



Clinical trial results:

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

Summary

EudraCT number	2014-001120-30
Trial protocol	ES CZ Outside EU/EEA FI IT
Global end of trial date	19 March 2019

Results information

Result version number	v1 (current)
This version publication date	12 January 2020
First version publication date	12 January 2020

Trial information

Trial identification

Sponsor protocol code	201334
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02853929
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	Rue de l'Institut 89, Rixensart, Belgium, B-1330
Public contact	GSK Response Center, GSKClinicalSupportHD@gsk.com, 044 2089-904466, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, GlaxoSmithKline, 044 2089-904466, GSKClinicalSupportHD@gsk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 March 2019
Global end of trial reached?	Yes
Global end of trial date	19 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The subjects were observed closely for at least 30 minutes following the administration of the vaccines, with appropriate medical treatment readily available in case of anaphylaxis.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 September 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 24
Country: Number of subjects enrolled	Canada: 141
Country: Number of subjects enrolled	Czech Republic: 67
Country: Number of subjects enrolled	Finland: 49
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Spain: 262
Worldwide total number of subjects	551
EEA total number of subjects	386

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	551
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects enrolled in the study were infants aged 9 months at the time of enrollment, born to mothers vaccinated with Boostrix in study 116945 BOOSTRIX-047 [NCT02377349] and who received primary vaccination Infanrix hexa co-administered with Prevenar 13 in study 201330 BOOSTRIX-048 [NCT0242264]

Pre-assignment

Screening details:

551 subjects were enrolled in this trial, out of which 540 received the booster dose of Infanrix hexa co-administered with Prevenar 13. 11 subjects did not receive booster vaccination even though subject number had been allocated.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	dTpa Group

Arm description:

This group included healthy male or female infants, aged 9 months at the time of enrollment, born to mothers who received a single dose of Boostrix during pregnancy and a dose of placebo immediately post-delivery. All enrolled subjects in this group who came back for subsequent visit received a booster dose of Infanrix hexa co-administered with Prevenar 13 according to the routine national/local immunization or study procedure

Arm type	Experimental
Investigational medicinal product name	Infanrix hexa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

All subjects in this group received a booster dose of Infanrix hexa co-administered with Prevenar 13 according to the routine national/local immunization schedule.

Investigational medicinal product name	Prevenar 13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

All subjects in this group received a booster dose of Infanrix hexa co-administered with Prevenar 13 according to the routine national/local immunization schedule.

Arm title	Control Group
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Arm description:

This group included healthy male or female infants, aged 9 months at the time of enrollment, born to mothers who received a dose of placebo during pregnancy and single dose of Boostrix immediately post-delivery. All enrolled subjects in this group who came back for subsequent visit received a booster dose of Infanrix hexa co-administered with Prevenar 13 according to the routine national/local immunization or study procedure

Arm type	Placebo
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Investigational medicinal product name	Prevenar 13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

All subjects in this group received a booster dose of Infanrix hexa co-administered with Prevenar 13 according to the routine national/local immunization schedule.

Investigational medicinal product name	Infanrix hexa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

All subjects in this group received a booster dose of Infanrix hexa co-administered with Prevenar 13 according to the routine national/local immunization schedule.

Number of subjects in period 1	dTpa Group	Control Group
Started	270	281
Vaccinated	263	277
Completed	259	277
Not completed	11	4
Consent withdrawn by subject	1	-
Subjects enrolled but not vaccinated	7	4
Lost to follow-up	3	-

Baseline characteristics

Reporting groups

Reporting group title	dTpa Group
Reporting group description:	
This group included healthy male or female infants, aged 9 months at the time of enrollment, born to mothers who received a single dose of Boostrix during pregnancy and a dose of placebo immediately post-delivery. All enrolled subjects in this group who came back for subsequent visit received a booster dose of Infanrix hexa co-administered with Prevenar 13 according to the routine national/local immunization or study procedure	
Reporting group title	Control Group
Reporting group description:	
This group included healthy male or female infants, aged 9 months at the time of enrollment, born to mothers who received a dose of placebo during pregnancy and single dose of Boostrix immediately post-delivery. All enrolled subjects in this group who came back for subsequent visit received a booster dose of Infanrix hexa co-administered with Prevenar 13 according to the routine national/local immunization or study procedure	

Reporting group values	dTpa Group	Control Group	Total
Number of subjects	270	281	551
Age Categorical			
Units: Participants			
Infants and toddlers (28 days-23 months)	270	281	551
Sex: Female, Male			
Units: Participants			
Female	127	128	255
Male	143	153	296
Race/Ethnicity, Customized			
Units: Subjects			
African Heritage / African American	4	9	13
Asian - East Asian Heritage	1	0	1
Asian - South East Asian Heritage	2	0	2
White - Arabic / North African Heritage	1	3	4
White - Caucasian / European Heritage	246	262	508
Other	16	7	23

End points

End points reporting groups

Reporting group title	dTpa Group
Reporting group description:	
This group included healthy male or female infants, aged 9 months at the time of enrollment, born to mothers who received a single dose of Boostrix during pregnancy and a dose of placebo immediately post-delivery. All enrolled subjects in this group who came back for subsequent visit received a booster dose of Infanrix hexa co-administered with Prevenar 13 according to the routine national/local immunization or study procedure	
Reporting group title	Control Group
Reporting group description:	
This group included healthy male or female infants, aged 9 months at the time of enrollment, born to mothers who received a dose of placebo during pregnancy and single dose of Boostrix immediately post-delivery. All enrolled subjects in this group who came back for subsequent visit received a booster dose of Infanrix hexa co-administered with Prevenar 13 according to the routine national/local immunization or study procedure	

Primary: Number of seroprotected subjects against anti-diphtheria (Anti-D), anti-tetanus (Anti-T), anti-hepatitis B (Anti-HBs), anti-poliovirus type 1, anti-poliovirus type 2, anti-poliovirus type 3 and anti-polyribosyl-ribitol phosphate (anti-PRP)

End point title	Number of seroprotected subjects against anti-diphtheria (Anti-D), anti-tetanus (Anti-T), anti-hepatitis B (Anti-HBs), anti-poliovirus type 1, anti-poliovirus type 2, anti-poliovirus type 3 and anti-polyribosyl-ribitol phosphate (anti-PRP) ^[1]
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End point description:

Seroprotected subjects were defined as subjects with antibody concentrations/titres above or equal (\geq) the assay cut-offs that are accepted immunological correlates of protection.

0.1 International units per milliliter (IU/ml) for anti-D and anti-T, 10 milli-International units per milliliter (mIU/mL) for anti-HB's, 8 Effective Dose 50 (ED50) for anti-polio virus (type 1,2,3) and 0.15 microgram/milliliter (μ g/mL) for anti-PRP were considered as immunological correlates of protection.

Analysis was performed on the According to Protocol (ATP) cohort for immunogenicity, which included all subjects who met eligibility criteria, received the booster dose of the study vaccines and for whom assay results were available for antibodies against at least one study vaccine antigen component, after vaccination

End point type	Primary
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End point timeframe:

At one month after the booster dose (Day 30)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis is not applicable for this endpoint, as this is not a confirmatory analysis.

End point values	dTpa Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	247		
Units: Participants				
Anti-D (N-221, 247)	221	247		
Anti-T (N-221, 247)	221	247		
Anti-HBs (N-216, 241)	215	239		
Anti-polio 1 (N-204, 228)	204	228		
Anti-polio 2 (N-201, 227)	201	227		
Anti-polio 3 (N-188, 210)	188	210		
Anti-PRP (N-221, 247)	221	246		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with a booster response to Pertussis antigens (Pertussis Toxoid (PT), Filamentous Haemagglutinin (FHA) and Pertactin (PRN))

End point title	Number of subjects with a booster response to Pertussis antigens (Pertussis Toxoid (PT), Filamentous Haemagglutinin (FHA) and Pertactin (PRN)) ^[2]
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End point description:

Booster response to PT, FHA and PRN antigens was defined as:

- 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 below 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
- Seronegative (S-) subjects are those who have antibody concentration less than (<) assay cut-off. Seropositive (S+) subjects are those who have antibody concentration \geq assay cut-off prior to vaccination.

Assay cut-off was 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti- FHA and 2.187 IU/mL for anti-PRN. Analysis was performed on the According to Protocol cohort for immunogenicity

End point type	Primary
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End point timeframe:

At one month after the booster dose (Day 30)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis is not applicable for this endpoint, as this is not a confirmatory analysis.

End point values	dTpa Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	215	241		
Units: Participants				
Anti-PT, S- (N-67, 42)	62	40		
Anti-PT, S+ (< 4*assay cut-off) (N-108,126)	98	124		
Anti-PT, S+ (≥ 4 *assay cut-off) (N-40, 73)	38	71		
Anti-PT, Overall (N-215, 241)	198	235		
Anti-FHA, S- (N-8, 3)	8	3		
Anti-FHA, S+ (< 4*assay cut-off) (N-84, 58)	83	58		
Anti-FHA, S+ (≥ 4 *assay cut-off) (N-123,180)	117	172		
Anti-FHA, Overall (N-215, 241)	208	233		
Anti-PRN, S- (N-35, 31)	34	31		
Anti-PRN, S+ (< 4*assay cut-off) (N-90, 77)	90	76		

Anti-PRN, S+ (≥ 4 *assay cut-off) (N-89,133)	86	133		
Anti-PRN, Overall (N-214, 241)	210	240		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seroprotected subjects against anti-diphtheria, anti-tetanus, anti-poliovirus type 1, anti-poliovirus type 2, anti-poliovirus type 3, anti-HBs and anti-PRP.

End point title	Number of seroprotected subjects against anti-diphtheria, anti-tetanus, anti-poliovirus type 1, anti-poliovirus type 2, anti-poliovirus type 3, anti-HBs and anti-PRP.
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End point description:

Seroprotected subjects were defined as subjects with antibody concentrations/titers above or equal (\geq) the assay cut-offs that are accepted immunological correlates of protection.

0.1 IU/mL for anti-D and anti-T, 10 mIU/mL for anti-HB's, 8 ED50 for anti-polio virus (type 1,2,3) and 0.15 μ g/mL for anti-PRP were considered as immunological correlates of protection. Analysis was performed on the According to Protocol (ATP) cohort for immunogenicity, which included all subjects who met eligibility criteria, received the booster dose of the study vaccines and for whom assay results were available for antibodies against at least one study vaccine antigen component, before vaccination.

End point type	Secondary
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End point timeframe:

Before the booster dose (Day 0)

End point values	dTpa Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	244		
Units: Participants				
Anti-D (N-223, 244)	181	220		
Anti-T (N-223, 244)	215	232		
Anti-HBs (N-219, 243)	206	229		
Anti-polio 1 (N- 213, 247)	188	212		
Anti-polio 2 (N-210, 236)	188	215		
Anti-polio 3 (N-205, 226)	188	215		
Anti-PRP (N-222, 244)	161	166		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seropositive subjects for anti-PT, anti-FHA and anti-PRN

End point title	Number of seropositive subjects for anti-PT, anti-FHA and anti-PRN
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End point description:

Seropositive subjects were defined as subjects whose antibody concentration/titre was greater than or equal to the assay cut-off.

Assay cut-off was 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA and 2.187 IU/mL for anti-PRN. Analysis was performed on the According to Protocol (ATP) cohort for immunogenicity, which included all subjects who met eligibility criteria, received the booster dose of the study vaccines and for whom assay results were available for antibodies against at least one study vaccine antigen component, before vaccination.

End point type	Secondary
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End point timeframe:

Before the booster dose (Day 0)

End point values	dTpa Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	244		
Units: Participants				
Anti-PT (N-223, 244)	153	201		
Anti-FHA (N-223, 244)	215	241		
Anti-PRN (N-223, 244)	187	213		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seropositive subjects for anti-pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F)

End point title	Number of seropositive subjects for anti-pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F)
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End point description:

Seropositive subjects were defined as subjects whose antibody concentration/titre was greater than or equal to the assay cut-off.

Assay cut-off's for anti-pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) are 0.080 µg/mL, 0.075 µg/mL, 0.061 µg/mL, 0.198 µg/mL, 0.111 µg/mL, 0.102 µg/mL, 0.063 µg/mL, 0.66 µg/mL, 0.160 µg/mL, 0.111 µg/mL, 0.199 µg/mL, 0.163 µg/mL, 0.073 µg/mL respectively. Analysis was performed on the According to Protocol (ATP) cohort for immunogenicity, which included all subjects who met eligibility criteria, received the booster dose of the study vaccines and for whom assay results were available for antibodies against at least one study vaccine antigen component, before vaccination.

End point type	Secondary
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End point timeframe:

Before the booster dose (Day 0)

End point values	dTpa Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	211	232		
Units: Participants				
Anti-pneumococcal serotype 1 (N-211, 232)	196	214		
Anti-pneumococcal serotype 3 (N-211, 232)	122	147		
Anti-pneumococcal serotype 4 (N-209, 232)	189	215		
Anti-pneumococcal serotype 5 (N-211, 229)	163	182		
Anti-pneumococcal serotype 6A (N-211, 232)	196	219		
Anti-pneumococcal serotype 6B (N-211, 232)	175	205		
Anti-pneumococcal serotype 7F (N-211, 232)	210	232		
Anti-pneumococcal serotype 9V (N-211, 232)	203	225		
Anti-pneumococcal serotype 14 (N-211, 232)	201	223		
Anti-pneumococcal serotype 18C (N-211, 232)	168	190		
Anti-pneumococcal serotype 19A (N-211, 232)	148	172		
Anti-pneumococcal serotype 19F (N-211, 232)	183	202		
Anti-pneumococcal serotype 23F (N-210, 229)	160	191		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-D, anti-T, anti-PT, anti-FHA, anti-PRN antibody concentrations

End point title	Anti-D, anti-T, anti-PT, anti-FHA, anti-PRN antibody concentrations
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End point description:

Antibody concentrations are presented as Geometric Mean Concentrations (GMCs) and expressed in IU/mL. Analysis was performed on the According to Protocol (ATP) cohort for immunogenicity, which included all subjects who met eligibility criteria, received the booster dose of the study vaccines and for whom assay results were available for antibodies against at least one study vaccine antigen component, before and after vaccination.

End point type	Secondary
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End point timeframe:

Before the booster dose (Day 0) and One month after the booster dose (Day 30)

End point values	dTpa Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	247		
Units: IU/ml				
geometric mean (confidence interval 95%)				
Anti-D at Day 0 (N-223, 244)	0.207 (0.184 to 0.234)	0.322 (0.285 to 0.363)		
Anti-D at Day 30 (N-221, 247)	6.114 (5.577 to 6.703)	8.402 (7.694 to 9.174)		
Anti-T at Day 0 (N-223, 244)	0.753 (0.646 to 0.878)	0.578 (0.506 to 0.659)		
Anti-T at Day 30 (N-221, 247)	8.200 (7.324 to 9.180)	6.758 (6.143 to 7.433)		
Anti-PT at Day 0 (N-223, 244)	4.4 (3.8 to 5.0)	6.3 (5.5 to 7.1)		
Anti-PT at Day 30 (N-221, 247)	52.4 (46.9 to 58.4)	80.3 (73.3 to 88.1)		
Anti-FHA at Day 0 (N-223, 244)	11.2 (9.6 to 13.1)	16.5 (14.4 to 18.8)		
Anti-FHA at Day 30 (N-221, 247)	152.5 (136.3 to 170.6)	187.2 (172.7 to 202.9)		
Anti-PRN at Day 0 (N-223, 244)	6.9 (5.8 to 8.2)	9.6 (8.3 to 11.2)		
Anti-PRN at Day 30 (N-220, 247)	333.9 (285.4 to 390.7)	262.3 (230.9 to 298.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-poliovirus type 1, 2, 3 antibody titres

End point title	Anti-poliovirus type 1, 2, 3 antibody titres
End point description:	
Anti-Poliovirus type 1, 2 and 3 antibody titers were expressed as Geometric Mean Titers (GMT). Analysis was performed on the According to Protocol (ATP) cohort for immunogenicity, which included all subjects who met eligibility criteria, received the booster dose of the study vaccines and for whom assay results were available for antibodies against at least one study vaccine antigen component, before and after vaccination.	
End point type	Secondary
End point timeframe:	
Before the booster dose (Day 0) and One month after the booster dose (Day 30)	

End point values	dTpa Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	237		
Units: Titers				
geometric mean (confidence interval 95%)				
Anti-polio 1 at Day 0 (N-213, 237)	64.9 (52.0 to 80.9)	83.3 (67.7 to 102.5)		

Anti-polio 1 at Day 30 (N-204, 228)	1611.7 (1381.2 to 1880.6)	1532.1 (1322.2 to 1775.3)		
Anti-polio 2 at Day 0 (N-210, 236)	71.7 (57.6 to 89.4)	79.2 (64.4 to 97.5)		
Anti-polio 2 at Day 30 (N-201, 227)	2232.4 (1931.2 to 2580.5)	2371.2 (2097.9 to 2680.1)		
Anti-polio 3 at Day 0 (N-205, 226)	106.0 (84.1 to 133.4)	118.4 (97.0 to 144.5)		
Anti-polio 3 at Day 30 (N-188, 210)	2944.6 (2529.4 to 3427.9)	2891.8 (2496.2 to 3350.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HBs antibody concentrations

End point title	Anti-HBs antibody concentrations
End point description:	
Antibody concentrations are presented as Geometric Mean Concentrations (GMCs) and expressed in mIU/mL.	
Analysis was performed on the According to Protocol (ATP) cohort for immunogenicity, which included all subjects who met eligibility criteria, received the booster dose of the study vaccines and for whom assay results were available for antibodies against at least one study vaccine antigen component, before and after vaccination.	
End point type	Secondary
End point timeframe:	
Before the booster dose (Day 0) and One month after the booster dose (Day 30)	

End point values	dTpa Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	243		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Anti-HBs at Day 0 (N-219, 243)	158.7 (129.9 to 194.0)	193.4 (158.4 to 236.1)		
Anti-HBs at Day 30 (N-216, 241)	4858.3 (3918.4 to 6023.7)	5031.2 (4072.7 to 6215.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) and anti-PRP antibody concentrations

End point title	Anti-pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) and anti-PRP antibody concentrations
End point description:	
Antibody concentrations are presented as Geometric Mean Concentrations (GMCs) and expressed in µg/mL.	
Analysis was performed on the According to Protocol (ATP) cohort for immunogenicity, which included all subjects who met eligibility criteria, received the booster dose of the study vaccines and for whom assay results were available for antibodies against at least one study vaccine antigen component, before and after vaccination.	
End point type	Secondary
End point timeframe:	
Before the booster dose (Day 0) and One month after the booster dose (Day 30)	

End point values	dTpa Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	247		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-PnPS 1 at Day 0 (N-211, 232)	0.22 (0.19 to 0.24)	0.27 (0.24 to 0.30)		
Anti-PnPS 1 at Day 30 (N-208, 236)	3.22 (2.88 to 3.60)	3.64 (3.28 to 4.04)		
Anti-PnPS 3 at Day 0 (N-211, 232)	0.08 (0.07 to 0.09)	0.10 (0.09 to 0.11)		
Anti-PnPS 3 at Day 30 (N-208, 235)	0.59 (0.53 to 0.65)	0.62 (0.57 to 0.69)		
Anti-PnPS 4 at Day 0 (N-209, 232)	0.15 (0.13 to 0.16)	0.19 (0.17 to 0.22)		
Anti-PnPS 4 at Day 30 (N-208, 234)	2.91 (2.54 to 3.33)	3.28 (2.89 to 3.72)		
Anti-PnPS 5 at Day 0 (N-211, 229)	0.33 (0.29 to 0.37)	0.34 (0.31 to 0.38)		
Anti-PnPS 5 at Day 30 (N-204, 229)	2.66 (2.39 to 2.97)	2.81 (2.52 to 3.14)		
Anti-PnPS 6A at Day 0 (N-211, 232)	0.38 (0.33 to 0.43)	0.44 (0.39 to 0.50)		
Anti-PnPS 6A at Day 30 (N-208, 236)	9.07 (8.05 to 10.22)	9.49 (8.45 to 10.67)		
Anti-PnPS 6B at Day 0 (N-211, 232)	0.29 (0.25 to 0.33)	0.33 (0.29 to 0.38)		
Anti-PnPS 6B at Day 30 (N-208, 236)	7.83 (6.82 to 8.98)	8.00 (7.06 to 9.06)		
Anti-PnPS 7F at Day 0 (N-211, 232)	0.49 (0.44 to 0.54)	0.56 (0.51 to 0.61)		
Anti-PnPS 7F at Day 30 (N-208, 235)	5.00 (4.55 to 5.50)	4.96 (4.50 to 5.48)		
Anti-PnPS 9V at Day 0 (N-211, 232)	0.26 (0.23 to 0.29)	0.32 (0.28 to 0.36)		
Anti-PnPS 9V at Day 30 (N-208, 235)	3.74 (3.35 to 4.16)	3.91 (3.52 to 4.35)		
Anti-PnPS 14 at Day 0 (N-211, 232)	0.97 (0.85 to 1.11)	1.19 (1.04 to 1.37)		
Anti-PnPS 14 at Day 30 (N-208, 236)	10.36 (9.22 to 11.64)	11.62 (10.34 to 13.06)		
Anti-PnPS 18C at Day 0 (N-211, 232)	0.19 (0.17 to 0.21)	0.23 (0.21 to 0.26)		

Anti-PnPS 18C at Day 30 (N-208, 236)	3.23 (2.86 to 3.65)	3.57 (3.21 to 3.98)		
Anti-PnPS 19A at Day 0 (N-211, 232)	0.32 (0.27 to 0.37)	0.37 (0.32 to 0.43)		
Anti-PnPS 19A at Day 30 (N-208, 236)	7.90 (7.06 to 8.83)	8.68 (7.82 to 9.63)		
Anti-PnPS 19F at Day 0 (N-211, 232)	0.37 (0.32 to 0.43)	0.47 (0.41 to 0.55)		
Anti-PnPS 19F at Day 30 (N-208, 236)	7.66 (6.84 to 8.57)	8.63 (7.75 to 9.62)		
Anti-PnPS 23F at Day 0 (N-210, 229)	0.14 (0.12 to 0.16)	0.19 (0.16 to 0.22)		
Anti-PnPS 23F at Day 30 (N-207, 235)	2.07 (1.83 to 2.34)	2.38 (2.10 to 2.69)		
Anti-PRP at Day 0 (N-222, 244)	0.371 (0.303 to 0.453)	0.292 (0.244 to 0.349)		
Anti-PRP at Day 30 (N-221, 247)	26.186 (22.610 to 30.327)	19.714 (16.891 to 23.010)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seropositive subjects for anti-PT, anti-FHA and anti-PRN.

End point title	Number of seropositive subjects for anti-PT, anti-FHA and anti-PRN.
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End point description:

Seropositive subjects were defined as subjects whose antibody concentration/titre was greater than or equal to the assay cut-off.

Assay cut-off was 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA and 2.187 IU/mL for anti-PRN. Analysis was performed on the According to Protocol (ATP) cohort for immunogenicity, which included all subjects who met eligibility criteria, received the booster dose of the study vaccines and for whom assay results were available for antibodies against at least one study vaccine antigen component, after vaccination.

End point type	Secondary
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End point timeframe:

At one month after the booster dose (Day 30)

End point values	dTpa Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	247		
Units: Participants				
Anti-PT (N-221, 247)	220	247		
Anti-FHA (N-221, 247)	221	247		
Anti-PRN (N-220, 247)	220	247		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with solicited local symptoms

End point title	Number of subjects with solicited local symptoms
End point description: Assessed solicited local symptoms were pain, redness, swelling. Any redness, swelling is defined as a symptom with a surface diameter greater than 0 millimeter. The analysis was performed on the Total vaccinated cohort (TVC), which included all vaccinated subjects for whom data were available and for those with booster vaccine administration documented.	
End point type	Secondary
End point timeframe: During the 4-day (Day 0-Day 3) follow-up period after booster vaccination of two vaccines (Infanrix hexa and Prevenar 13)	

End point values	dTpa Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	257	275		
Units: Participants				
Pain (N-257, 275)	134	154		
Redness (N-257, 275)	143	169		
Swelling (N-257, 275)	119	122		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with solicited general symptoms

End point title	Number of subjects with solicited general symptoms
End point description: Assessed solicited general symptoms were Drowsiness, Fever, Irritability/Fussiness and Loss of appetite. Fever was defined as temperature ≥ 37.5 degree Celsius ($^{\circ}\text{C}$) /99.5 degree Fahrenheit ($^{\circ}\text{F}$) for oral, axillary or tympanic route, or $\geq 38.0^{\circ}\text{C}/100.4^{\circ}\text{F}$ on rectal route. The analysis was performed on the Total vaccinated cohort (TVC), which included all vaccinated subjects for whom data were available and for those with booster vaccine administration documented.	
End point type	Secondary
End point timeframe: During the 4-day (Day 0-Day 3) follow-up period after booster vaccination	

End point values	dTpa Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	275		
Units: Participants				
Drowsiness (N-258, 275)	128	138		
Irritability (N-258, 275)	163	188		
Loss of Appetite (N-258, 275)	104	116		

Fever (N-258, 275)	73	85		
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Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with unsolicited adverse events (AEs)

End point title	Number of subjects with unsolicited adverse events (AEs)
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End point description:

An AE was any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The analysis was performed on the Total vaccinated cohort (TVC), which included all vaccinated subjects for whom data were available

End point type	Secondary
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End point timeframe:

During the 31-day (Day 0-Day 30) follow-up period after booster vaccination

End point values	dTpa Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	277		
Units: Participants				
Any AEs (N-263, 277)	94	111		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with serious adverse events (SAEs)

End point title	Number of subjects with serious adverse events (SAEs)
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End point description:

SAE is any untoward medical occurrence that results in death, is life threatening, requires hospitalisation or prolongation of existing hospitalisation, resulting in disability/incapacity.

The analysis was performed on the Total vaccinated cohort (TVC), which included all vaccinated subjects for whom data were available

End point type	Secondary
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End point timeframe:

From booster dose up to study end (approximately 6 or 7 months, per subject)

End point values	dTpa Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	277		
Units: Participants				
Any SAEs (N-263, 277)	0	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with an ASQ-3 score (Ages & Stages Questionnaires, third edition) in the black zone

End point title	Number of subjects with an ASQ-3 score (Ages & Stages Questionnaires, third edition) in the black zone
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End point description:

Neurodevelopmental status was measured by ASQ-3 score scale [ASQ-3, 2016] in the black zone. The ASQ-3 included a series of questions designed to assess 5 areas of development (communication, gross motor, fine motor, problem solving, and personal-social). Any subject who scored below the cut-off i.e., a score more than 2 Standard Deviations (SDs) below the mean score for the U.S. reference group (i.e., black zone in the score chart) in any of the 5 domains of the ASQ-3 was to be referred to a developmental specialist for a formal neurodevelopmental assessment (using the Bayley Scale for Infant Development, Version III [BSID-III]).

The analysis was performed on Total enrolled cohort, which included enrolled subjects with available results.

End point type	Secondary
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End point timeframe:

At 9 months of age, 18 months of age, and 9 or 18 months of age

End point values	dTpa Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	269	281		
Units: Participants				
Any domain at Month 9 (N-269, 281)	27	28		
Communication at Month 9 (N-269, 281)	1	3		
Gross motor skills at Month 9 (N-269, 281)	14	19		
Fine motor at Month 9 (N-269, 281)	8	3		
Problem solving at Month 9 (N-269, 281)	7	6		
Personal- Social at Month 9 (N-269, 281)	2	2		
Any domain at Month 18 (N-257, 274)	6	5		
Communication at Month 18 (N-257, 274)	1	0		
Gross motor skills at Month 18 (N-257, 274)	3	2		
Fine motor at Month 18 (N-257, 274)	1	1		
Problem solving at Month 18 (N-257, 274)	1	3		

Personal- Social at Month 18 (N-257, 274)	0	0		
Any domain at Month 9 or 18 (N-269, 281)	31	31		
Communication at Month 9 or 18 (N-269, 281)	2	3		
Gross motor skills at Month 9 or 18 (N-269, 281)	16	20		
Fine motor at Month 9 or 18 (N-269, 281)	9	4		
Problem solving at Month 9 or 18 (N-269, 281)	8	8		
Personal- Social at Month 9 or 18 (N-269, 281)	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects referred for formal neurodevelopmental evaluation using BSID-III (Bayley Scale for Infant Development, Version III)

End point title	Number of subjects referred for formal neurodevelopmental evaluation using BSID-III (Bayley Scale for Infant Development, Version III)
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End point description:

Any subject who scored below the cut-off i.e., a score more than 2 Standard Deviations (SDs) below the mean score for the U.S. reference group (i.e., black zone in the score chart) in any of the 5 domains of the ASQ-3 was referred to a developmental specialist for a formal neurodevelopmental assessment (using the Bayley Scale for Infant Development, Version III BSID-III).

The analysis was performed on subjects from the Total enrolled cohort, who scored, below the defined cut-off in any of the 5 domains, when using the ASQ-3 score scale.

End point type	Secondary
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End point timeframe:

At 9 months of age, 18 months of age, and 9 or 18 months of age

End point values	dTpa Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	31		
Units: Participants				
Any Domain at Month 9 (N-27, 28)	16	14		
Any Domain at Month 18 (N-6, 5)	6	3		
Any Domain at Month 9 or 18 (N-31, 31)	20	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated proportion of infants with at least one of the indicators of neurodevelopmental impairment using BSID-III (Bayley Scale for Infant Development, Version III)

End point title	Estimated proportion of infants with at least one of the indicators of neurodevelopmental impairment using BSID-III (Bayley Scale for Infant Development, Version III)
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End point description:

The estimated proportion (expressed in percentage) of infants with a BSID-III indicator of neurodevelopmental delay was based on ASQ-3 black zone indicator and subsequent BSID-III assessment using the following formula: $100 * (\text{Number of subjects with ASQ-3 below cut off} / \text{Number of enrolled subjects with available results}) * (\text{Number of subjects with at least one indicator of neurodevelopmental delay using BSID III} / \text{Number of subjects referred for BSID III evaluation})$. The analysis was performed on Total enrolled cohort, which included enrolled subjects with available results.

End point type	Secondary
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End point timeframe:

At 9 months of age, 18 months of age, and 9 or 18 months of age

End point values	dTpa Group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	269	281		
Units: Percentage of Infants				
number (confidence interval 95%)				
Any domain at Month 9 (N-269, 281)	4.39 (2.1 to 8.0)	5.69 (3.0 to 9.6)		
Any domain at Month 18 (N-257, 274)	1.17 (0.2 to 3.4)	0.61 (0.1 to 2.8)		
Any domain at Month 9 or 18 (N-269, 281)	4.61 (2.3 to 8.2)	5.84 (3.2 to 9.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited symptoms were collected during 4-day (Day 0-Day 3) and Unsolicited AEs were collected during 31-day (Day 0-Day 30) follow-up period after each vaccination. SAEs were collected from booster dose up to study end (approx. 6/7 months, per subject)

Adverse event reporting additional description:

Safety analysis has been performed on the vaccinated subjects

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	Control Group
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Reporting group description:

This group included healthy male or female infants, aged 9 months at the time of enrollment, born to mothers who received a dose of placebo during pregnancy and single dose of Boostrix immediately post-delivery. All enrolled subjects in this group who came back for subsequent visit received a booster dose of Infanrix hexa co-administered with Prevenar 13 according to the routine national/local immunization or study procedure

Reporting group title	dTpa Group
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Reporting group description:

This group included healthy male or female infants, aged 9 months at the time of enrollment, born to mothers who received a single dose of Boostrix during pregnancy and a dose of placebo immediately post-delivery. All enrolled subjects in this group who came back for subsequent visit received a booster dose of Infanrix hexa co-administered with Prevenar 13 according to the routine national/local immunization or study procedure

Serious adverse events	Control Group	dTpa Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 277 (1.08%)	0 / 263 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Respiratory, thoracic and mediastinal disorders			
Sleep apnoea syndrome			
subjects affected / exposed	1 / 277 (0.36%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Periorbital cellulitis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	1 / 277 (0.36%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Control Group	dTpa Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	257 / 277 (92.78%)	232 / 263 (88.21%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Mastocytoma			
subjects affected / exposed	1 / 277 (0.36%)	0 / 263 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 277 (0.00%)	1 / 263 (0.38%)	
occurrences (all)	0	1	
Discomfort			
subjects affected / exposed	0 / 277 (0.00%)	1 / 263 (0.38%)	
occurrences (all)	0	2	
Crying			
subjects affected / exposed	0 / 277 (0.00%)	2 / 263 (0.76%)	
occurrences (all)	0	2	
Fatigue			
subjects affected / exposed	1 / 277 (0.36%)	0 / 263 (0.00%)	
occurrences (all)	1	0	
Injection site bruising			
subjects affected / exposed	0 / 277 (0.00%)	1 / 263 (0.38%)	
occurrences (all)	0	1	
Injection site erythema			
subjects affected / exposed	169 / 277 (61.01%)	143 / 263 (54.37%)	
occurrences (all)	169	143	
Injection site induration			

subjects affected / exposed occurrences (all)	1 / 277 (0.36%) 1	1 / 263 (0.38%) 1	
Injection site mass subjects affected / exposed occurrences (all)	2 / 277 (0.72%) 2	0 / 263 (0.00%) 0	
Injection site pain subjects affected / exposed occurrences (all)	154 / 277 (55.60%) 154	134 / 263 (50.95%) 134	
Pyrexia subjects affected / exposed occurrences (all)	101 / 277 (36.46%) 109	81 / 263 (30.80%) 85	
Injection site swelling subjects affected / exposed occurrences (all)	122 / 277 (44.04%) 122	119 / 263 (45.25%) 119	
Vaccination site irritation subjects affected / exposed occurrences (all)	0 / 277 (0.00%) 0	1 / 263 (0.38%) 1	
Vaccination site pain subjects affected / exposed occurrences (all)	1 / 277 (0.36%) 1	0 / 263 (0.00%) 0	
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	0 / 277 (0.00%) 0	1 / 263 (0.38%) 1	
Hypersensitivity subjects affected / exposed occurrences (all)	1 / 277 (0.36%) 1	0 / 263 (0.00%) 0	
Seasonal allergy subjects affected / exposed occurrences (all)	0 / 277 (0.00%) 0	1 / 263 (0.38%) 1	
Reproductive system and breast disorders Genital erythema subjects affected / exposed occurrences (all)	0 / 277 (0.00%) 0	1 / 263 (0.38%) 1	
Respiratory, thoracic and mediastinal disorders			

Bronchospasm subjects affected / exposed occurrences (all)	2 / 277 (0.72%) 2	1 / 263 (0.38%) 1	
Cough subjects affected / exposed occurrences (all)	5 / 277 (1.81%) 5	1 / 263 (0.38%) 1	
Dyspnoea subjects affected / exposed occurrences (all)	1 / 277 (0.36%) 1	0 / 263 (0.00%) 0	
Rhinorrhoea subjects affected / exposed occurrences (all)	2 / 277 (0.72%) 2	0 / 263 (0.00%) 0	
Sinus congestion subjects affected / exposed occurrences (all)	1 / 277 (0.36%) 1	0 / 263 (0.00%) 0	
Psychiatric disorders Initial insomnia subjects affected / exposed occurrences (all)	1 / 277 (0.36%) 1	0 / 263 (0.00%) 0	
Irritability subjects affected / exposed occurrences (all)	189 / 277 (68.23%) 191	163 / 263 (61.98%) 164	
Injury, poisoning and procedural complications Animal bite subjects affected / exposed occurrences (all)	1 / 277 (0.36%) 1	0 / 263 (0.00%) 0	
Arthropod sting subjects affected / exposed occurrences (all)	1 / 277 (0.36%) 1	0 / 263 (0.00%) 0	
Head injury subjects affected / exposed occurrences (all)	0 / 277 (0.00%) 0	1 / 263 (0.38%) 1	
Mouth injury subjects affected / exposed occurrences (all)	1 / 277 (0.36%) 1	0 / 263 (0.00%) 0	
Scratch			

subjects affected / exposed occurrences (all)	0 / 277 (0.00%) 0	1 / 263 (0.38%) 1	
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 277 (0.36%)	0 / 263 (0.00%)	
occurrences (all)	1	0	
Phimosi			
subjects affected / exposed	0 / 277 (0.00%)	1 / 263 (0.38%)	
occurrences (all)	0	1	
Nervous system disorders			
Somnolence			
subjects affected / exposed	138 / 277 (49.82%)	128 / 263 (48.67%)	
occurrences (all)	138	128	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 277 (0.36%)	0 / 263 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 277 (0.36%)	0 / 263 (0.00%)	
occurrences (all)	1	0	
Anal fissure			
subjects affected / exposed	0 / 277 (0.00%)	1 / 263 (0.38%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	0 / 277 (0.00%)	1 / 263 (0.38%)	
occurrences (all)	0	1	
Enteritis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 263 (0.38%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	6 / 277 (2.17%)	6 / 263 (2.28%)	
occurrences (all)	6	7	
Toothache			
subjects affected / exposed	1 / 277 (0.36%)	2 / 263 (0.76%)	
occurrences (all)	1	2	

Teething subjects affected / exposed occurrences (all)	2 / 277 (0.72%) 2	4 / 263 (1.52%) 4	
Vomiting subjects affected / exposed occurrences (all)	8 / 277 (2.89%) 8	10 / 263 (3.80%) 11	
Skin and subcutaneous tissue disorders			
Dermatitis subjects affected / exposed occurrences (all)	1 / 277 (0.36%) 1	1 / 263 (0.38%) 1	
Dermatitis diaper subjects affected / exposed occurrences (all)	2 / 277 (0.72%) 2	3 / 263 (1.14%) 3	
Eczema subjects affected / exposed occurrences (all)	2 / 277 (0.72%) 2	1 / 263 (0.38%) 1	
Pruritus subjects affected / exposed occurrences (all)	1 / 277 (0.36%) 1	0 / 263 (0.00%) 0	
Rash subjects affected / exposed occurrences (all)	6 / 277 (2.17%) 6	2 / 263 (0.76%) 2	
Urticaria subjects affected / exposed occurrences (all)	2 / 277 (0.72%) 2	0 / 263 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal stiffness subjects affected / exposed occurrences (all)	0 / 277 (0.00%) 0	1 / 263 (0.38%) 1	
Infections and infestations			
Bronchiolitis subjects affected / exposed occurrences (all)	1 / 277 (0.36%) 1	0 / 263 (0.00%) 0	
Bronchitis subjects affected / exposed occurrences (all)	6 / 277 (2.17%) 6	5 / 263 (1.90%) 5	

Candida infection		
subjects affected / exposed	0 / 277 (0.00%)	1 / 263 (0.38%)
occurrences (all)	0	1
Candida nappy		
subjects affected / exposed	0 / 277 (0.00%)	2 / 263 (0.76%)
occurrences (all)	0	2
Cellulitis		
subjects affected / exposed	1 / 277 (0.36%)	0 / 263 (0.00%)
occurrences (all)	1	0
Croup infectious		
subjects affected / exposed	0 / 277 (0.00%)	2 / 263 (0.76%)
occurrences (all)	0	2
Conjunctivitis		
subjects affected / exposed	5 / 277 (1.81%)	9 / 263 (3.42%)
occurrences (all)	5	9
Ear infection		
subjects affected / exposed	12 / 277 (4.33%)	9 / 263 (3.42%)
occurrences (all)	13	9
Cystitis		
subjects affected / exposed	0 / 277 (0.00%)	1 / 263 (0.38%)
occurrences (all)	0	1
Exanthema subitum		
subjects affected / exposed	1 / 277 (0.36%)	1 / 263 (0.38%)
occurrences (all)	1	1
Fungal skin infection		
subjects affected / exposed	0 / 277 (0.00%)	1 / 263 (0.38%)
occurrences (all)	0	1
Gastroenteritis adenovirus		
subjects affected / exposed	1 / 277 (0.36%)	0 / 263 (0.00%)
occurrences (all)	1	0
Gastroenteritis		
subjects affected / exposed	5 / 277 (1.81%)	3 / 263 (1.14%)
occurrences (all)	5	3
Gastroenteritis viral		
subjects affected / exposed	1 / 277 (0.36%)	0 / 263 (0.00%)
occurrences (all)	1	0

Gingivitis		
subjects affected / exposed	0 / 277 (0.00%)	1 / 263 (0.38%)
occurrences (all)	0	1
Hand-foot-and-mouth disease		
subjects affected / exposed	2 / 277 (0.72%)	2 / 263 (0.76%)
occurrences (all)	2	2
Herpangina		
subjects affected / exposed	1 / 277 (0.36%)	0 / 263 (0.00%)
occurrences (all)	1	0
Hordeolum		
subjects affected / exposed	1 / 277 (0.36%)	0 / 263 (0.00%)
occurrences (all)	1	0
Impetigo		
subjects affected / exposed	1 / 277 (0.36%)	1 / 263 (0.38%)
occurrences (all)	1	1
Injection site cellulitis		
subjects affected / exposed	1 / 277 (0.36%)	0 / 263 (0.00%)
occurrences (all)	1	0
Influenza		
subjects affected / exposed	0 / 277 (0.00%)	2 / 263 (0.76%)
occurrences (all)	0	2
Laryngitis		
subjects affected / exposed	2 / 277 (0.72%)	4 / 263 (1.52%)
occurrences (all)	2	4
Lung infection		
subjects affected / exposed	1 / 277 (0.36%)	0 / 263 (0.00%)
occurrences (all)	1	0
Nasopharyngitis		
subjects affected / exposed	10 / 277 (3.61%)	12 / 263 (4.56%)
occurrences (all)	11	13
Oral candidiasis		
subjects affected / exposed	0 / 277 (0.00%)	1 / 263 (0.38%)
occurrences (all)	0	1
Oral fungal infection		
subjects affected / exposed	0 / 277 (0.00%)	1 / 263 (0.38%)
occurrences (all)	0	1

Otitis media		
subjects affected / exposed	1 / 277 (0.36%)	2 / 263 (0.76%)
occurrences (all)	1	3
Oral herpes		
subjects affected / exposed	0 / 277 (0.00%)	1 / 263 (0.38%)
occurrences (all)	0	1
Otitis media acute		
subjects affected / exposed	2 / 277 (0.72%)	2 / 263 (0.76%)
occurrences (all)	2	2
Pharyngitis		
subjects affected / exposed	4 / 277 (1.44%)	3 / 263 (1.14%)
occurrences (all)	4	4
Pharyngitis streptococcal		
subjects affected / exposed	1 / 277 (0.36%)	0 / 263 (0.00%)
occurrences (all)	1	0
Pharyngotonsillitis		
subjects affected / exposed	2 / 277 (0.72%)	0 / 263 (0.00%)
occurrences (all)	2	0
Pneumonia		
subjects affected / exposed	0 / 277 (0.00%)	1 / 263 (0.38%)
occurrences (all)	0	1
Respiratory tract infection		
subjects affected / exposed	5 / 277 (1.81%)	5 / 263 (1.90%)
occurrences (all)	6	5
Respiratory tract infection viral		
subjects affected / exposed	1 / 277 (0.36%)	0 / 263 (0.00%)
occurrences (all)	1	0
Rhinitis		
subjects affected / exposed	3 / 277 (1.08%)	2 / 263 (0.76%)
occurrences (all)	3	2
Skin infection		
subjects affected / exposed	0 / 277 (0.00%)	1 / 263 (0.38%)
occurrences (all)	0	1
Roseola		
subjects affected / exposed	1 / 277 (0.36%)	1 / 263 (0.38%)
occurrences (all)	1	1

Tonsillitis			
subjects affected / exposed	4 / 277 (1.44%)	4 / 263 (1.52%)	
occurrences (all)	4	4	
Upper respiratory tract infection			
subjects affected / exposed	9 / 277 (3.25%)	9 / 263 (3.42%)	
occurrences (all)	9	9	
Urinary tract infection			
subjects affected / exposed	0 / 277 (0.00%)	1 / 263 (0.38%)	
occurrences (all)	0	1	
Vaginal infection			
subjects affected / exposed	1 / 277 (0.36%)	0 / 263 (0.00%)	
occurrences (all)	1	0	
Varicella			
subjects affected / exposed	1 / 277 (0.36%)	0 / 263 (0.00%)	
occurrences (all)	1	0	
Viral rash			
subjects affected / exposed	1 / 277 (0.36%)	0 / 263 (0.00%)	
occurrences (all)	1	0	
Viral infection			
subjects affected / exposed	3 / 277 (1.08%)	1 / 263 (0.38%)	
occurrences (all)	3	1	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 277 (0.36%)	1 / 263 (0.38%)	
occurrences (all)	2	1	
Vulvovaginitis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 263 (0.38%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	116 / 277 (41.88%)	104 / 263 (39.54%)	
occurrences (all)	116	104	
Iron deficiency			
subjects affected / exposed	1 / 277 (0.36%)	0 / 263 (0.00%)	
occurrences (all)	1	0	
Lactose intolerance			

subjects affected / exposed	1 / 277 (0.36%)	0 / 263 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 December 2016	<ul style="list-style-type: none">• Given the fact that only infants born from mothers vaccinated in the study (116945[DTPA (BOOSTRIX)-047] and vaccinated in the previous study 201330 DTPA(BOOSTRIX)-048 PRI] can be enrolled in the current study, the enrolment in these studies has an impact on this current study (e.g. cohorts to be investigated). Initially, the DTPA (BOOSTRIX)-047 and DTPA (BOOSTRIX)-048 PRI studies were opened only in countries using 3-dose primary vaccination series plus a booster vaccination at 12 to 18 months of age against diphtheria, tetanus and pertussis in infants. Nevertheless, the 2-dose primary vaccination schedule with a booster vaccination at 11 to 13 months of age in infants is also meaningful for different regions in the world (e.g. Europe). It was therefore decided to open the DTPA BOOSTRIX)-047 and DTPA (BOOSTRIX)-048 PRI, and therefore the current booster study to countries using 2-dose primary vaccination series with a booster vaccination at 11 to 13 months of age with the aim to increase the scientific value of the study and generate clinical data in diverse infant vaccination schedules. This protocol is amended to include the possibility to administered the booster vaccine dose at 11 to 13 months of age, in addition to the 12 to 18 months of age initially planned.• An inclusion criterion was updated to specify that only infant having received the full vaccination series as per protocol requirement in the study DTPA (BOOSTRIX)-048 PRI can be enrolled in the current study (and not only infant born from mother vaccinated in the DTPA (BOOSTRIX)-047).• The vaccination sites were updated to allow vaccination either in the thigh or deltoid, according to the national recommendation, to comply with the Australian recommendations.• Other minor changes have been made to correct typos and improve clarity and alignment within the document.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported