis specific immune responses.

6.2. Results

6.2.1. Recruitment/ Number analysed

Of 687 pregnant women vaccinated during the study DTPA-047, 583 (84.9%) were included in the ATP cohort for immunogenicity (291 subjects in the dTpa Group and 292 subjects in the Control Group).

In study DTPA-048, of the 601 vaccinated infants, 542 (90.2%) were included in the ATP cohort for immunogenicity (268 subjects in the dTpa Group and 274 subjects in the Control Group).

In study DTPA-049, of the 540 vaccinated infants/toddlers, 479 (88.7%) were included in the ATP cohort for immunogenicity (229 subjects in the dTpa Group and 250 subjects in the Control Group).

Tables 3, 4 and 5 summarize the number of subjects who were vaccinated, completed the study or were withdrawn for all 3 studies, including the reasons for withdrawal.

Table 3. Number of subjects enrolled into the study DTPA-047 as well as excluded from ATP analysis with reasons for exclusion (All enrolled pregnant subjects)

	Total			dTpa Group		Control Group		NOGRP	
Title	n	s	%	n	s	n	s	n	s
All enrolled subjects	725			344		346		35	
Subject excluded from stat analyses (code 900)	1	1		1	1	0	0	0	0
Study vaccine dose not administrated but subject number allocated (code 1030)	37	37		2	2	0	0	35	35
Total vaccinated cohort	687		100	341		346		0	
Randomisation failure (code 1050)	2	2		0	0	2	2	0	0
Randomisation code broken at the investigator site (code 1060)	7	7		2	2	5	5	0	0
ATP cohort for safety	678		98.7	339		339		0	
Protocol violation (inclusion/exclusion criteria) (code 2010)	9	11		6	7	3	4	0	0
Non-compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	34	38		20	22	14	16	0	0
Essential serological data missing (code 2100)	52	61		22	26	30	35	0	0
ATP cohort for immunogenicity	583		84.9	291		292		0	

dTpa Group=Mothers received dTpa during pregnancy
Control Group=Mothers received placebo during pregnancy
NOGRP=No assigned group
Note: Subjects may have more than 1 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

Table 4. Number of subjects enrolled into the study DTPA-048 as well as excluded from ATP analysis with reasons for exclusion (All enrolled subjects)

	Total			dTpa Group		Control Group	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Total cohort	601			296		305	
Total vaccinated cohort	**601**		**100**	**296**		**305**	
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
Study vaccine dose not administered according to protocol (code 1070)	2	2		2	2	0	0
Vaccine temperature deviation (code 1080)	4	5		2	3	2	2
ATP cohort for safety	**592**		**98.5**	**291**		**301**	
Protocol violation (inclusion/exclusion criteria) (code 2010)	7	8		4	5	3	3
Non-compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	11	11		4	4	7	7
Non-compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	8	9		3	4	5	5
Essential serological data missing (code 2100)	24	29		12	16	12	13
ATP cohort for immunogenicity	**542**		**90.2**	**268**		**274**	

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 1 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 primary study 116945 [DTPA(BOOSTRIX)-047] were carried forward for this follow up study except for the visit specific elimination codes (2090, 2100 and 2120).

Table 5. Number of subjects enrolled into the study DTPA-049 as well as the number excluded from ATP analysis with reasons for exclusion (All enrolled subjects)

	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

In all 3 studies, similar proportion of subjects were withdrawn from the ATP cohort for immunogenicity in both groups.

For study DTPA-047, the ATP cohort for immunogenicity consists of 84.6 and 84.4% of the total vaccinated cohort for dTpa and control groups, respectively.

For study DTPA-048, the ATP cohort for immunogenicity consists of 90.5 and 89.8% of the total vaccinated cohort for dTpa and control groups, respectively.

For study DTPA-049, the ATP cohort for immunogenicity consists of 87.1 and 90.3% of the TVC for dTpa and control groups, respectively.

This is acceptable.

6.2.2. Demographics

The demographic characteristics for the ATP cohort for immunogenicity were well balanced between groups across the 3 studies (Table 6). The geographic ancestry reflected the regions where the studies were conducted with more than 90% of subjects of White/Caucasian origin in all studies.

In study DTPA-047, the mean age was 32.5 years (SD 4.5) in dTpa group and 32.6 years (SD 4.4) in the control group. The mean gestational age at vaccination and at delivery (in weeks) was comparable between both groups.

In study DTPA-048, the average age of subjects was 8.8 months (±1.7). Of the 542 subjects, 47.2% were females. A total of 11.2% of subjects were given a 2-dose schedule, while majority of the subjects (88.7%) received the study vaccines as a 3-dose schedule. More than 50% of the subjects' mothers received Boostrix during 27-32 gestational weeks of the foetus.

In study DTPA-049, the average age of subjects was 14.9 months (±2.5). Of the 479 subjects, 45.1% were females. Percentages of subjects vaccinated with either a 2-dose or a 3-dose schedule were comparable with those observed in study DTPA-048.

Table 6. Summary of demographic characteristics (ATP cohort for immunogenicity)

Characteristics	Parameters or categories	Value or n	%	Value or n	%
Study DTPA-047 - ATP cohort for immunogenicity					
		dTpa Group N=291		Control Group N=292	
Age at dose 1 (years)	Mean	32.5	-	32.6	-
	SD	4.5	-	4.4	-
Geographic Ancestry	African Heritage/African American	2	0.7	5	1.7
	American Indian or Alaskan Native	2	0.7	0	0.0
	Asian	6	2.1	1	0.3
	White - Arabic/North African Heritage	2	0.7	5	1.7
	White - Caucasian/European Heritage	271	93.1	274	93.8
	Other	8	2.7	7	2.4

Characteristics	Parameters or categories	Value or n	%	Value or n	%
Gestational weeks at dose 1	Mean	31.6	-	31.6	-
	SD	2.6	-	2.7	-
Gestational weeks at delivery	Mean	39.3	-	39.4	-
	SD	1.1	-	1.1	-
Breast feeding	Never	10	3.5	22	7.7
	No	23	8.1	30	10.5
	Yes	250	88.3	235	81.9
	Missing	8	-	5	-
Formula feeding	No	194	66.7	191	65.4
	Yes	90	30.9	96	32.9
	Missing	7	2.4	5	1.7
Study DTPA-048 - ATP cohort for immunogenicity					
		dTpa Group N=268		**Control Group N=274**	
Age at dose 1 (weeks)	Mean	8.7	-	8.9	-
	SD	1.6	-	1.7	-
Gender	Female	129	48.1	127	46.4
	Male	139	51.9	147	53.6
Geographic Ancestry	African Heritage / African American	4	1.5	8	2.9
	Asian	4	1.5	0	0.0
	White - Arabic / North African Heritage	1	0.4	2	0.7
	White - Caucasian / European Heritage	242	90.3	258	94.2
	Other	17	6.3	6	2.2
Dose schedule	2-dose schedule	27	10.1	34	12.4
	3-dose schedule	241	89.9	240	87.6
Study DTPA-049 - ATP cohort for immunogenicity					
		dTpa Group N=229		**Control Group N=250**	
Age at vaccination (months)	Mean	15.0	-	14.8	-
	SD	2.5	-	2.5	-
Gender	Female	105	45.9	111	44.4
	Male	124	54.1	139	55.6
Geographic Ancestry	African Heritage / African American	4	1.7	7	2.8
	Asian	3	1.3	0	0.0
	White - Arabic / North African Heritage	1	0.4	2	0.8
	White - Caucasian / European Heritage	206	90.0	235	94.0
	Other	15	6.6	6	2.4
Primary vaccination dose schedule (DTPA-048)	2-dose schedule	22	9.6	32	12.8
	3-dose schedule	207	90.4	218	87.2

Study DTPA-047:

dTpa Group: *Boostrix* during pregnancy + placebo post-delivery; Control Group: placebo during pregnancy + *Boostrix* post-delivery

Studies DTPA-048 and DTPA-049:

All subjects in these 2 studies kept the same study group as their mothers in study DTPA-047 and received *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule (2- or 3-dose schedule in study DTPA-048 and one booster vaccination in study DTPA-049).

ATP=according-to-protocol; N=number of subjects; n=number of subjects in a given category; %=n/Number of subjects with available results x 100; SD=Standard deviation; Q1=1st Quartile; Q3=3rd Quartile.

2-dose schedule = subjects who received 2 doses 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 doses of *Infanrix hexa* at 2,3,4 months of age or 2,4,6 months of age, co-administered with *Prevenar 13*.
Data source: DTPA (BOOSTRIX)-047 (116945) Report Amendment 2 Main (05-Jul-2019) Table 21 (modified); DTPA (BOOSTRIX)-048 (201330) Report Amendment 1 Main (23-Sep-2019) Table 25 (modified); DTPA (BOOSTRIX)-049 BST 048 (201334) Report (31-Oct-2019) Table 16 (modified).

Assessor's comment

Demographic characteristics are appropriately balanced between groups.

6.2.3. Immunogenicity results

6.2.3.1. Immune responses to Diphtheria and Tetanus toxoids (Table 7)

Anti-D and anti-T Ab titers were not assessed in cord blood samples at birth.

Before the first dose of Infanrix hexa in infants born to mothers vaccinated with Boostrix or placebo in study DTPA-047, 82.6% of infants in the dTpa group and 43.7% in the control group were seroprotected against diphtheria; 99.2% of infants in the dTpa group and 88.9% in the control group were seroprotected against tetanus. Anti-D and anti-T Ab GMCs were higher in the dTpa group compared to the control group.

One month after completion of the primary vaccination, seroprotection against diphtheria and tetanus reached 100% for infants in both groups. The anti-D Ab GMCs were lower in the dTpa group compared to the control group (0.423 versus 2.746). Consequently, the percentage of subjects that had Ab titer ≥ 1.0 IU/ml was lower in the dTpa group when compared to the control group (76.5% versus 92.3%). There was no significant difference observed in the GMC values for anti-T in both study groups.

Before the booster dose, 81.2% of infants in the dTpa group and 90.2% in the control group were seroprotected against diphtheria. The 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. No differences were observed in the GMCs between the 2 groups for anti-T.

One month after the booster vaccination, seroprotection against diphtheria and tetanus reached 100% for infants in both groups. A trend for lower anti-D GMC value was still observed in the dTpa group (6.114) when compared to the control group (8.402). Anti-T Ab GMCs were within the same range when comparing the 2 study groups.

Table 7. Percentage of subjects with anti-D and anti-T antibody concentration ≥ 0.1 IU/mL and geometric mean concentrations, before and 1 month after vaccination (ATP cohort for immunogenicity)

					≥0.1 IU/mL				GMC		
							95% CI			95% CI	
Antibody	Group	Study	Timing	N	n	%	LL	UL	value	LL	UL
anti-D	dTpa	DTPA-048	Pre-Pri	242	200	82.6	77.3	87.2	0.423	0.354	0.506
			Post-Pri	264	264	100	98.6	100	1.747	1.598	1.910
		DTPA-049	Pre-Bst	223	181	81.2	75.4	86.1	0.207	0.184	0.234
			Post-Bst	221	221	100	98.3	100	6.114	5.577	6.703
	Control	DTPA-048	Pre-Pri	252	110	43.7	37.4	50.0	0.089	0.076	0.103
			Post-Pri	271	271	100	98.6	100	2.746	2.502	3.015
		DTPA-049	Pre-Bst	244	220	90.2	85.7	93.6	0.322	0.285	0.363
			Post-Bst	247	247	100	98.5	100	8.402	7.694	9.174
anti-T	dTpa	DTPA-048	Pre-Pri	242	240	99.2	97.0	99.9	2.152	1.925	2.406
			Post-Pri	266	266	100	98.6	100	2.347	2.135	2.582
		DTPA-049	Pre-Bst	223	215	96.4	93.1	98.4	0.753	0.646	0.878
			Post-Bst	221	221	100	98.3	100	8.200	7.324	9.180
	Control	DTPA-048	Pre-Pri	253	225	88.9	84.4	92.5	0.378	0.330	0.434
			Post-Pri	271	271	100	98.6	100	2.278	2.069	2.508
		DTPA-049	Pre-Bst	244	232	95.1	91.6	97.4	0.578	0.506	0.659
			Post-Bst	247	247	100	98.5	100	6.758	6.143	7.433

dTpa Group: infants born to mothers receiving *Boostrix* during pregnancy + placebo post-delivery in study DTPA-047; Control Group: infants born to mothers receiving placebo during pregnancy + *Boostrix* post-delivery in study DTPA-047. All subjects in these studies received *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule (2- or 3-dose schedule in study DTPA-048 and 1 booster vaccination in study DTPA-049).

ATP=according-to-protocol; D=diphtheria; GMC=geometric mean antibody concentration calculated on all subjects; IU=international units; T=tetanus.

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-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/toddlers

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

Data source: DTPA (BOOSTRIX)-048 (201330) Report Amendment 1 Main (23-Sep-2019) Table 27 (modified); DTPA (BOOSTRIX)-049 BST 048 (201334) Report Main (31-Oct-2019) Table 18 (modified)

Assessor's comment

As expected, higher percentages of infants born to mothers vaccinated during pregnancy were seroprotected (cut-off ≥ 0.1 IU/ml) against diphtheria and tetanus before the primary vaccination (dTpa group) when compared to the infants born to mothers vaccinated post-delivery (control group). These higher percentages were also observed when considering the threshold associated with long term protection (≥ 1.0 IU/ml, for both anti-D [28.5% and 4.0% for dTpa and control groups] and anti-T [88.4% and 17.4% for dTpa and control groups] Ab). This is reflected by the difference in GMC between both groups.

All subjects were seroprotected against diphtheria and tetanus 1 month after primary vaccination with Infanrix hexa.

The percentage of infants achieving the anti-T Ab cut-off of 1.0 IU/ml and the anti-T GMT values post-primary vaccination were similar between groups. This was not the case for the immune response to

diphtheria toxoid. A trend for lower percentage of infants achieving the anti-D Ab cut-off of 1.0 IU/ml and lower anti-D GMT values were observed in the dTpa group when compared to the control group.

In line with these observations, the percentage of seroprotected subjects against diphtheria before the boost was lower for dTpa group. Around 20%, instead of 10%, of the infants born to mothers vaccinated during pregnancy would be susceptible to diphtheria infection during a certain laps of time between post-primary and booster vaccination. Lower anti-D GMT were also observed before the booster dose in infants born to mothers vaccinated during pregnancy compared to infants whose mothers did not receive dTpa immunisation during pregnancy in studies described in Maertens 2016, in Zimmermann 2019 and in Barug 2020. Conversely, no difference in pre-boost anti-D titers were observed between similar groups in Munoz 2014. During the assessment of study DTPA-049, the MAH was invited to discuss the clinical and epidemiological relevance of these observations (see also 6.2.3.6. Immune responses to Prevenar 13) in the present submission. The discussion mainly relies on post-boost data.

All subjects were seroprotected against diphtheria and tetanus 1 month after the booster vaccination with Infanrix hexa. Most of the dTpa and control subjects achieved the threshold of 1.0 IU/ml associated with long term protection, even if lower an anti-D GMC value was still 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 MI.

6.2.3.2. Immune response to HBs antigen (Tables 8 and 9)

Anti-HBs Ab titers were neither assessed in cord blood samples at birth nor in infant's samples before the primary vaccination.

One month post-primary vaccination, 99.2% of subjects in the dTpa group and 98.5% of subjects in the control group had seroprotective anti-HBs Ab concentrations (≥10 mIU/mL). anti-HBs Ab GMCs were within the same range in both groups.

Before booster vaccination, 94.1% of subjects in the dTpa group and 94.2% of subjects in the control group were still seroprotected against hepatitis B.

One month post-booster vaccination, seroprotection against hepatitis B was 99.5% in the dTpa group and 99.2% in the control group. Anti-HBs Ab GMCs were within the same range in both groups resulting in a similar proportion of subjects achieving anti-HBs Ab titers ≥100 mIU/mL.

Table 8. Percentage of subjects with anti-HBs Ab concentration ≥10 mIU/ml, ≥100 mIU/ml, and GMC, before and 1 month after the last dose of the primary vaccination (ATP cohort for immunogenicity)

				≥6.2 mIU/mL				≥10 mIU/mL				≥100 mIU/mL				GMC		
						95% CI				95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-HBs	dTpa Group	Post-Pri	253	252	99.6	97.8	100	251	99.2	97.2	99.9	237	93.7	89.9	96.3	1322.8	1116.7	1567.0
antibody	Control Group	Post-Pri	263	262	99.6	97.9	100	259	98.5	96.2	99.6	254	96.6	93.6	98.4	1339.2	1132.8	1583.3

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
Post-Pri=blood sample collected 1 month after the last dose of the primary vaccination course

Table 9. 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 ≥ 10 mIU/ml) against Hepatitis B 1 month after primary vaccination, before and 1 month after the boost with Infanrix hexa were high. Percentages of subjects mounting an Ab response ≥ 100 mIU/ml (threshold considered as a measure of an especially robust immune response) and GMC were similar between groups suggesting that maternal immunization does not interfere with the infant's vaccine induced-protection against Hepatitis B.

6.2.3.3. Immune responses to poliovirus types 1, 2 and 3 (Tables 10 and 11)

Anti-poliovirus Ab titers were neither assessed in cord blood samples at birth nor in infant's samples before the primary vaccination.

One month post-primary vaccination, the percentage of subjects seroprotected against poliovirus types 1, 2 and 3 (anti-poliovirus types 1, 2 and 3 antibody titres ≥8 ED50) was >95% of subjects in both groups. Ab GMCs were within the same range for both the dTpa and control groups.

Before the booster vaccination, ≥ 88 % of subjects in both groups were seroprotected against poliovirus types 1, 2 and 3.

One month post-booster vaccination, the seroprotective threshold of 8 ED50 for antipoliovirus types 1, 2 and 3 was reached by all subjects in both groups. There were no differences between the 2 groups in terms of anti-poliovirus GMTs.

Table 10. Percentage of subjects with anti-poliovirus type 1, 2, and 3 Ab concentrations ≥ 8 ED50 and GMT, 1 month after the last dose of the primary vaccination (ATP cohort for immunogenicity)

				≥8 ED50				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
anti-Polio 1 antibody	dTpa Group	Post-Pri	237	233	98.3	95.7	99.5	432.1	351.8	530.9
	Control Group	Post-Pri	244	242	99.2	97.1	99.9	489.9	402.6	596.0
anti-Polio 2 antibody	dTpa Group	Post-Pri	241	239	99.2	97.0	99.9	424.6	342.7	526.2
	Control Group	Post-Pri	245	235	95.9	92.6	98.0	388.4	306.3	492.6
anti-Polio 3 antibody	dTpa Group	Post-Pri	230	228	99.1	96.9	99.9	730.6	596.5	894.9
	Control Group	Post-Pri	237	236	99.6	97.7	100	775.6	645.9	931.3

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.
GMT=geometric mean antibody titre calculated on all subjects; N=number of subjects with available results; n/%=number/percentage of subjects with titre equal to or above specified value; 95% CI=95% confidence interval; LL=Lower Limit, UL=Upper Limit; Post-Pri=blood sample collected 1 month after the last dose of the primary vaccination course.

Table 11. Percentage of subjects with anti-poliovirus type 1, 2 and 3 Ab concentrations ≥ 8 ED50 and GMT, 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

Percentages of infants that were seroprotected (cut-off ≥ 8 ED50) against poliovirus types 1, 2 and 3 at 1 month after primary vaccination with Infanrix hexa were high. All the children were seroprotected against the 3 types of poliovirus one month after the booster dose with Infanrix hexa. No difference between the 2 groups in terms of anti-poliovirus GMT was observed suggesting that the MI does not interfere with the infant's vaccine responses specific to poliovirus.

6.2.3.4. Immune responses to Haemophilus influenzae type b PRP (Tables 12 and 13)

Anti-PRP Ab titers were neither assessed in cord blood samples at birth nor in infant's samples before the primary vaccination.

One month post-primary vaccination, 95.9% of subjects in the dTpa group and 94.5% of subjects in the control group had seroprotective anti-PRP antibody concentrations. No significant difference was observed in the GMC values for anti-PRP in both groups.

Before booster vaccination, 72.5% of subjects in the dTpa group and 68.0% of subjects in the control group were seroprotected against Hib. A trend for slightly lower anti-PRP GMC values was observed in the control group compared to the dTpa group.

One month post-booster vaccination, 100% of subjects in the dTpa group and 99.6% of subjects in the control group had seroprotective anti-PRP antibody concentrations. Moreover, 99.5% subjects in the dTpa group and 97.6% subjects in the control group had anti-PRP Ab levels ≥1.0 µg/mL, indicative of long term protection. The trend for slightly lower anti-PRP GMC values was still observed after the boost in the control group compared to the dTpa group.

Table 12. Percentage of subjects with anti-PRP Ab concentration ≥ assay cut-off, 0.15 µg/ml, 1.0 µg/ml and GMC, 1 month after the last dose of the primary vaccination (ATP cohort for immunogenicity)

				≥0.066 µg/mL				≥0.15 µg/mL				≥1 µg/mL				GMC		
						95% CI				95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-PRP	dTpa Group	Post-Pri	266	262	98.5	96.2	99.6	255	95.9	92.7	97.9	172	64.7	58.6	70.4	1.862	1.554	2.231
antibody	Control Group	Post-Pri	271	264	97.4	94.8	99.0	256	94.5	91.0	96.9	177	65.3	59.3	71.0	1.717	1.428	2.064

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
Post-Pri=blood sample collected 1 month after the last dose of the primary vaccination course

Table 13. 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 ≥0.15 µg/ml) against *Haemophilus influenzae* type b 1 month after primary vaccination as well as after the booster dose with Infanrix hexa were high. In addition, most of the subjects of both groups achieved the Ab threshold associated with long-term protection (1.0 µg/ml).

6.2.3.5. Immune responses to Bordetella pertussis antigens (PT, FHA, PRN)(Tables 14 and 15)

The primary objective of study DTPA-047, to demonstrate that the concentration of maternally transferred antibodies against pertussis in the dTpa group is superior to that in the control group in terms of GMCs for the pertussis Ab, as measured in the cord blood at birth, was demonstrated. The LL of the 95% CI of the GMC ratio between groups (dTpa group divided by the control group) for anti-PT, anti-FHA and anti-PRN antibodies was 7.02, 13.48 and 15.86, respectively, which is well above the pre-defined criterion of 1.5.

Table 14. GMC ratio between groups and their 95% CIs for anti-PT, anti-FHA and anti-PRN Ab in cord blood samples (ATP cohort for immunogenicity)

					GMC Ratio (dTpa Group/Control Group)		
	dTpa Group		Control Group			95% CI	
Antibody	N	GMC	N	GMC	GMC ratio	LL	UL
anti-PT	290	46.9	292	5.5	8.47	**7.02**	10.20
anti-FHA	291	366.1	292	22.7	16.11	**13.48**	19.24
anti-PRN	290	301.8	291	14.6	20.65	**15.86**	26.88

dTpa Group: *Boostrix* during pregnancy + placebo post-delivery; Control Group: placebo during pregnancy + *Boostrix* post-delivery
ATP=according-to-protocol; FHA=filamentous haemagglutinin; GMC=geometric mean antibody concentration calculated on all subjects; PRN=pertactin; PT=pertussis toxoid.
N=number of subjects with available results
95% CI=95% confidence interval for the adjusted GMC ratio. The associated CI was computed using a 2--sample t test assuming heterogeneity of variance. LL=lower limit, UL=upper limit
Bold = indicates that this value met the statistical superiority criterion
Data source: DTPA (BOOSTRIX)-047 (116945) Report Amendment 2 Main (05-Jul-2019) Table 25

All other objectives, i.e. the secondary objectives of study DTPA-047 and the primary and secondary objectives of studies DTPA-048 and DTPA-049 were descriptive.

As already mentioned above and extensively discussed with the Belgian and the German Regulatory Authorities during a Scientific-Technical Advice meeting that took place on 3 June 2019, the vaccine seroresponse rate could be underestimated for infants born from dTpa vaccinated mothers compared to the group of infants born from unvaccinated mothers. 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 primary vaccination in the dTpa and in the control groups. Therefore, seropositive rates and booster responses were not considered.

In the cord blood (study DTPA-047), the anti-pertussis antibody GMCs were higher in the dTpa group when compared to the control group for the 3 antigens.

Before the first dose of Infanrix hexa primary vaccination, the maternal antibodies against pertussis antigens were found to be persistent in the subjects and it was observed that subjects in dTpa group had higher antibody concentrations when compared to the subjects in control group. Pre-vaccination GMC were always higher in the dTpa group.

At 1 month after the subjects received the last dose of Infanrix hexa, all subjects in dTpa group had detectable anti-pertussis Ab (i.e. above or equal to the assay cut-off) but lower GMC values were

observed in the dTpa group when compared to the control group for Ab against all 3 pertussis antigens. One infant in the control group was not seropositive for anti-PRN Ab.

Before the booster dose of Infanrix hexa, the GMCs for the anti-pertussis antibodies were slightly lower in the dTpa group when compared to control group.

At 1 month after the booster dose of Infanrix hexa, 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 and anti-FHA when compared to the control group. However, lower GMC value in the dTpa group compared to the control group was not observed for anti-PRN. 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).

Table 15. Overall GMCs across all timepoints (and percentage of subjects with Ab concentration ≥ the assay cut-off) (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	dTpa	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	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	dTpa	PRE	289	273	94.5	91.2	96.8	13.7	11.8	15.8

				≥ Assay cut-off*				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
		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	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	dTpa	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	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

Study DTPA-047:

dTpa Group: *Boostrix* during pregnancy + placebo post-delivery; Control Group: placebo during pregnancy + *Boostrix* post-delivery

Studies DTPA-048 and DTPA-049:

All subjects in these 2 studies kept the same study group as their mothers in study DTPA-047 and received *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule (2- or 3-dose schedule in study DTPA-048 and one booster vaccination in study DTPA-049).

*Assay cut-off was 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, 2.187 IU/mL for anti-PRN

Solid horizontal line separates the maternal and infant/toddler studies.

ATP=according-to-protocol; FHA=filamentous haemagglutinin; GMC=geometric mean antibody concentration calculated on all subjects; PRN=pertactin; PT=pertussis toxoid.

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

PI(D30)=Post-booster vaccination (pregnancy dose) blood sampling time-point, 1-month after booster dose

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/toddlers

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

Data source: DTPA (BOOSTRIX)-049 BST 048 (201334) Report (31-Oct-2019) Table 23

Assessor's comment

As expected, higher concentrations of Ab specific to PT, FHA and PRN were detected in the cord blood sample of infants born to mothers vaccinated with Boostrix during the pregnancy when compared to those born to mothers vaccinated post-delivery. The primary objective of study DTPA-047 was met. The LL of the 95% CI of the GMC ratio between groups for anti-PT, anti-FHA and anti-PRN antibodies was above the pre-defined criterion of 1.5. The maternal Ab specific to the pertussis antigens were still detectable before the infant's primary vaccination and, in line with the cord blood's findings, Ab GMC values were higher in the dTpa group when compared to the control group.

Conversely, at one month post-primary vaccination, lower GMC were observed for anti-PT, anti-FHA and anti-PRN Ab in the dTpa group when compared to the control group. 95% CI were not overlapping for all three antigens.

Although, 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 to non-vaccinated mothers, a blunting of the PT- and FHA- Ab responses was 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 GMC values 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*.

Findings of both studies DTPA-048 and DTPA-049 are in line with those of other studies that have assessed the blunting of pertussis response after the primary and the booster vaccination administered around 12 months of age (Hardy-Fairbanks 2013, Munoz 2014, Maertens 2016, Halperin 2018, Barug 2019). Overall, all these publications show a trend for lower GMC of pertussis antigens-specific Ab in infants born to dTpa vaccinated mothers during the pregnancy compared to infants born to unvaccinated or post-partum vaccinated mothers. This is true for post-primary vaccination and post-boost vaccination. The blunting of the majority of the antigen-specific Ab responses observed post-primary vaccination was still observed post-boost. None of these studies have assessed the vaccine efficacy of MI in protecting infants from pertussis disease in parallel.

Several studies assessed the vaccine efficacy/effectiveness of MI in preventing pertussis in young infants. Overall, MI does protect infants from pertussis disease before primary vaccination (Amirthalingam 2016, Baxter 2017, Bellido-Blasco 2017, Becker-Dreps 2018, , Saul 2018). Although the duration of the (additional) protection of MI varies across studies, no deleterious effect of MI was evidenced during and/or shortly after the primary vaccination (up to 5-6 months of age).

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

6.2.3.6. Immune responses to Prevenar 13 (Tables 16 and 17)

Overall, at 1 month after the subjects received the last dose of Prevenar 13, all subjects in both groups developed anti-pneumococcal (anti-PnPS) antibodies for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. In both groups, >74% of subjects presented Ab ≥0.35 µg/mL. A trend for lower SPR was however observed for 5 out of 13 serotypes (4, 5, 6B, 9V and 23F). GMTs induced in dTpa group were generally slightly lower than those induced in the control group.

Before the booster dose of Prevenar 13, percentages of subjects with Ab titers against pneumococcal antigens ≥0.35 µg/mL were variable. 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 Prevenar 13, >79% of subjects presented Ab ≥0.35 µg/mL in both groups for anti-pneumococcal Ab serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. There were no differences between the 2 groups in terms of anti-pneumococcal Ab GMCs.

Table 16. Percentage of subjects with anti-pneumococcal serotypes Ab concentration ≥ to the assay cut-off, 0.35 µg/ml and GMC, 1 month after the last dose of the primary vaccination (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	Post-Pri	232	232	100	98.4	100	222	95.7	92.2	97.9	1.61	1.43	1.80
	Control Group	Post-Pri	237	237	100	98.5	100	227	95.8	92.4	98.0	1.92	1.73	2.14
anti-PnPS 3 antibody (ECL)	dTpa Group	Post-Pri	232	228	98.3	95.6	99.5	173	74.6	68.5	80.0	0.54	0.49	0.60
	Control Group	Post-Pri	237	235	99.2	97.0	99.9	181	76.4	70.4	81.6	0.60	0.55	0.67
anti-PnPS 4 antibody (ECL)	dTpa Group	Post-Pri	232	232	100	98.4	100	214	92.2	88.0	95.3	1.20	1.07	1.35
	Control Group	Post-Pri	237	236	99.6	97.7	100	228	96.2	92.9	98.2	1.56	1.40	1.75
anti-PnPS 5 antibody (ECL)	dTpa Group	Post-Pri	226	218	96.5	93.1	98.5	199	88.1	83.1	92.0	1.09	0.96	1.24
	Control Group	Post-Pri	234	224	95.7	92.3	97.9	214	91.5	87.1	94.7	1.27	1.13	1.43
anti-PnPS 6A antibody (ECL)	dTpa Group	Post-Pri	232	228	98.3	95.6	99.5	221	95.3	91.7	97.6	2.16	1.89	2.47
	Control Group	Post-Pri	237	234	98.7	96.3	99.7	226	95.4	91.8	97.7	2.59	2.27	2.95
anti-PnPS 6B antibody (ECL)	dTpa Group	Post-Pri	232	215	92.7	88.5	95.7	185	79.7	74.0	84.7	1.37	1.12	1.68
	Control Group	Post-Pri	237	223	94.1	90.3	96.7	200	84.4	79.1	88.8	1.44	1.20	1.73
anti-PnPS 7F antibody (ECL)	dTpa Group	Post-Pri	232	232	100	98.4	100	229	98.7	96.3	99.7	2.39	2.15	2.65
	Control Group	Post-Pri	237	237	100	98.5	100	236	99.6	97.7	100	2.67	2.43	2.93
anti-PnPS 9V antibody (ECL)	dTpa Group	Post-Pri	232	232	100	98.4	100	212	91.4	87.0	94.7	1.33	1.19	1.50
	Control Group	Post-Pri	237	237	100	98.5	100	227	95.8	92.4	98.0	1.64	1.47	1.83
anti-PnPS 14 antibody (ECL)	dTpa Group	Post-Pri	232	232	100	98.4	100	229	98.7	96.3	99.7	5.70	4.99	6.52
	Control Group	Post-Pri	237	235	99.2	97.0	99.9	233	98.3	95.7	99.5	6.57	5.71	7.56
anti-PnPS 18C antibody (ECL)	dTpa Group	Post-Pri	232	229	98.7	96.3	99.7	220	94.8	91.1	97.3	1.61	1.42	1.82
	Control Group	Post-Pri	237	235	99.2	97.0	99.9	223	94.1	90.3	96.7	1.79	1.59	2.01
anti-PnPS 19A antibody (ECL)	dTpa Group	Post-Pri	232	227	97.8	95.0	99.3	216	93.1	89.0	96.0	1.61	1.43	1.82
	Control Group	Post-Pri	237	232	97.9	95.1	99.3	227	95.8	92.4	98.0	2.01	1.78	2.27

				≥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 19F antibody (ECL)	dTpa Group	Post-Pri	232	232	100	98.4	100	230	99.1	96.9	99.9	2.57	2.35	2.82
	Control Group	Post-Pri	237	237	100	98.5	100	233	98.3	95.7	99.5	3.24	2.92	3.60
anti-PnPS 23F antibody (ECL)	dTpa Group	Post-Pri	230	224	97.4	94.4	99.0	182	79.1	73.3	84.2	0.86	0.74	0.99
	Control Group	Post-Pri	236	229	97.0	94.0	98.8	203	86.0	80.9	90.2	1.02	0.88	1.17

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.
*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
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
Post-Pri=blood sample collected 1 month after the last dose of the primary vaccination course

Table 17. 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

A trend for higher GMC of Ab specific to most of the serotypes was observed for the control group compared to the dTpa group, post primary vaccination. Percentages of subjects achieving the cut-off of 0.35 µg/ml, considered as the protective threshold, were generally high but were slightly lower for 5 out of 13 serotypes when compared to percentages observed in the control group. Difference in immune responses, post-primary vaccination, to various serotypes of *Streptococcus pneumoniae* in infants born to mothers dTpa vaccinated compared to infants born to unvaccinated mothers during pregnancy was also described in the literature (Zimmerman 2019, Barug 2020).

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 to 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. Only few data are currently available in the literature. Lower anti-PnPS specific to several serotypes, including 4 and 18C, were also observed before the booster dose in infants born to mothers vaccinated during pregnancy compared to infants whose mothers did not receive dTpa immunisation during pregnancy (Zimmermann 2019). Conversely, no difference in the level of pre-boost anti-PnPS specific to several serotypes was observed between similar groups in Barug 2020. During the assessment of study DTPA-049, the MAH was invited to discuss the clinical and epidemiological relevance of these observations (see also 6.2.3.1. Immune responses to Diphtheria and Tetanus toxoids) in the present submission. The MAH has now specified that these findings are not considered conclusive since the analyses were exploratory.

One month post-boost, similar proportion of infants achieved the threshold associated with protection between groups. GMC values were in general slightly lower for infants in dTpa group when compared to infants in control group but CI 95% were always overlapping.
Overall, post-boost results indicate that the MI did not impact the proportion of the infants achieving the seroprotection threshold for the 13 pneumococcal serotypes.

6.3. Discussion

Maternal immunisation (MI) with combined reduced-antigen content diphtheria-tetanus-acellular pertussis (dTpa) vaccines is currently recommended by several national health authorities worldwide with the aim of passively protecting the neonates and young infants from pertussis disease. Effectiveness of MI against pertussis disease in the first months of life (before infant's primary vaccination) has been described in the literature (Amirthalingam 2016, Baxter 2017, Bellido-Blasco 2017, Becker-Dreps 2018, , Saul 2018). Consequently, vaccination during pregnancy is currently included in the therapeutic indication of dTpa vaccines.
Nevertheless, growing evidences indicate that MI with a dTpa vaccine also results in immune interference with infant's vaccination in these infants born to mothers dTpa-vaccinated during the pregnancy when compared to those born to dTpa- unvaccinated or post-partum vaccinated mothers.

In 2013-2014, GSK has initiated a MI clinical development programme, that included 3 Phase IV studies, to gain further insights on the immunogenicity and safety of maternal vaccination with the dTpa vaccine Boostrix and the impact on infants'/toddlers' immune responses after their primary and booster vaccination with Infanrix hexa. The first study, DTPA-047, was a randomized, placebo-controlled, multicentre study that evaluated the immunogenicity and safety of Boostrix when administered to pregnant women aged 18–45 years during the third trimester of pregnancy. Both other studies, DTPA-048 and DTPA-049, were non-randomised, open label, multicentre studies that evaluated the immunogenicity and safety of Infanrix hexa given in the primary vaccination schedule (DTPA-048) or as a booster dose (DTPA-049) to infants and toddlers born to mothers participating in study DTPA-047. In DTPA-048, Infanrix hexa was administered with Prevenar 13 in a 2- or 3- dose schedule according to the country of enrolment. In DTPA-049, Infanrix hexa was co-administered with Prevenar 13. All the toddlers included in the study DTPA-049 completed their primary vaccination in study DTPA-048.

Immunogenicity assessment consisted in the measurement of specific Ab. Only Ab specific to the 3 pertussis antigens (PT, FHA, PRN) were assessed in cord blood samples (DTPA-047), whereas anti-D and anti-T Ab were measured before and after primary or booster infant's vaccination in parallel to the

pertussis-specific immune responses (DTPA -048 and -049). Humoral immune responses to all other components of the paediatric Infanrix hexa vaccine were assessed in infants and toddlers after the primary vaccination (DTPA-048) as well as before and after the booster vaccination (DTPA-049). The clinical protections 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 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. Regarding pertussis immune responses, criteria defining seroresponse as per protocol were not appropriate, particularly for infants with high level of specific Ab pre-vaccination. Since there is no correlate of protection (CoP) regarding the *B. pertussis* infection, results expression in term of GMC was deemed more relevant.

The primary objective of study DTPA-047 was met. The concentration of maternally transferred Ab against the 3 pertussis antigens, as measured in the cord blood at birth, in the dTpa group was demonstrated to be superior to that in the control group. The LL of the 95% CI of the GMC ratio between groups for anti-PT, anti-FHA and anti-PRN Ab was above the pre-defined criterion of 1.5. The maternal Ab against the pertussis antigens were found to be persistent, although at lower GMC, at 8-9 weeks of age. These results confirm the reported active transplacental transport of Ab (Healy, 2016, Hardy-Fairbanks 2013, Munoz 2014, Maertens 2016, Villarreal Pérez 2017, Halperin 2018, Barug 2019, Perret 2020) and strongly suggest the involvement of the maternal Ab in the protection of the offspring against (severe) pertussis disease during the first months of life. The positive impact of the MI in protecting infants against infections was also demonstrated for diphtheria and tetanus diseases; percentages of seroprotected infants against both diseases were higher in the dTpa group when compared to the control group at 8-9 weeks of age. These high percentages in the dTpa group indicate that the neonates were protected from birth until the start of the primary vaccination.

In line with the literature, MI was shown to interfere with the infants' immune responses to the hexavalent primary and boost vaccination. The blunting effect was specific to certain homologous and heterologous antigens. Whereas no immune interferences were observed, at any timepoint tested, for tetanus, Hepatitis B, poliovirus type 1, 2 and 3 and *Haemophilus influenzae* type b infections, blunting of the immune responses specific to diphtheria, *Streptococcus pneumoniae or B. pertussis* were observed.

Lower anti-D GMT were observed post-primary and post-booster vaccination in the dTpa group when compared to the control group. This lower anti-D GMC results in a lower percentage of infants achieving the cut-off associated with long term protection against diphtheria (≥ 1.0 IU/ml anti-D Ab) post-primary vaccination and a lower percentage of seroprotected subjects against diphtheria (≥ 0.1 IU/ml anti-D Ab) before the boost in the dTpa group (81.2%) when compare to the control group (90.2%).

Similarly, a trend for lower GMC of Ab specific to most of the serotypes of *Streptococcus pneumoniae* was observed for the dTpa group compared to the control group, both at post-primary and post-booster vaccination timepoints. This trend translates into lower percentages of subjects achieving the cut-off of 0.35 µg/ml in the dTpa group for 5 out 13 serotypes when compared to the control group post-primary vaccination. Lower percentage of *Streptococcus pneumoniae* seroprotected subjects at pre-booster timepoint was observed for serotypes 4 (13.4 vs 27.2%) and 18C (19.9 vs 34.2%) in dTpa group as compared to the control group. These results should however be interpreted with caution since the analyses of the immune responses specific to *Streptococcus pneumoniae* were exploratory. Meanwhile, these results suggest that around twofold of the infants born to 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. Published clinical trials also reported lower level of anti-D (Maertens 2016, Zimmermann 2019, Barug 2020) and lower level of anti-PnPs specific to several serotypes, including 4 and 18C, (Zimmermann 2019) before the booster dose in infants born to 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 or levels of anti-PnPs specific to several serotypes were observed between similar groups in Munoz 2014 and in Barug 2020 respectively. Differences in vaccine-induced immune response specific to pneumococcal serotypes that are evidenced in the literature and the present study might be due to the difference in carrier proteins included in the vaccines. Nevertheless, the duration of this potential window of susceptibility and the clinical consequences of these observations are not yet known. More data need to be accumulated. Because of these uncertainties, the study limitation and the overall scarcity of the data, these observations are not deemed to be reflected in the SmPC.

In addition, although GMT of Ab specific to diphtheria and to various serotypes of *Streptococcus pneumoniae* tend to be lower in dTpa group compared to the control group at 1 month after the boost vaccination, all subjects were seroprotected against diphtheria and >99% of the subjects of dTpa group achieved the anti-D Ab threshold associated with long-term protection. 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-vaccination is not likely to be clinically relevant in the short term.

Results and interpretation of immune responses to pertussis antigens are more difficult to interpret since there is currently no correlate of vaccine protection.

Lower GMC were observed at one month post-primary vaccination for anti-PT, anti-FHA and anti-PRN Ab in the dTpa group when compared to the control group. One month post-boost, lower PT- and FHA-Ab responses were still observed in infants whose mothers did receive dTpa immunisation during pregnancy when compare to control infants. Conversely, anti-PRN titers were higher for the dTpa group when compared to the control group. The observed results are in line with those of other studies that have assessed the induction of pertussis-specific immune response after the primary vaccination (Ladhani 2015, Villarreal Pérez 2017) or after both the primary and the booster vaccination administered around 12 months of age (Hardy-Fairbanks 2013, Munoz 2014, Maertens 2016, Halperin 2018, Barug 2019) in infants born to dTpa vaccinated versus unvaccinated mothers during pregnancy. Overall, all these publications show a trend for lower GMC of pertussis antigens-specific Ab in infants born to dTpa vaccinated mothers during the pregnancy compared to in infants born to unvaccinated or post-partum vaccinated mothers. This is true for post-primary vaccination and post-boost vaccination. The blunting of the majority of the antigen-specific Ab responses observed post-primary vaccination was still observed post-boost. The blunting effect was observed with different vaccines used for maternal and childhood immunisation, suggesting that the blunting effect is not product-specific. This class effect is reviewed in Kandeil 2020. In the absence of CoP, the clinical relevance of these observations is not known. Similarly, it is not known whether it could also reflect an altered induction of immune memory and the 'real' (long-term) impact of MI for the infants can therefore not be determined. Comparable fold increases of the anti-pertussis antigens Ab GMC from the pre-booster to the 1-month after booster were observed in both dTpa and control groups of study DTPA-049, suggesting that infants of both groups developed an immune memory against *B. pertussis*. Yet, even if these data 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.

Current epidemiological (UK and US) data are reassuring regarding the absence of any clinical impact of the blunting of infants immune responses during and/or shortly after the primary vaccination. Uncertainties yet remain for the long-term clinical protection (> 2 years following vaccination). Upcoming epidemiological data from countries where the vaccine coverage of pregnant women is high would help to further insight the potential impact on the protection against pertussis disease. A close monitoring of the epidemiology is warranted to better assess the impact of MI on the short and the long-term and, if needed, to adapt the vaccination strategies, i.e. choice of the vaccine and schedule (2 vs 3 doses, additional dose etc). As recommended by the VWP, the MAH should follow and report these data in PSURs.

Implications for the SmPC:

MI has proved its benefit in protecting neonates against (severe) pertussis disease during the first months of life. On the other hand, MI has been shown to interfere with immune responses of infants to their childhood vaccination.

As previously discussed at VWP, these data could be reflected in the SmPC in section 5.1. Accordingly, the MAH proposes the following wording to be added in section 5.1:

'Immunogenicity in infants and toddlers born to mothers vaccinated with dTpa during pregnancy

The immunogenicity of Infanrix hexa in infants and toddlers born to healthy mothers vaccinated with dTpa at 27-36 weeks of pregnancy was evaluated in two clinical studies.
Infanrix hexa was co-administered with a 13-valent pneumococcal conjugate vaccine to infants at 2, 4 and 6 months or 2, 3 and 4 months in three-dose primary vaccination schedules (n=241), or at 3 and 5 months or 2 and 4 months in two-dose primary vaccination schedules (n=27); and to the same infants/toddlers from 11 to 18 months as booster dose (n=229).

Post-primary and post-booster vaccination, immunological data did not show clinically relevant interference of maternal vaccination with dTpa on the infant's and toddler's responses to diphtheria, tetanus, hepatitis B, inactivated poliovirus, Haemophilus influenzae type b or pneumococcal antigens.

Lower antibody concentrations against pertussis antigens post-primary (PT, FHA and PRN) and post-booster (PT, FHA) vaccination were observed in infants and toddlers born to mothers vaccinated with dTpa during pregnancy. The fold-increases of anti-pertussis antibody concentrations from the pre-booster to the 1-month post-booster time point were in the same range for infants and toddlers born to mothers vaccinated with dTpa or with placebo, demonstrating effective priming of the immune system.
In the absence of correlates of protection for pertussis, the clinical relevance of these observations remains to be fully understood. However, current epidemiological data on pertussis disease following the implementation of dTpa maternal immunisation do not suggest any clinical relevance of this immune interference.'

The proposed wording is deemed appropriate.

7. Clinical Safety aspects

7.1. Methods – analysis of data submitted

7.1.1. Safety objectives and endpoints

The safety and reactogenicity of the study vaccines were evaluated as secondary objectives. The safety and reactogenicity of Boostrix are not in the scope of the current submission, therefore the safety endpoints that were followed in study DTPA-047 are not described in the present report.

The safety objectives in studies DTPA-048 and DTPA-049 were evaluated based on the following endpoints:

- ✓ Occurrence of solicited local and general adverse events (AEs) during the 4-day (Days 0–3) follow-up period after each vaccination
- ✓ Occurrence of unsolicited AEs during the 31-day (Days 0–30) follow-up period after each vaccination
- ✓ Occurrence of serious AEs (SAEs) from first vaccination dose (study DTPA-048) or booster dose (study DTPA-049) to study end

In addition to these safety endpoints, neurodevelopmental status was to be assessed at 9 and 18 months of age adjusted for prematurity in study DTPA-049. The neurodevelopmental status was evaluated based on the following endpoints:

- ✓ 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.

7.1.2. Statistical analysis of safety endpoints

7.1.2.1. Study cohorts

The primary analysis in both studies (DTPA-048 and DTPA-049) was performed on the TVC, defined as all subjects with at least 1 vaccine administration documented. In study DTPA-049, the neurodevelopmental delay analysis was performed on the Total enrolled cohort, which included all subjects enrolled in that study. The congenital anomalies analysis from study DTPA-049 was performed

on the Total enrolled cohort infants, defined as delivered infants in study DTPA-047 followed up until the end of the booster study DTPA-049.

7.1.2.2. Statistical methods

All safety objectives were descriptive. For each study, the following analyses were tabulated:

- ✓ The percentage of doses and/or subjects reporting solicited local and general AEs within 4-day follow-up period with exact 95% CIs, unsolicited AEs and SAEs, including fatal SAEs classified by the MedDRA Preferred Terms with exact 95% CIs.
- ✓ Neurodevelopmental status of the subjects was assessed in the context of Boostrix vaccination during pregnancy 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 a formal neurodevelopmental evaluation using BSID-III and those with at least 1 indicator of neurodevelopmental impairment using BSID-III was also tabulated.

7.2. Results - studies DTPA-048 and DTPA-049

7.2.1. Extent of exposure

A total of 601 subjects were included in the TVC in study DTPA-048. Of these, 540 subjects were included in the TVC in study DTPA-049. The number of doses distributed as well as the number of subjects receiving 1, 2 or 3 doses of Infanrix hexa and Prevenar 13 are summarised in Table below.

Table 18. Number of subjects and doses evaluated for safety in studies DTPA-048 and DTPA-049

Study DTPA-048							
dTpa Group (N=296)				Control Group (N=305)			
Infanrix hexa (total number of doses: 849)		*Prevenar 13* (total number of doses: 812)		*Infanrix hexa* (total number of doses: 869)		*Prevenar 13* (total number of doses: 831)	
Number of subjects	Number of doses	Number of subjects	Number of doses	Number of subjects	Number of doses	Number of subjects	Number of doses
3	1	3	1	3	1	3	1
33	2	70	2	40	2	78	2
260	3	223	3	262	3	224	3
Study DTPA-049							
dTpa Group (N=263)				Control Group (N=277)			
Infanrix hexa (total number of doses: 263)		*Prevenar 13* (total number of doses: 263)		*Infanrix hexa* (total number of doses: 277)		*Prevenar 13* (total number of doses: 276)	
Number of subjects	Number of doses	Number of subjects	Number of doses	Number of subjects	Number of doses	Number of subjects	Number of doses
263	1	263	1	277	1	276	1

N = number of subjects in a group receiving at least 1 dose of the study vaccine
Data source: DTPA (BOOSTRIX)-048 (201330) Report Amendment 1 Main (23-Sep-2019) Table 8.1; DTPA (BOOSTRIX)-049 BST 048 (201334) Report Main (31-Oct-2019) Table 8.1

7.2.2. Solicited AEs

7.2.2.1. Solicited local AEs

In study DTPA-048, during the 4-day post-vaccination period following primary vaccination, redness was the most frequently reported solicited local AE at the Infanrix hexa injection site, with incidences of 62.9% in the dTpa Group and 61.1% in the Control Group (overall/subject). Pain and swelling were reported for 56.1% and 46.6% of subjects, respectively, in the dTpa Group and for 54.8% and 45.5% of subjects, respectively, in the Control Group (overall/subject). The most frequently reported solicited local AE following vaccination with Prevenar 13 was redness and was reported in 55.6% of subjects in the dTpa Group and 56.1% of subjects in the Control Group, respectively. Pain and swelling were reported for 53.9% and 38.9% of subjects, respectively, in the dTpa Group, and for 50.5% and 42.2% of subjects, respectively, in the Control Group (overall/subject).

Grade 3 solicited local AEs at the Infanrix hexa injection site were reported by ≤3.4% of subjects in the dTpa Group and by ≤4.6% of subjects in the Control Group. At the Prevenar 13 injection site, grade 3 solicited local AEs were reported by ≤3.1% of subjects in the dTpa Group and by ≤3.6% of subjects in the Control Group.

In study DTPA-049, during the 4-day post-vaccination period following booster vaccination, redness was the most frequently reported solicited local AE at the Infanrix hexa injection site, reported for 49.0% and 53.5% of subjects in the dTpa and Control Groups, respectively. Pain and swelling were

reported for 46.3% and 40.1% of subjects, respectively, in the dTpa Group and for 49.8% and 38.5% of subjects, respectively in the Control Group. Redness was also the most frequently reported solicited AE at the Prevenar 13 injection site, reported for 46.7% and 48.2% of subjects in the dTpa and Control Groups, respectively. Pain and swelling were reported for 44.0% and 33.9% of subjects, respectively, in the dTpa Group, and for 45.3% and 31.4% of subjects, respectively, in the Control Group.

Grade 3 solicited local AEs at the Infanrix hexa injection site were reported for no more than 8.2% and 8.7% of subjects in the dTpa and Control Groups, respectively. Grade 3 solicited local AEs at the Prevenar 13 injection site were reported for no more than 5.4% and 5.8% of subjects in the dTpa and Control Groups, respectively.

7.2.2.2. Solicited general AEs

In study DTPA-048, the most frequently reported solicited general AE during the 4-day period following primary vaccination was irritability/fussiness, reported for 86.7% of subjects in the dTpa Group and 84.8% of subjects in the Control Group. Irritability/fussiness was also the most frequently reported grade 3 solicited general AE, reported for 12.2% of subjects in each group. Fever was reported at similar incidence in both groups (42.9% of subjects in the dTpa Group and 41.6% of subjects in the Control Group). Grade 3 fever was reported for 1.4% of subjects in the dTpa Group and 0.3% of subjects in the Control Group. Grade 3 solicited general AEs considered by the investigator as causally related to vaccination were reported for ≤10.9% of subjects in the dTpa Group and ≤11.6% of subjects in the Control Group.

In study DTPA-049, the most frequently reported solicited general AE during the 4-day period following booster vaccination was irritability, reported for 63.2% and 68.4% of subjects in the dTpa and Control Groups, respectively. Irritability was also the most frequently reported grade 3 solicited general AE, reported for 5.0% and 10.2% of subjects in the dTpa and Control Groups, respectively. Fever was reported for 28.3% and 30.9% of subjects in the dTpa and Control Groups, respectively. Grade 3 fever was reported for no more than 2.7% of subjects across both groups. Grade 3 solicited general AEs considered by the investigator as causally related to vaccination were reported for no more than 4.3% and 9.5% of subjects in the dTpa and Control Groups, respectively.

7.2.3. Unsolicited AEs

In study DTPA-048, during the 31-day period following each Infanrix hexa primary vaccination co-administered with Prevenar 13:

- ✓ at least 1 unsolicited AE was reported for 54.4% and 56.7% of subjects in the dTpa and Control Groups, respectively. The most frequently reported unsolicited AE was upper respiratory tract infection reported for 12.2% and 10.8% of subjects in the dTpa and Control Groups, respectively.
- ✓ at least 1 grade 3 unsolicited AE was reported for 5.1% and 5.9% of subjects in the dTpa and Control Groups, respectively. The most frequently reported grade 3 unsolicited AEs were teething in the dTpa Group, reported for 4 (1.4%) subjects, and pyrexia in the Control Group, reported for 3 (1%) subjects.
- ✓ at least 1 unsolicited AE considered as causally related to vaccination was reported for 3.7% and 4.3% of subjects in the dTpa and Control Groups, respectively. The most commonly reported AEs were mass at the injection site in the dTpa Group, reported for 4 (0.5%) subjects; and injection

site bruising, injection site mass and increase in body temperature in the Control Group, reported each for 2 (0.2%) subjects. No grade 3 causally related unsolicited AEs were reported.

In study DTPA-049, during the 31-day period following the booster dose of Infanrix hexa co-administered with Prevenar 13:

- ✓ at least 1 unsolicited AE was reported for 35.7% and 40.1% of subjects in the dTpa and Control Groups, respectively. The most frequently reported unsolicited AEs were pyrexia and nasopharyngitis in the dTpa Group, reported for 4.6% of subjects, and pyrexia in the Control Group, reported for 7.9% of subjects.
- ✓ at least 1 grade 3 unsolicited AE was reported for 7.2% and 5.8% of subjects in the dTpa and Control Groups, respectively. The most frequently reported grade 3 unsolicited AEs were ear infection in the dTpa Group, reported for 2.3% of subjects, and pyrexia in the Control Group, reported for 1.4% of subjects.
- ✓ at least 1 unsolicited AE considered as causally related to vaccination was reported for 3.8% and 3.6% of subjects in the dTpa and Control Groups, respectively. The most commonly reported AEs were vomiting in the dTpa Group (1.5% of subjects) and injection site mass in the Control Group (0.7% of subjects). No grade 3 causally related unsolicited AEs were reported.

7.2.4. SAEs and fatal outcomes

During study DTPA-048, a total of 9 SAEs were reported for 7 subjects (2.4%) in the dTpa Group and a total of 23 SAEs were reported for 17 subjects (5.6%) in the Control Group. None of the reported SAEs were considered by the investigator to be causally related to vaccination, and no fatal cases were reported in this study. At the end of the study, all SAEs recovered/resolved or were recovering/resolving except for 5 SAEs (3 SAEs in the dTpa Group and 2 SAEs in the Control Group).

Following booster vaccination with Infanrix hexa co-administered with Prevenar 13 in study DTPA-049, a total of 3 SAEs were reported for 3 subjects (1.1%) in the Control Group; no SAEs were reported in the dTpa Group. None of the reported SAEs were assessed by the investigator as causally related to vaccination. All SAEs had resolved/recovered by the end of the study.

During the entire study period for study DTPA-049 (from Visit 1, at the age of 9 months of the subject, up to Visit 3 [1-month post-booster dose], at the age of 18-19 months, depending on the national recommendation for the administration of the booster dose), a total of 12 SAEs were reported for 3 subjects in the dTpa Group and a total of 7 SAEs were reported for 5 subjects in the Control Group. Throughout the study period, 1 fatal case was reported in the dTpa Group for a 16 months-old male subject before the administration of the booster dose. The subject had a history of congenital cytomegalovirus infection who developed enterovirus gastroenteritis, encephalopathy, refractory shock, gastroenteritis astroviral, intracranial hypertension, dehydration and rhabdomyolysis 310 days after receiving the third dose of Infanrix hexa and Prevenar 13 in study DTPA-048. The patient had enterovirus and astrovirus infections concurrently.

Death occurred after 2 days. Given the long time to onset of events and the underlying infection, the case was assessed by the investigator as not related to the primary vaccination received in study DTPA-048.

Except for the fatal case, all SAEs had recovered/resolved by the end of study DTPA-049 (2 of which recovered/resolved with sequelae). None of these SAEs nor the fatal case were considered by the investigator as causally related to vaccination.

7.2.5. Other significant AEs

7.2.5.1. AEs leading to withdrawal

In study DTPA-048, 1 subject in the dTpa Group was withdrawn from the study due to 2 SAEs (enterorrhagia and cow's milk allergy, assessed by the investigator as not related to vaccination). No subjects withdrew from study DTPA-049 due to AEs/SAEs after the administration of the booster dose.

7.2.5.2. Medically attended visits

In study DTPA-048, at least 1 unsolicited AE with medically attended visit was reported for 36.5% of subjects in the dTpa Group and 37.7% of subjects in the Control Group, respectively. In study DTPA-049, at least 1 unsolicited AE with medically attended visit was reported for 22.8% of subjects in the dTpa Group and 25.6% of subjects in the Control Group.

7.2.5.3. Congenital anomalies

Congenital anomalies were evaluated in the context of Boostrix vaccination of pregnant women. The analysis for the congenital anomalies was performed on the Total enrolled cohort infants (DTPA-047) and is reported from delivered infants in study DTPA-047 up to the end of the booster study DTPA-049. In the dTpa Group, at least 1 congenital anomaly in infants was reported for 35 subjects (10.4%), of which atrial septal defect (1.5%) and plagiocephaly (1.2%) were the most commonly reported. In the Control Group, at least 1 congenital anomaly in infants was reported for 44 subjects (12.9%), of which atrial septal defect (2.3%) and phimosis (1.5%) were the most commonly reported.

7.2.6. Neurodevelopmental status (study DTPA-049)

Neurodevelopmental status was evaluated in the context of Boostrix vaccination of pregnant women, on the Total enrolled cohort (infants in study DTPA-049).

At 9 or 18 months of age, 11.5% and 11.0% of subjects in the dTpa and Control Groups, 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 and Control Groups, respectively, had at least 1 indicator of neurodevelopmental delay.

Assessor's comment

In study DTPA-048, 601 infants (296 and 305 in the dTpa and control groups respectively) received both Infanrix hexa and Prevenar 13 vaccines and were evaluated for safety. A total of 1718 doses (849 and 869 doses in dTpa and control groups respectively) of Infanrix hexa were administrated. A total of 1643 doses (812 and 831 in dTpa and control groups respectively) of Prevenar 13 were administrated.

In study DTPA-049, 540 infants (263 and 277 in the dTpa and control groups respectively) received both Infanrix hexa and Prevenar 13 vaccines and were evaluated for safety. A total of 540 doses (263 and 277 doses in dTpa and control groups respectively) of Infanrix hexa and Prevenar 13 were administrated.

Both vaccines were well tolerated. The safety profile was similar in both groups, regardless of exposure/non-exposure of the mothers to Boostrix during pregnancy. The frequency of the reported solicited and unsolicited AEs were in line with the frequency described in the Infanrix hexa PI.

The neurodevelopmental evaluation performed in study DTPA-049 at 9 and 18 months of age showed similar results in both dTpa and control groups regardless of the vaccination status of the mothers.

SAEs were reported with a similar incidence across groups in both studies, and none of them was considered by the investigator to be causally related to vaccination. One fatal case was reported in the dTpa group for a 16 months-old male subject before the administration of the booster dose. The case was considered by the investigator as not related to the primary vaccination. This subject should not have been included in the study since he did not satisfy all the inclusion criteria at study entry.

7.3. Discussion

Both vaccines were well tolerated. The safety profile was similar in both groups, regardless of exposure/non-exposure of the mothers to Boostrix during pregnancy. The frequency of the reported solicited and unsolicited AEs were in line with the frequency described in the Infanrix hexa PI.

The neurodevelopmental evaluation performed in study DTPA-049 at 9 and 18 months of age showed similar results in both dTpa and control groups regardless of the vaccination status of the mothers.

SAEs were reported with a similar incidence across groups in both studies, and none of them was considered by the investigator to be causally related to vaccination. One fatal case was reported in the dTpa group for a 16 months-old male subject before the administration of the booster dose. The case was considered by the investigator as not related to the primary vaccination.

Implications for the SmPC:
The assessor agrees with the MAH which considers that there were no new identified AEs nor changes required in the frequency or severity of AEs listed in the Infanrix hexa PI. Moreover, the safety and reactogenicity profiles of Infanrix hexa and Prevenar 13 are not influenced by the maternal vaccination with Boostrix.

The MAH proposed the following wording to be added in the section 4.8:

'*In two clinical studies, Infanrix hexa has been administered to more than 500 subjects born to mothers vaccinated with dTpa (n=341) or placebo (n=346) during the third trimester of pregnancy (see section 5.1). The safety profile of Infanrix hexa was similar regardless of exposure/non-exposure to dTpa during pregnancy.*.'

The MAH also took the opportunity to update of the Table summarizing the Adverse Reactions to reclassify the frequency for "Fatigue" and "Somnolence". In the current PI, "Drowsiness" was encoded under the MedDRA Preferred Term "Fatigue", a subjective feeling that cannot be reported by infants and toddlers. Conversely, "Somnolence" describe the observation of the infants' and toddlers' behaviours. Hence "Somnolence" is a more appropriate MedDRA Preferred Term for "Drowsiness" in this population. This recoding will also align the PI of Infanrix hexa with the PIs of GSK's lower valent DTPa combination vaccines.

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

The assessor agrees with the proposed updates.

8. Changes to the Product Information

As a result of this variation, sections 4.8 and 5.1 of the SmPC are being updated to describe the safety and immunogenicity in infants and toddlers born to mothers vaccinated with dTpa during pregnancy. The frequency of ARs was modified following the reclassification of frequency for "Fatigue" and "Somnolence".

The MAH was requested to propose a more appropriate wording for both statements in the sections 4.8 and 5.1. Updated version of the PI is now deemed appropriate.

Changes are also made to the PI to bring it in line with the current QRD template version 10.1.

The Package Leaflet (PL) is updated accordingly. The posology information in the PL was also updated to align it with the SmPC.

9. Request for supplementary information

9.1. Other concerns

Clinical aspects

1. The MAH is requested to propose a more appropriate wording for both statements that described the safety and immunogenicity in infants and toddlers born to mothers vaccinated with dTpa during pregnancy in the sections 4.8 and 5.1. See PI document.

10. Assessment of the responses to the request for supplementary information

10.1. Other concerns

Clinical aspects

Question 1

The MAH is requested to propose a more appropriate wording for both statements that described the safety and immunogenicity in infants and toddlers born to mothers vaccinated with dTpa during pregnancy in the sections 4.8 and 5.1. See PI document.

A. Section 4.8. Undesirable effects.
Relevant characteristics of the population should be briefly described such as number of included subjects and timing of the vaccination during the pregnancy.

Summary of the MAH's response

The exact number of mothers vaccinated during pregnancy with dTpa or with placebo and the trimester of pregnancy during which women were vaccinated have been included in the proposed wording. The Company also proposes to add a cross-reference to the section 5.1 Pharmacodynamic properties as this section contains more information on the two clinical trials.

Exact wording included in the PI:

In two clinical studies, Infanrix hexa has been administered to more than 500 subjects born to mothers vaccinated with dTpa (n=341) or placebo (n=346) during the third trimester of pregnancy (see section 5.1). The safety profile of Infanrix hexa was similar regardless of exposure/non-exposure to dTpa during pregnancy.'

Assessment of the MAH's response

Issue resolved

B. Section 5.1. Pharmacodynamic properties
The proposed wording is not considered appropriate and specific enough. Clinical data should be replace by immunological data. Immunological data did show immune interference. The characteristics of the population should be better described. All characteristics that are relevant to appropriately assess the accuracy of the information

need to be included (such as exact number of infants and toddlers included in the studies, range of gestational weeks when MI, infant's vaccination schedule, etc). Immune responses specific to the 3 pertussis antigens (PT, FHA, PRN) should be described in term of GMCs, both post-primary and post-booster vaccination. It should also be indicated that the fold increases of the anti-pertussis antigens Ab GMC from the prebooster to the 1-month after booster were in the same range for both dTpa and control groups. It should be specified that, because internationally agreed correlates of protection are lacking, the clinical significance of blunting is not yet fully understood; The clinical relevance of these observed interference are currently unknown but current limited epidemiological data on pertussis disease do not suggest any clinical concern of this immune interference on the short term. The MAH is required to propose a revised wording of this section.

Summary of the MAH's response

The Company acknowledges the assessor's comment regarding the appropriateness and specificity of the wording in the PI. As requested, the following edits and precisions have been made:

- The term "Clinical data" has been replaced by "Immunological data";
- The range of gestational weeks for pregnant women at the time of vaccination as well as the infant's 2-dose or 3-dose vaccination schedule and the exact number of infants (per vaccination schedule) and toddlers in both clinical trials have been included to provide characteristics of the population;
- The lower antibody concentrations (GMCs) observed post-primary vaccination for all 3 pertussis antigens (PT, FHA and PRN) and post-booster vaccination for PT and FHA, respectively, have been described in the PI. The fact that the fold increases of the anti-pertussis antibody GMCs from the pre-booster to the 1-month post-booster time point were in the same range for both the dTpa and control groups has also been detailed. Finally, the statements on the clinical relevance of the observed interference of maternal antibodies on the infant's and toddler's anti-pertussis antibody responses requested by the assessor have been added in the PI.

Exact wording included in the PI:

'*Immunogenicity in infants and toddlers born to mothers vaccinated with dTpa during pregnancy*

The immunogenicity of Infanrix hexa in infants and toddlers born to healthy mothers vaccinated with dTpa at 27-36 weeks of pregnancy was evaluated in two clinical studies.
Infanrix hexa was co-administered with a 13-valent pneumococcal conjugate vaccine to infants at 2, 4 and 6 months or 2, 3 and 4 months in three-dose primary vaccination schedules (n=241), or at 3 and 5 months or 2 and 4 months in two-dose primary vaccination schedules (n=27); and to the same infants/toddlers from 11 to 18 months as booster dose (n=229).

Post-primary and post-booster vaccination, immunological data did not show clinically relevant interference of maternal vaccination with dTpa on the infant's and toddler's responses to diphtheria, tetanus, hepatitis B, inactivated poliovirus, Haemophilus influenzae type b or pneumococcal antigens.

Lower antibody concentrations against pertussis antigens post-primary (PT, FHA and PRN) and postbooster (PT, FHA) vaccination were observed in infants and toddlers born to mothers vaccinated with dTpa during pregnancy. The fold-increases of anti-pertussis antibody concentrations from the prebooster to the 1-month post-booster time point were in the same range for infants and toddlers born to mothers vaccinated with dTpa or with placebo, demonstrating effective priming of the immune system.
In the absence of correlates of protection for pertussis, the clinical relevance of these observations remains to be fully understood. However, current epidemiological data on pertussis disease following the implementation of dTpa maternal immunisation do not suggest any clinical relevance of this immune interference.'

Assessment of the MAH's response

Issue resolved

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly.