Clinical trial results:
A Phase III Randomized, Double-Blind, Active-Comparator Controlled Clinical Trial to Study the Safety, Tolerability, and Immunogenicity of V419 in Healthy Infants When Given at 2, 3, 4, and 12 Months.

Summary

EudraCT number	2010-021490-37
Trial protocol	BE FI DE
Global end of trial date	13 March 2013

Results information

Result version number	v1
This version publication date	27 April 2016
First version publication date	02 August 2015

Trial information

Trial identification

Sponsor protocol code	V419-007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01341639
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur MSD S.N.C.
Sponsor organisation address	162 avenue Jean Jaurès - CS 50712, Lyon Cedex 07, France, 69367
Public contact	Clinical Trials Disclosure, Sanofi Pasteur MSD S.N.C., ClinicalTrialsDisclosure@spmsd.com
Scientific contact	Clinical Trials Disclosure, Sanofi Pasteur MSD S.N.C., ClinicalTrialsDisclosure@spmsd.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000394-PIP01-08
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	13 March 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 March 2013
Global end of trial reached?	Yes
Global end of trial date	13 March 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

#1. To evaluate the immunogenicity of PR5I when given at 2, 3, 4, and 12 months.

#2. To compare the immunogenicity response elicited by PR5I to that of INFANRIX™ hexa when given at 2, 3, 4, and 12 months.

Protection of trial subjects:

This study was conducted in healthy infants.
Subjects with known or suspected hypersensitivity to any of the vaccine components or history of a life-threatening reaction to a vaccine containing the same substances as the study vaccines or concomitant vaccines were excluded.
Vaccines were administered by qualified study personnel.
After each vaccination, subjects were kept under observation for 30 minutes to ensure their safety.
Adequate treatment provisions, including epinephrine, were available for immediate use in case of anaphylactic or anaphylactoid reactions occurring during or immediately following vaccination.

Background therapy: -

Evidence for comparator:

This study was conducted in healthy infants to assess the safety, tolerability, and immunogenicity of 4 doses of the hexavalent PR5I when given at 2, 3, 4, and 12 months of age. INFANRIX™ hexa was chosen as the active comparator because it was the only hexavalent pediatric vaccine licensed in Europe at the time this study was conducted.

Actual start date of recruitment	26 May 2011
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	Belgium: 94
Country: Number of subjects enrolled	Finland: 892
Country: Number of subjects enrolled	Germany: 231
Worldwide total number of subjects	1217
EEA total number of subjects	1217

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	1217
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:

Study subjects were enrolled from 26 May 2011 (first subject entered) in 40 active centres in 3 European countries (Belgium, Finland, and Germany).

Pre-assignment

Screening details:

1271 subjects were screened.
1250 subjects were randomised.
1217 subjects were included (33 subjects from 1 centre in Germany were excluded after an audit).
1188 subjects received the 3 doses of the infant series and completed period 1.
1172 subjects received the toddler dose (period 2).

Period 1

Period 1 title	Infant Series
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The parent(s)/legal representative of the subject, the Investigator, laboratory testing personnel, and sponsor/sponsor representative personnel were blinded to the vaccination group assigned.
Because INFANRIX™ hexa is to be reconstituted and PR5I is ready to use, an unblinded individual at each study site who was otherwise not involved in the conduct of the study was required to prepare study vaccines to maintain the study blind.

Arms

Are arms mutually exclusive?	Yes
Arm title	PR5I

Arm description:

Subjects received at 2, 3 and 4 months of age 1 dose of PR5I (DTaP-HB-IPV-Hib = Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), and Haemophilus influenzae type b conjugate vaccine (adsorbed)) by intramuscular route (IM) + 1 dose of Prevenar 13 (PCV-13 = Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)) by IM route (opposite leg) + 1 dose of RotaTeq (pentavalent combination live vaccine of 5 human-bovine reassortant rotavirus strains) by oral route.
Blood samples were collected on Day 0 (D0) before any vaccination and at Month 5 (M5), i.e. 1 month after the 3rd dose of infant series.

Arm type	Experimental
Investigational medicinal product name	PR5I vaccine
Investigational medicinal product code	DTaP-HB-IPV-Hib
Other name	V419
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular route (upper anterolateral thigh), one dose at 2, 3 and 4 months of age.

Investigational medicinal product name	Prevenar 13™
Investigational medicinal product code	PCV-13
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular route (upper anterolateral thigh, separate limb from hexavalent vaccine), one dose at 2, 3 and 4 months of age.

Investigational medicinal product name	RotaTeq™
Investigational medicinal product code	RotaTeq
Other name	
Pharmaceutical forms	Oral solution in single-dose container
Routes of administration	Oral use

Dosage and administration details:

2 mL, oral route, one dose at 2, 3 and 4 months of age.

Arm title	INFANRIX hexa

Arm description:

Subjects received at 2, 3 and 4 months of age 1 dose of INFANRIX hexa (DTaP-HBV-IPV-Hib = Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), and Haemophilus influenzae type b conjugate vaccine (adsorbed)) by intramuscular route (IM) + 1 dose of Prevenar 13 (PCV-13 = Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)) by IM route (opposite leg) + 1 dose of RotaTeq (pentavalent combination live vaccine of 5 human-bovine reassortant rotavirus strains) by oral route.
Blood samples were collected on Day 0 (D0) before any vaccination and at Month 5 (M5), i.e. 1 month after the 3rd dose of infant series.

Arm type	Active comparator
Investigational medicinal product name	INFANRIX™ hexa
Investigational medicinal product code	DTaP-HBV-IPV-Hib
Other name	
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular route (upper anterolateral thigh), one dose at 2, 3 and 4 months of age.

Investigational medicinal product name	Prevenar 13™
Investigational medicinal product code	PCV-13
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular route (upper anterolateral thigh, separate limb from hexavalent vaccine), one dose at 2, 3 and 4 months of age.

Investigational medicinal product name	RotaTeq™
Investigational medicinal product code	RotaTeq
Other name	
Pharmaceutical forms	Oral solution in single-dose container
Routes of administration	Oral use

Dosage and administration details:

2 mL, oral route, one dose at 2, 3 and 4 months of age.

Number of subjects in period 1	PR5I	INFANRIX hexa
Started	611	606
Completed	598	590
Not completed	13	16
Consent withdrawn by subject	11	8
Adverse event, non-fatal	-	5
Not vaccinated	1	1

Lost to follow-up	-	2
Protocol deviation	1	-

Period 2

Period 2 title	Toddler Dose
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The parent(s)/legal representative of the subject, the Investigator, laboratory testing personnel, and sponsor/sponsor representative personnel were blinded to the vaccination group assigned.
Because INFANRIX™ hexa is to be reconstituted and PR5I is ready to use, an unblinded individual at each study site who was otherwise not involved in the conduct of the study was required to prepare study vaccines to maintain the study blind.

Arms

Are arms mutually exclusive?	Yes
Arm title	PR5I

Arm description:

Subjects (arm 1 - period 1) received at 12 months of age 1 dose of PR5I (DTaP-HB-IPV-Hib = Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), and Haemophilus influenzae type b conjugate vaccine (adsorbed)) by intramuscular route (IM) + 1 dose of ProQuad (measles, mumps, rubella and varicella (live attenuated)) vaccine by subcutaneous route (SC). Blood samples were collected at Month 12 (M12) before any Toddler dose and 1 month after Toddler dose.

Arm type	Experimental
Investigational medicinal product name	PR5I vaccine
Investigational medicinal product code	DTaP-HB-IPV-Hib
Other name	V419
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular route (upper anterolateral thigh), one dose at 12 months of age.

Investigational medicinal product name	ProQuad™
Investigational medicinal product code	MMRV
Other name	ProQuad
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL, subcutaneous route (upper anterolateral thigh, separate limb from the hexavalent vaccine), 1 dose at 12 months of age.
Note: The 2nd dose of ProQuad vaccine (SC route) and the 4th dose of Prevenar 13 (PCV-13 = Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)) (IM route) were given at 13 months of age (last visit).
Prevenar 13 was administered at the lower thigh when administered concomitantly with ProQuad.

Arm title	INFANRIX hexa

Arm description:

Subjects (arm 2 - period 1) received at 12 months of age 1 dose of INFANRIX hexa (DTaP-HBV-IPV-Hib = Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), and Haemophilus influenzae type b conjugate vaccine (adsorbed)) by intramuscular route (IM) + 1 dose of ProQuad (measles, mumps, rubella and varicella (live attenuated)) vaccine by subcutaneous route (SC).
Blood samples were collected at Month 12 (M12) before any Toddler dose and 1 month after the Toddler dose.

Arm type	Active comparator
Investigational medicinal product name	INFANRIX™ hexa
Investigational medicinal product code	DTaP-HBV-IPV-Hib
Other name	
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular route (upper anterolateral thigh), one dose at 2, 3 and 4 months of age.

Investigational medicinal product name	ProQuad™
Investigational medicinal product code	MMRV
Other name	ProQuad
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL, subcutaneous route (upper anterolateral thigh, separate limb from the hexavalent vaccine), 1 dose at 12 months of age.
Note: The 2nd dose of ProQuad vaccine (SC route) and the 4th dose of Prevenar 13 (PCV-13 = Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)) (IM route) were given at 13 months of age (last visit).
Prevenar 13 was administered at the lower thigh when administered concomitantly with ProQuad.

Number of subjects in period 2[1]	PR5I	INFANRIX hexa
Started	590	582
Completed	539	548
Not completed	51	34
Subjects did not receive ProQuad	51	34

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: # In the PR5I arm, 8 subjects discontinued the study between the Infant Series and Toddler Dose: 2 "lost to follow-up" and 6 "consent withdrawn by subject".
In the INFANRIX hexa arm, 9 subjects discontinued the study between the Infant Series and Toddler Dose: 1 "physician decision", 1 "lost to follow-up" and 7 "consent withdrawn by subject".

Baseline characteristics

Reporting groups	
Reporting group title	PR5I

Reporting group description:

Subjects received at 2, 3 and 4 months of age 1 dose of PR5I (DTaP-HB-IPV-Hib = Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), and Haemophilus influenzae type b conjugate vaccine (adsorbed)) by intramuscular route (IM) + 1 dose of Prevenar 13 (PCV-13 = Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)) by IM route (opposite leg) + 1 dose of RotaTeq (pentavalent combination live vaccine of 5 human-bovine reassortant rotavirus strains) by oral route.
Blood samples were collected on Day 0 (D0) before any vaccination and at Month 5 (M5), i.e. 1 month after the 3rd dose of infant series.

Reporting group title	INFANRIX hexa

Reporting group description:

Subjects received at 2, 3 and 4 months of age 1 dose of INFANRIX hexa (DTaP-HBV-IPV-Hib = Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), and Haemophilus influenzae type b conjugate vaccine (adsorbed)) by intramuscular route (IM) + 1 dose of Prevenar 13 (PCV-13 = Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)) by IM route (opposite leg) + 1 dose of RotaTeq (pentavalent combination live vaccine of 5 human-bovine reassortant rotavirus strains) by oral route.
Blood samples were collected on Day 0 (D0) before any vaccination and at Month 5 (M5), i.e. 1 month after the 3rd dose of infant series.

Reporting group values	PR5I	INFANRIX hexa	Total
Number of subjects	611	606	1217
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	611	606	1217
Age continuous Units: days			
arithmetic mean	61.4	61.5	
standard deviation	± 6.9	± 6.9	-
Gender categorical Units: Subjects			
Female	291	290	581
Male	320	316	636

End points

End points reporting groups

Reporting group title	PR5I

Reporting group description:

Subjects received at 2, 3 and 4 months of age 1 dose of PR5I (DTaP-HB-IPV-Hib = Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), and Haemophilus influenzae type b conjugate vaccine (adsorbed)) by intramuscular route (IM) + 1 dose of Prevenar 13 (PCV-13 = Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)) by IM route (opposite leg) + 1 dose of RotaTeq (pentavalent combination live vaccine of 5 human-bovine reassortant rotavirus strains) by oral route.
Blood samples were collected on Day 0 (D0) before any vaccination and at Month 5 (M5), i.e. 1 month after the 3rd dose of infant series.

Reporting group title	INFANRIX hexa

Reporting group description:

Subjects received at 2, 3 and 4 months of age 1 dose of INFANRIX hexa (DTaP-HBV-IPV-Hib = Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), and Haemophilus influenzae type b conjugate vaccine (adsorbed)) by intramuscular route (IM) + 1 dose of Prevenar 13 (PCV-13 = Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)) by IM route (opposite leg) + 1 dose of RotaTeq (pentavalent combination live vaccine of 5 human-bovine reassortant rotavirus strains) by oral route.
Blood samples were collected on Day 0 (D0) before any vaccination and at Month 5 (M5), i.e. 1 month after the 3rd dose of infant series.

Reporting group title	PR5I

Reporting group description:

Subjects (arm 1 - period 1) received at 12 months of age 1 dose of PR5I (DTaP-HB-IPV-Hib = Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), and Haemophilus influenzae type b conjugate vaccine (adsorbed)) by intramuscular route (IM) + 1 dose of ProQuad (measles, mumps, rubella and varicella (live attenuated)) vaccine by subcutaneous route (SC).
Blood samples were collected at Month 12 (M12) before any Toddler dose and 1 month after Toddler dose.

Reporting group title	INFANRIX hexa

Reporting group description:

Subjects (arm 2 - period 1) received at 12 months of age 1 dose of INFANRIX hexa (DTaP-HBV-IPV-Hib = Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), and Haemophilus influenzae type b conjugate vaccine (adsorbed)) by intramuscular route (IM) + 1 dose of ProQuad (measles, mumps, rubella and varicella (live attenuated)) vaccine by subcutaneous route (SC).
Blood samples were collected at Month 12 (M12) before any Toddler dose and 1 month after the Toddler dose.

Primary: Acceptability of antibody (Ab) response rates to Haemophilus influenzae type b (PRP), diphtheria, tetanus, and poliovirus types 1, 2 & 3 one month after the 3rd dose of PR5I (4 months of age)

End point title	Acceptability of antibody (Ab) response rates to Haemophilus influenzae type b (PRP), diphtheria, tetanus, and poliovirus types 1, 2 & 3 one month after the 3rd dose of PR5I (4 months of age)[1][2]

End point description:

% of subjects with an Ab titre ≥0.15 µg/mL for Haemophilus influenzae type b (Hib) (polyribosylribitol phosphate, PRP); ≥0.01 IU/mL for diphtheria & tetanus; ≥8 (1/dil) for inactivated poliovirus types 1, 2 & 3 (IPV1, 2 & 3) 1 month Post-Dose 3 of PR5I.
Ab titres were measured by Radioimmunoassay (RIA) for PRP, Micrometabolic inhibition test (MIT) for diphtheria & poliovirus, and Enzyme-Linked Immunosorbent Assay (ELISA) for tetanus.
Analysis was done on the Per Protocol Revised Windows (PP-RW) population, i.e. PP population using a blood draw sample window of Days 28 to 51 Post-Dose 3 or Post-Toddler dose.
The immune response to PR5I vaccine was considered as acceptable if the lower bounds of the 2-sided 95% CI for the response rates were greater than the predetermined lower limits for PRP (80%), diphtheria (80%), tetanus (90%), and IPV1, 2 & 3 (90%).

Acceptability was met for all considered PR5I antigens.
Note: (N=***) represents the number of assessed subjects.

End point type	Primary

End point timeframe:

1 month after the 3rd dose of PR5I (Post-Dose 3).

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: This end point includes only one arm.
Acceptability criteria were met for all the considered PR5I antigens, as described above.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The objective of this end point was to evaluate the acceptability of PR5I antigen response rates. So this end point included only the PR5I arm.

End point values	PR5I			
Subject group type	Reporting group			
Number of subjects analysed	550			
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-PRP ≥0.15 µg/mL (N=550)	98.36 (96.92 to 99.25)			
Anti-Diphtheria ≥0.01 IU/mL (N= 542)	99.82 (98.98 to 100)			
Anti-Tetanus ≥0.01 IU/mL (N=538)	100 (99.32 to 100)			
Anti-IPV1 ≥8 (1/dil) (N=547)	100 (99.33 to 100)			
Anti-IPV2 ≥8 (1/dil) (N=547)	99.82 (98.99 to 100)			
Anti-IPV3 ≥8 (1/dil) (N=545)	100 (99.33 to 100)			

Statistical analyses

No statistical analyses for this end point

Primary: Acceptability of antibody (Ab) response or seroresponse rates to all antigens contained in PR5I vaccine one month after the Toddler dose of PR5I (12 months of age)

End point title	Acceptability of antibody (Ab) response or seroresponse rates to all antigens contained in PR5I vaccine one month after the Toddler dose of PR5I (12 months of age)[3]

End point description:

% of subjects with an Ab titre ≥1.0 µg/mL for Hib (PRP); ≥10 mIU/mL for Hepatitis B (HBsAg) (measured by enhanced Chemiluminescence assay (ECi)); ≥0.1 IU/mL for diphtheria & tetanus; ≥8 (1/dil) for IPV1, 2 & 3, and % of pertussis seroresponder subjects (Pertussis toxoid (PT), Filamentous haemagglutinin (FHA), Fimbriae types 2 & 3 (FIM) & Pertactin (PRN) (measured by ELISA)) 1 month Post-Toddler dose of PR5I.
Seroresponse was defined: (1) If pre-Dose 1 Ab concentration (cc) was <4X LLOQ (lower limit of quantitation), postvaccination Ab cc was ≥4X LLOQ, (2) If pre-Dose 1 Ab cc was ≥4X LLOQ, postvaccination Ab cc was ≥prevaccination levels.
Analysis was done on the PP-RW population.
The immune response to PR5I vaccine was considered as acceptable if the lower bounds of the 2-sided 95% CI for the response rates were greater than the predetermined lower limits.
Acceptability was met for all PR5I antigens.

Note: (N=***) represents the number of assessed subjects.

End point type	Primary

End point timeframe:

1 month after the Toddler dose of PR5I (Post-Toddler Dose).

Notes:

[3] - 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: This end point includes only one arm.
Acceptability criteria were met for all the considered PR5I antigens: lower bounds of the 2-sided 95% CI of the % of subjects presented below greater than 75% for PRP, PT, FHA, FIM & PRN, 80% for diphtheria, and 90% for HBsAg, tetanus and IPV1, 2 & 3.

End point values	PR5I			
Subject group type	Reporting group			
Number of subjects analysed	551			
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-PRP ≥1.0 µg/mL (N=439)	94.99 (92.51 to 96.83)			
Anti-HBsAg ≥10 mIU/mL (N=551)	99.64 (98.7 to 99.96)			
Anti-Diphtheria ≥0.1 IU/mL (N= 531)	99.81 (98.96 to 100)			
Anti-Tetanus ≥0.1 IU/mL (N=528)	100 (99.3 to 100)			
Anti-PT seroresponse (N=543)	99.82 (98.98 to 100)			
Anti-FHA seroresponse (N=542)	97.23 (95.48 to 98.44)			
Anti-FIM seroresponse (N=508)	99.61 (98.59 to 99.95)			
Anti-PRN seroresponse (N=543)	98.9 (97.61 to 99.59)			
Anti-IPV1 ≥8 (1/dil) (N=538)	99.81 (98.97 to 100)			
Anti-IPV2 ≥8 (1/dil) (N=538)	100 (99.32 to 100)			
Anti-IPV3 ≥8 (1/dil) (N=541)	100 (99.32 to 100)			

Statistical analyses

No statistical analyses for this end point

Primary: Non-inferiority of antibody (Ab) response rates to Haemophilus influenzae type b (PRP), diphtheria, tetanus and poliovirus types 1, 2 & 3 one month after the 3rd dose of PR5I (4 months of age) as compared with INFANRIX hexa

End point title	Non-inferiority of antibody (Ab) response rates to Haemophilus influenzae type b (PRP), diphtheria, tetanus and poliovirus types 1, 2 & 3 one month after the 3rd dose of PR5I (4 months of age) as compared with INFANRIX hexa

End point description:

Percentage of subjects with an Ab titre ≥0.15 µg/mL for Hib (polyribosylribitol phosphate, PRP); ≥0.01 IU/mL for diphtheria and tetanus; ≥8 (1/dil) for inactivated poliovirus types 1, 2 & 3 (IPV1, IPV2 & IPV3) 1 month Post-Dose 3 of PR5I or INFANRIX hexa.
Ab titres were measured by RIA for PRP, MIT for diphtheria and poliovirus, and ELISA for tetanus.

Analysis was done on the PP-RW population.
Note: (N=***, ***) represents the number of assessed subjects in the PR5I and INFANRIX hexa groups, respectively.

End point type	Primary

End point timeframe:

1 month after the 3rd dose of PR5I or INFANRIX hexa (Post-Dose 3).

End point values	PR5I	INFANRIX hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	550	530		
Units: Percentage of subjects				
number (not applicable)				
Anti-PRP ≥0.15 µg/mL (N=550, 521)	98.36	86.99		
Anti-Diphtheria ≥0.01 IU/mL (N= 542, 517)	99.81	99.81		
Anti-Tetanus ≥0.01 IU/mL (N=538, 519)	100	100		
Anti-IPV1 ≥8 (1/dil) (N=547, 528)	100	99.81		
Anti-IPV2 ≥8 (1/dil) (N=547, 530)	99.82	99.62		
Anti-IPV3 ≥8 (1/dil) (N=545, 525)	100	100		

Statistical analyses

Statistical analysis title	Non-inferiority for PRP

Statistical analysis description:

The estimate of the difference between PR5I & INFANRIX hexa groups in PRP response rate (based on Ab titre ≥0.15 µg/mL) was calculated with its 1-sided P-value & 2-sided 95% confidence interval (CI). If the lower bound of the 95% CI was greater than -10% (non-inferiority margin), it was concluded that PR5I group response rate was non-inferior to INFANRIX hexa group response rate.
Analysis was done on the PP-RW population: N=550, 521 (PR5I group, INFANRIX hexa group).

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1080
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
P-value	< 0.001
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages of subjects
Point estimate	11.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.44
upper limit	14.68

Notes:

[4] - Statistical analysis was based on the Miettinen & Nurminen method stratified by country.

Statistical analysis title	Non-inferiority for Diphtheria

Statistical analysis description:

The estimate of the difference between PR5I & INFANRIX hexa groups in Diphtheria response rate (based on Ab titre ≥0.01 IU/mL) was calculated with its 1-sided P-value & 2-sided 95% confidence interval (CI). If the lower bound of the 95% CI was greater than -10% (non-inferiority margin), it was concluded that PR5I group response rate was non-inferior to INFANRIX hexa group response rate.
Analysis was done on the PP-RW population: N=542, 517 (PR5I group, INFANRIX hexa group).

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1080
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
P-value	< 0.001
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages of subjects
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.95
upper limit	0.96

Notes:

[5] - Statistical analysis was based on the Miettinen & Nurminen method stratified by country.

Statistical analysis title	Non-inferiority for Tetanus

Statistical analysis description:

The estimate of the difference between PR5I & INFANRIX hexa groups in Tetanus response rate (based on Ab titre ≥0.01 IU/mL) was calculated with its 1-sided P-value & 2-sided 95% confidence interval (CI). If the lower bound of the 95% CI was greater than -5% (non-inferiority margin), it was concluded that PR5I group response rate was non-inferior to INFANRIX hexa group response rate.
Analysis was done on the PP-RW population: N=538, 519 (PR5I group, INFANRIX hexa group).

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1080
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
P-value	< 0.001
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages of subjects
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.71
upper limit	0.74

Notes:

[6] - Statistical analysis was based on the Miettinen & Nurminen method stratified by country.

Statistical analysis title	Non-inferiority for IPV1

Statistical analysis description:

The estimate of the difference between PR5I & INFANRIX hexa groups in IPV1 response rate (based on Ab titre ≥8 (1/dil)) was calculated with its 1-sided P-value & 2-sided 95% confidence interval (CI). If the lower bound of the 95% CI was greater than -5% (non-inferiority margin), it was concluded that PR5I group response rate was non-inferior to INFANRIX hexa group response rate.
Analysis was done on the PP-RW population: N=547, 528 (PR5I group, INFANRIX hexa group).

Comparison groups	PR5I v INFANRIX hexa

Number of subjects included in analysis	1080
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
P-value	< 0.001
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages of subjects
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	1.07

Notes:

[7] - Statistical analysis was based on the Miettinen & Nurminen method stratified by country.

Statistical analysis title	Non-inferiority for IPV2

Statistical analysis description:

The estimate of the difference between PR5I & INFANRIX hexa groups in IPV2 response rate (based on Ab titre ≥8 (1/dil)) was calculated with its 1-sided P-value & 2-sided 95% confidence interval (CI). If the lower bound of the 95% CI was greater than -5% (non-inferiority margin), it was concluded that PR5I group response rate was non-inferior to INFANRIX hexa group response rate.
Analysis was done on the PP-RW population: N=547, 530 (PR5I group, INFANRIX hexa group).

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1080
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
P-value	< 0.001
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages of subjects
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.69
upper limit	1.21

Notes:

[8] - Statistical analysis was based on the Miettinen & Nurminen method stratified by country.

Statistical analysis title	Non-inferiority for IPV3

Statistical analysis description:

The estimate of the difference between PR5I & INFANRIX hexa groups in IPV3 response rate (based on Ab titre ≥8 (1/dil)) was calculated with its 1-sided P-value & 2-sided 95% confidence interval (CI). If the lower bound of the 95% CI was greater than -5% (non-inferiority margin), it was concluded that PR5I group response rate was non-inferior to INFANRIX hexa group response rate.
Analysis was done on the PP-RW population: N=545, 525 (PR5I group, INFANRIX hexa group).

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1080
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
P-value	< 0.001
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages of subjects
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.73

Notes:

[9] - Statistical analysis was based on the Miettinen & Nurminen method stratified by country.

Primary: Non-inferiority of antibody (Ab) seroprotection rates for Hepatitis B and seroresponse rates for Pertussis antigens one month after the Toddler dose of PR5I (12 months of age) as compared with INFANRIX hexa

End point title	Non-inferiority of antibody (Ab) seroprotection rates for Hepatitis B and seroresponse rates for Pertussis antigens one month after the Toddler dose of PR5I (12 months of age) as compared with INFANRIX hexa

End point description:

Percentage of subjects with an anti-HBsAg Ab titre ≥10 mIU/mL for Hepatitis B, and percentage of pertussis seroresponder subjects (Pertussis toxoid (PT), Filamentous haemagglutinin (FHA), and Pertactin (PRN)) 1 month after the Toddler dose of PR5I or INFANRIX hexa.
Seroresponse was defined: (1) If pre-Dose 1 Ab concentration (cc) was <4X LLOQ (lower limit of quantitation), postvaccination Ab cc was ≥4X LLOQ, (2) If pre-Dose 1 Ab cc was ≥4X LLOQ, postvaccination Ab cc was ≥prevaccination levels.
Ab titres were measured by ECi for HBsAg, and ELISA for PT, FHA & PRN.
Analysis was done on the PP-RW population.
Note: (N=***, ***) represents the number of assessed subjects in the PR5I and INFANRIX hexa groups, respectively.

End point type	Primary

End point timeframe:

1 month after the Toddler dose of PR5I or INFANRIX hexa (Post-Toddler Dose).

End point values	PR5I	INFANRIX hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	551	531		
Units: Percentage of subjects				
number (not applicable)				
Anti-HBsAg ≥10 mIU/mL (N=551, 531)	99.64	99.06		
Anti-PT seroresponse (N=543, 523)	99.82	98.49		
Anti-FHA seroresponse (N=542, 524)	97.22	99.81		
Anti-PRN seroresponse (N=543, 523)	98.89	98.86		

Statistical analyses

Statistical analysis title	Non-inferiority for HBsAg

Statistical analysis description:

The estimate of the difference between PR5I & INFANRIX hexa groups in HBsAg response rate (based on Ab titre ≥10 mIU/mL) was calculated with its 1-sided P-value & 2-sided 95% confidence interval (CI). If the lower bound of the 95% CI was greater than -10% (non-inferiority margin), it was concluded that PR5I group response rate was non-inferior to INFANRIX hexa group response rate.
Analysis was done on the PP-RW population: N=551, 531 (PR5I group, INFANRIX hexa group).

Comparison groups	PR5I v INFANRIX hexa

Number of subjects included in analysis	1082
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
P-value	< 0.001
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages of subjects
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	1.85

Notes:

[10] - Statistical analysis was based on the Miettinen & Nurminen method stratified by country.

Statistical analysis title	Non-inferiority for PT

Statistical analysis description:

The estimate of the difference between PR5I & INFANRIX hexa groups in the percentage of seroresponder subjects for PT was calculated with its 1-sided P-value & 2-sided 95% confidence interval (CI). If the lower bound of the 95% CI was greater than -10% (non-inferiority margin), it was concluded that PR5I group response rate was non-inferior to INFANRIX hexa group response rate.
Analysis was done on the PP-RW population: N=543, 523 (PR5I group, INFANRIX hexa group).

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1082
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
P-value	< 0.001
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages of subjects
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	2.86

Notes:

[11] - Statistical analysis was based on the Miettinen & Nurminen method stratified by country.

Statistical analysis title	Non-inferiority for FHA

Statistical analysis description:

The estimate of the difference between PR5I & INFANRIX hexa groups in the percentage of seroresponder subjects for FHA was calculated with its 1-sided P-value & 2-sided 95% confidence interval (CI). If the lower bound of the 95% CI was greater than -10% (non-inferiority margin), it was concluded that PR5I group response rate was non-inferior to INFANRIX hexa group response rate.
Analysis was done on the PP-RW population: N=542, 524 (PR5I group, INFANRIX hexa group).

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1082
Analysis specification	Pre-specified
Analysis type	non-inferiority[12]
P-value	< 0.001
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages of subjects
Point estimate	-2.59

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.39
upper limit	-1.29

Notes:

[12] - Statistical analysis was based on the Miettinen & Nurminen method stratified by country.

Statistical analysis title	Non-inferiority for PRN

Statistical analysis description:

The estimate of the difference between PR5I & INFANRIX hexa groups in the percentage of seroresponder subjects for PRN was calculated with its 1-sided P-value & 2-sided 95% confidence interval (CI). If the lower bound of the 95% CI was greater than -10% (non-inferiority margin), it was concluded that PR5I group response rate was non-inferior to INFANRIX hexa group response rate. Analysis was done on the PP-RW population: N=543, 523 (PR5I group, INFANRIX hexa group).

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1082
Analysis specification	Pre-specified
Analysis type	non-inferiority[13]
P-value	< 0.001
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages of subjects
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	1.52

Notes:

[13] - Statistical analysis was based on the Miettinen & Nurminen method stratified by country.

Secondary: Acceptability of antibody (Ab) response rates to measles, mumps, rubella and varicella one month after the Toddler dose of ProQuad (12 months of age) administered concomitantly with PR5I

End point title	Acceptability of antibody (Ab) response rates to measles, mumps, rubella and varicella one month after the Toddler dose of ProQuad (12 months of age) administered concomitantly with PR5I

End point description:

Percentage of subjects with an Ab titre ≥255 mIU/mL for measles, ≥10 Ab units/mL for mumps, ≥10 IU/mL for rubella, and ≥5 gpELISA units/mL for varicella 1 month after injection of the Toddler dose (12 months) of ProQuad administered concomitantly with PR5I.
All Ab titres were measured by ELISA, except Ab to varicella determined by glycoprotein ELISA.
Analysis was done on the PP-RW population.
The immune response to ProQuad vaccine regarding its concomitant use with PR5I was considered as acceptable if the lower bounds of the 2-sided 95% CI for the response rates were greater than the predetermined lower limits: 90% for measles, mumps & rubella, and 76% for varicella.
Acceptability was met for all ProQuad antigens.

End point type	Secondary

End point timeframe:

1 month after the Toddler dose of ProQuad administered concomitantly with PR5I (Post-Toddler Dose).

End point values	PR5I			
Subject group type	Reporting group			
Number of subjects analysed	467			
Units: Percentages				
number (confidence interval 95%)				
Anti-Measles ≥255 mIU/mL	96.15 (93.98 to 97.7)			
Anti-Mumps ≥10 Ab units/mL	94.86 (92.45 to 96.68)			
Anti-Rubella ≥10 IU/mL	98.29 (96.65 to 99.26)			
Anti-Varicella ≥5 gpELISA units/mL	97.64 (95.82 to 98.82)			

Statistical analyses

No statistical analyses for this end point

Secondary: Non-inferiority of antibody (Ab) response rates to measles, mumps, rubella and varicella one month after the Toddler dose of ProQuad (12 months of age) administered concomitantly with PR5I versus INFANRIX hexa

End point title	Non-inferiority of antibody (Ab) response rates to measles, mumps, rubella and varicella one month after the Toddler dose of ProQuad (12 months of age) administered concomitantly with PR5I versus INFANRIX hexa

End point description:

Percentage of subjects with an Ab titre ≥255 mIU/mL for measles, ≥10 Ab units/mL for mumps, ≥10 IU/mL for rubella, and ≥5 gpELISA units/mL for varicella 1 month after injection of the Toddler dose (12 months) of ProQuad administered concomitantly with PR5I and INFANRIX hexa.
All Ab titres were measured by ELISA, except Ab to varicella determined by glycoprotein ELISA.
Analysis was done on the PP-RW population.
Note: (N=***, ***) represents the number of assessed subjects in the PR5I and INFANRIX hexa groups, respectively.

End point type	Secondary

End point timeframe:

1 month after the Toddler dose of ProQuad, administered concomitantly with PR5I or INFANRIX hexa (Post-Toddler Dose).

End point values	PR5I	INFANRIX hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	467	474		
Units: Percentage of subjects				
number (not applicable)				
Anti-Measles ≥255 mIU/mL (N= 467, 474)	96.15	96.41		
Anti-Mumps ≥10 Ab units/mL (N= 467, 474)	94.86	91.78		
Anti-Rubella ≥10 IU/mL (N= 467, 474)	98.28	97.89		
Anti-Varicella ≥5 gpELISA units/mL (N= 467, 471)	97.64	97.66		

Statistical analyses

Statistical analysis title	Non-inferiority for Measles

Statistical analysis description:

The estimate of the difference between PR5I & INFANRIX hexa groups in Measles response rate (based on Ab titre ≥255 mIU/mL) was calculated with its 1-sided P-value & 2-sided 95% confidence interval (CI). If the lower bound of the 95% CI was greater than -5% (non-inferiority margin), it was concluded that PR5I group response rate was non-inferior to INFANRIX hexa group response rate.
Analysis was done on the PP-RW population: N=467, 474 (PR5I group, INFANRIX hexa group).

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	941
Analysis specification	Pre-specified
Analysis type	non-inferiority[14]
P-value	< 0.001
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages of subjects
Point estimate	-0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.82
upper limit	2.25

Notes:

[14] - Statistical analysis was based on the Miettinen & Nurminen method stratified by country.

Statistical analysis title	Non-inferiority for Mumps

Statistical analysis description:

The estimate of the difference between PR5I & INFANRIX hexa groups in Mumps response rate (based on Ab titre ≥10 Ab units/mL) was calculated with its 1-sided P-value & 2-sided 95% confidence interval (CI). If the lower bound of the 95% CI was greater than -5% (non-inferiority margin), it was concluded that PR5I group response rate was non-inferior to INFANRIX hexa group response rate.
Analysis was done on the PP-RW population: N=467, 474 (PR5I group, INFANRIX hexa group).

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	941
Analysis specification	Pre-specified
Analysis type	non-inferiority[15]
P-value	< 0.001
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages of subjects
Point estimate	3.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	6.4

Notes:

[15] - Statistical analysis was based on the Miettinen & Nurminen method stratified by country.

Statistical analysis title	Non-inferiority for Rubella

Statistical analysis description:

The estimate of the difference between PR5I & INFANRIX hexa groups in Rubella response rate (based on Ab titre ≥10 IU/mL) was calculated with its 1-sided P-value & 2-sided 95% confidence interval (CI). If the lower bound of the 95% CI was greater than -5% (non-inferiority margin), it was concluded that PR5I group response rate was non-inferior to INFANRIX hexa group response rate.
Analysis was done on the PP-RW population: N=467, 474 (PR5I group, INFANRIX hexa group).

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	941
Analysis specification	Pre-specified
Analysis type	non-inferiority[16]
P-value	< 0.001
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages of subjects
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	2.34

Notes:

[16] - Statistical analysis was based on the Miettinen & Nurminen method stratified by country.

Statistical analysis title	Non-inferiority for Varicella

Statistical analysis description:

The estimate of the difference between PR5I & INFANRIX hexa groups in Varicella response rate (based on Ab titre ≥5 gpELISA units/mL) was calculated with its 1-sided P-value & 2-sided 95% confidence interval (CI). If the lower bound of the 95% CI was greater than -10% (non-inferiority margin), it was concluded that PR5I group response rate was non-inferior to INFANRIX hexa group response rate.
Analysis was done on the PP-RW population: N=467, 471 (PR5I group, INFANRIX hexa group).

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	941
Analysis specification	Pre-specified
Analysis type	non-inferiority[17]
P-value	< 0.001
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages of subjects
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.11
upper limit	2.06

Notes:

[17] - Statistical analysis was based on the Miettinen & Nurminen method stratified by country.

Secondary: Global safety from D1 to D15 after any vaccination

End point title	Global safety from D1 to D15 after any vaccination

End point description:

Injection-site and systemic adverse events (AEs) were reported daily on the Vaccination Report Card (VRC) by the parent(s) or legal representative from Day 1 (D1) to D15 after each hexavalent vaccination.
Solicited injection-site and systemic AEs were reported daily from D1 to D5 after each hexavalent vaccination.
AEs at injection sites were always considered as vaccine-related (Injection-Site Reactions (ISRs)).
The investigator had to assess whether systemic AEs were related (V-related) or not to the vaccine.
All AEs (related and unrelated) are displayed here.
Analysis was done on the All Subjects as Treated (ASaT) population, i.e. all randomised subjects (N=1215) who received at least 1 vaccination and who had safety follow-up.

End point type	Secondary

End point timeframe:

From Day 1 (D1) to D15 after each hexavalent vaccination.

End point values	PR5I	INFANRIX hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	610	603		
Units: Percentages of subjects				
number (not applicable)				
At least 1 ISR or systemic AE (D1-D15)	98.9	99.5		
At least 1 ISR or V-related systemic AE (D1-D15)	98.5	98.8		
At least 1 ISR (D1-D15)	92.1	91		
At least 1 solicited ISR (D1-D5)	90.8	89.9		
At least 1 systemic AE (D1-D15)	98.4	99.3		
At least 1 V-related systemic AE (D1-D15)	95.6	96.5		
At least 1 solicited systemic AE (D1-D5)	97	98.5		
At least 1 V-related solicited systemic AE (D1-D5)	94.9	96.2		

Statistical analyses

Statistical analysis title	ISRs or systemic AEs

Statistical analysis description:

The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% confidence interval (CI) were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. The aim of the 95% CI was to investigate whether an overall trend of risk differences existed. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.
Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	-0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	0.4

Statistical analysis title	ISRs or vaccine-related systemic AEs

Statistical analysis description:

The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% confidence interval (CI) were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. The aim of the 95% CI was to investigate whether an overall trend of risk differences existed. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.
Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	1.1

Statistical analysis title	At least 1 ISR

Statistical analysis description:

The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% confidence interval (CI) were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. The aim of the 95% CI was to investigate whether an overall trend of risk differences existed. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.
Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	4.3

Statistical analysis title	At least 1 solicited ISR

Statistical analysis description:

The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% confidence interval (CI) were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. The aim of the 95% CI was to investigate whether an overall trend of risk differences existed. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.
Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	4.3

Statistical analysis title	At least 1 systemic AE

Statistical analysis description:

The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% confidence interval (CI) were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. The aim of the 95% CI was to investigate whether an overall trend of risk differences existed. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.
Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	0.3

Statistical analysis title	At least 1 vaccine-related systemic AE

Statistical analysis description:

The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% confidence interval (CI) were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. The aim of the 95% CI was to investigate whether an overall trend of risk differences existed. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.
Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa

Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	1.3

Statistical analysis title	At least 1 solicited systemic AE

Statistical analysis description:

The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% confidence interval (CI) were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. The aim of the 95% CI was to investigate whether an overall trend of risk differences existed. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.
Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	0.2

Statistical analysis title	At least 1 vaccine-related solicited systemic AE

Statistical analysis description:

The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% confidence interval (CI) were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. The aim of the 95% CI was to investigate whether an overall trend of risk differences existed. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.
Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	-1.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	1.1

Secondary: Proportion of subjects reporting solicited ISRs from D1 to D5 after any vaccination

End point title	Proportion of subjects reporting solicited ISRs from D1 to D5 after any vaccination

End point description:

Adverse events at injection sites were always considered as related to vaccine (Injection-Site Reactions (ISRs)).
Solicited ISRs were defined as injection-site erythema, injection-site pain, and injection-site swelling occurring from Day 1 (D1) to D5 after vaccination.
Analysis was done on the All Subjects as Treated (ASaT) population, i.e. all randomised subjects (N=1215) who received at least 1 vaccination and who had safety follow-up.

End point type	Secondary

End point timeframe:

From Day 1 (D1) to D5 after any vaccination.

End point values	PR5I	INFANRIX hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	610	603		
Units: Percentage of subjects				
number (not applicable)				
Injection-site erythema	69	64.2		
Injection-site pain	73.6	71.8		
Injection-site swelling	56.9	52.9		

Statistical analyses

Statistical analysis title	Injection-site erythema

Statistical analysis description:

The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% confidence interval (CI) were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. The aim of the 95% CI was to investigate whether an overall trend of risk differences existed. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.
Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa

Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	10.1

Statistical analysis title	Injection-site pain

Statistical analysis description:

The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% confidence interval (CI) were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. The aim of the 95% CI was to investigate whether an overall trend of risk differences existed. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.
Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	6.8

Statistical analysis title	Injection-site swelling

Statistical analysis description:

The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% confidence interval (CI) were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. The aim of the 95% CI was to investigate whether an overall trend of risk differences existed. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.
Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	9.6

Secondary: Proportion of subjects reporting unsolicited ISRs from D1 to D15 after any vaccination

End point title	Proportion of subjects reporting unsolicited ISRs from D1 to D15 after any vaccination

End point description:

Adverse events at injection sites were always considered as related to vaccine (Injection-Site Reactions (ISRs)).
Unsolicited ISRs occurring from Day 1 (D1) to D15 after any vaccination were reported daily on the VRC by the parent(s) or legal representative.
Unsolicited ISRs with incidence ≥1% are reported below.
Analysis was done on the All Subjects as Treated (ASaT) population, i.e. all randomised subjects (N=1215) who received at least 1 vaccination and who had safety follow-up.

End point type	Secondary

End point timeframe:

From Day 1 (D1) to D15 after any vaccination.

End point values	PR5I	INFANRIX hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	610	603		
Units: Percentage of subjects				
number (not applicable)				
Injection-site bruising	2.8	2.7		
Injection-site haematoma	1.5	0.8		
Injection-site haemorrhage	1.3	2		
Injection-site induration	14.6	18.2		
Injection-site nodule	1.3	1.5		
Injection-site warmth	3	1.8		

Statistical analyses

Statistical analysis title	Injection-site bruising

Statistical analysis description:

The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% confidence interval (CI) were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. The aim of the 95% CI was to investigate whether an overall trend of risk differences existed. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.
Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa

Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	2.1

Statistical analysis title	Injection-site haematoma

Statistical analysis description:

The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% confidence interval (CI) were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. The aim of the 95% CI was to investigate whether an overall trend of risk differences existed. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.
Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	2.1

Statistical analysis title	Injection-site haemorrhage

Statistical analysis description:

The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% confidence interval (CI) were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. The aim of the 95% CI was to investigate whether an overall trend of risk differences existed. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.
Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	-0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	0.8

Statistical analysis title	Injection-site induration

Statistical analysis description:

The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% confidence interval (CI) were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. The aim of the 95% CI was to investigate whether an overall trend of risk differences existed. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.
Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	-3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.8
upper limit	0.5

Statistical analysis title	Injection-site nodule

Statistical analysis description:

The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% confidence interval (CI) were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. The aim of the 95% CI was to investigate whether an overall trend of risk differences existed. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.
Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	1.3

Statistical analysis title	Injection-site warmth

Statistical analysis description:

The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% confidence interval (CI) were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. The aim of the 95% CI was to investigate whether an overall trend of risk differences existed. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.
Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	3

Secondary: Proportion of subjects reporting solicited systemic adverse events (AEs) from D1 to D5 after any vaccination

End point title	Proportion of subjects reporting solicited systemic adverse events (AEs) from D1 to D5 after any vaccination

End point description:

Solicited systemic AEs were defined as crying, decreased appetite, irritability, pyrexia (rectal temperature ≥38.0°C), somnolence, and vomiting occurring from Day 1 (D1) to D5 after vaccination. The investigator had to assess whether these systemic AEs were related or not to the vaccines. All (related and unrelated) are displayed here.
Analysis was done on the All Subjects as Treated (ASaT) population, i.e. all randomised subjects (N=1215) who received at least 1 vaccination and who had safety follow-up.

End point type	Secondary

End point timeframe:

From Day 1 (D1) to D5 after any vaccination.

End point values	PR5I	INFANRIX hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	610	603		
Units: Percentage of subjects				
number (not applicable)				
Crying	85.4	87.9		
Decreased appetite	63.9	67		
Irritability	87.9	85.7		
Pyrexia	71.5	73.1		
Somnolence	76.9	80.1		
Vomiting	31.8	31		

Statistical analyses

Statistical analysis title	Crying

Statistical analysis description:

The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% confidence interval (CI) were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. The aim of the 95% CI was to investigate whether an overall trend of risk differences existed. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.
Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	1.4

Statistical analysis title	Decreased appetite

Statistical analysis description:

The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% confidence interval (CI) were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. The aim of the 95% CI was to investigate whether an overall trend of risk differences existed. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.
Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	2.3

Statistical analysis title	Irritability

Statistical analysis description:

The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% confidence interval (CI) were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. The aim of the 95% CI was to investigate whether an overall trend of risk differences existed. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.
Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	6

Statistical analysis title	Pyrexia

Statistical analysis description:

The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% confidence interval (CI) were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. The aim of the 95% CI was to investigate whether an overall trend of risk differences existed. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.
Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	3.4

Statistical analysis title	Somnolence

Statistical analysis description:

The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% confidence interval (CI) were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. The aim of the 95% CI was to investigate whether an overall trend of risk differences existed. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.
Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa

Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.8
upper limit	1.4

Statistical analysis title	Vomiting

Statistical analysis description:

The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% confidence interval (CI) were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. The aim of the 95% CI was to investigate whether an overall trend of risk differences existed. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.
Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	6

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Unsolicited non-serious and serious adverse events (AEs) were collected from D1 to D15 after each hexavalent vaccination.
Vaccine-related serious AEs and deaths were collected for the duration of the study.

Adverse event reporting additional description:

Analysis of AEs was done on the All Subjects as Treated (ASaT) population, i.e. all randomised subjects (N=1215) who received at least 1 vaccination and who had safety follow-up.
Unsolicited non-serious systemic AEs (vaccine-related or not) with incidence ≥2.5% are presented hereafter.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	PR5I

Reporting group description:

Subjects received 1 dose of PR5I (DTaP-HB-IPV-Hib) by intramuscular route (IM) at 2, 3, 4 and 12 months of age, 1 dose of Prevenar 13 (PCV-13) by IM route (opposite leg) at 2, 3, 4 and 13 months of age, 1 dose of RotaTeq by oral route at 2, 3 and 4 months of age, and 1 dose of ProQuad by subcutaneous route at 12 and 13 months of age.
Respectively, 453 (74.3%) subjects reported at least 1 unsolicited non-serious systemic AE, and 310 (50.8%) subjects reported at least 1 vaccine-related unsolicited non-serious systemic AE within 15 days after any vaccination.

Reporting group title	INFANRIX hexa

Reporting group description:

Subjects received 1 dose of INFANRIX hexa (DTaP-HBV-IPV-Hib) by intramuscular route (IM) at 2, 3, 4 and 12 months of age, 1 dose of Prevenar 13 (PCV-13) by IM route (opposite leg) at 2, 3, 4 and 13 months of age, 1 dose of RotaTeq by oral route at 2, 3 and 4 months of age, and 1 dose of ProQuad by subcutaneous route at 12 and 13 months of age.
Respectively, 458 (76.0%) subjects reported at least 1 unsolicited non-serious systemic AE, and 291 (48.3%) subjects reported at least 1 vaccine-related unsolicited non-serious systemic AE within 15 days after any vaccination.

Serious adverse events	PR5I	INFANRIX hexa	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 610 (2.79%)	13 / 605 (2.15%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Outside D1-D15 period, Prolymphocytic leukaemia			
subjects affected / exposed	1 / 610 (0.16%)	0 / 605 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural			

complications			
D1-D15, Concussion			
subjects affected / exposed	2 / 610 (0.33%)	0 / 605 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
D1-D15, Subdural haematoma			
subjects affected / exposed	1 / 610 (0.16%)	0 / 605 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
D1-D15, Benign familial neonatal convulsions			
subjects affected / exposed	0 / 610 (0.00%)	1 / 605 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
D1-D15, Convulsion			
subjects affected / exposed	1 / 610 (0.16%)	0 / 605 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
D1-D15, Febrile convulsion			
subjects affected / exposed	1 / 610 (0.16%)	0 / 605 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
D1-D15, Pyrexia			
subjects affected / exposed	2 / 610 (0.33%)	2 / 605 (0.33%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
D1-D15, Inguinal hernia			
subjects affected / exposed	1 / 610 (0.16%)	0 / 605 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
D1-D15, Oesophagitis			

subjects affected / exposed	0 / 610 (0.00%)	1 / 605 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
D1-D15, Swollen tongue			
subjects affected / exposed	0 / 610 (0.00%)	1 / 605 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
D1-D15, Neuroendocrine cell hyperplasia of infancy			
subjects affected / exposed	0 / 610 (0.00%)	1 / 605 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
D1-D15, Muscle spasms			
subjects affected / exposed	0 / 610 (0.00%)	1 / 605 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
D1-D15, Bronchiolitis			
subjects affected / exposed	2 / 610 (0.33%)	0 / 605 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
D1-D15, Bronchitis			
subjects affected / exposed	1 / 610 (0.16%)	0 / 605 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
D1-D15, Bronchitis viral			
subjects affected / exposed	0 / 610 (0.00%)	1 / 605 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
D1-D15, Exanthema subitum			

subjects affected / exposed	1 / 610 (0.16%)	0 / 605 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
D1-D15, Gastroenteritis			
subjects affected / exposed	1 / 610 (0.16%)	0 / 605 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
D1-D15, Pneumonia			
subjects affected / exposed	1 / 610 (0.16%)	0 / 605 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
D1-D15, Pyelonephritis			
subjects affected / exposed	1 / 610 (0.16%)	2 / 605 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
D1-D15, Pyelonephritis acute			
subjects affected / exposed	1 / 610 (0.16%)	0 / 605 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
D1-D15, Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	2 / 610 (0.33%)	3 / 605 (0.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
D1-D15, Respiratory tract infection			
subjects affected / exposed	1 / 610 (0.16%)	0 / 605 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
D1-D15, Skin infection			
subjects affected / exposed	0 / 610 (0.00%)	1 / 605 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
D1-D15, Urosepsis			

subjects affected / exposed	1 / 610 (0.16%)	0 / 605 (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: 2.5 %

Non-serious adverse events	PR5I	INFANRIX hexa	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	453 / 610 (74.26%)	458 / 605 (75.70%)	
General disorders and administration site conditions			
Crying			
subjects affected / exposed	52 / 610 (8.52%)	37 / 605 (6.12%)	
occurrences (all)	52	37	
Irritability			
subjects affected / exposed	59 / 610 (9.67%)	43 / 605 (7.11%)	
occurrences (all)	59	43	
Pyrexia			
subjects affected / exposed	165 / 610 (27.05%)	150 / 605 (24.79%)	
occurrences (all)	165	150	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	18 / 610 (2.95%)	31 / 605 (5.12%)	
occurrences (all)	18	31	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	12 / 610 (1.97%)	25 / 605 (4.13%)	
occurrences (all)	12	25	
Constipation			
subjects affected / exposed	24 / 610 (3.93%)	29 / 605 (4.79%)	
occurrences (all)	24	29	
Diarrhoea			
subjects affected / exposed	98 / 610 (16.07%)	83 / 605 (13.72%)	
occurrences (all)	98	83	
Flatulence			
subjects affected / exposed	44 / 610 (7.21%)	39 / 605 (6.45%)	
occurrences (all)	44	39	

Vomiting			
subjects affected / exposed	22 / 610 (3.61%)	21 / 605 (3.47%)	
occurrences (all)	22	21	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	34 / 610 (5.57%)	35 / 605 (5.79%)	
occurrences (all)	34	35	
Skin and subcutaneous tissue disorders			
Eczema infantile			
subjects affected / exposed	19 / 610 (3.11%)	10 / 605 (1.65%)	
occurrences (all)	19	10	
Rash			
subjects affected / exposed	35 / 610 (5.74%)	27 / 605 (4.46%)	
occurrences (all)	35	27	
Rash generalised			
subjects affected / exposed	18 / 610 (2.95%)	8 / 605 (1.32%)	
occurrences (all)	18	8	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	24 / 610 (3.93%)	34 / 605 (5.62%)	
occurrences (all)	24	34	
Otitis media			
subjects affected / exposed	30 / 610 (4.92%)	26 / 605 (4.30%)	
occurrences (all)	30	26	
Upper respiratory tract infection			
subjects affected / exposed	67 / 610 (10.98%)	74 / 605 (12.23%)	
occurrences (all)	67	74	
Rhinitis			
subjects affected / exposed	77 / 610 (12.62%)	85 / 605 (14.05%)	
occurrences (all)	77	85	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	37 / 610 (6.07%)	23 / 605 (3.80%)	
occurrences (all)	37	23	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 November 2010	# Correction of an error regarding the adverse event causality definitions. # Other changes: a EudraCT number of 2010-021490-37 was assigned for V419-007 since protocol finalization, the protocol footer was changed from "US IND, ex-US study" to "Non-U.S. IND, Ex-U.S. Study", updated SmPC documents for Prevenar 13™ and RotaTeq™ were added to Section 7, editorial changes were made to the table describing the study design and vaccination group assignments, and changes were made to 2 paragraphs (describing the assignment of baseline number [Section 3.2.4.2] and clinical and laboratory measurements for immunogenicity [Section 3.3.1]).
22 December 2010	# 1. Revision of the timing of when non-study vaccines could be received during the study. 2. Addition of Table 3-2 'Solicited Injection-Site Reactions (Definitions, Terminology and Severity Scales)' in Section 3.4.1 (Clinical and Laboratory Measurements for Safety) in order to revise the scale for grading injection-site pain and tenderness to more directly reflect pain at the injection site. 3. Redefinition of a sub-responder to tetanus from a titer of <0.01 IU/mL to <0.1 IU/mL. 4. Addition of a text regarding the analyses of serious adverse events within 7 and 14 days following any of Doses 1 to 3 of PR5I or Control vaccines in Section 3.5.3.2 (Safety) and Section 3.5.5.2 (Statistical Methods for Safety Analysis). # Other changes in the amendment included adding further information to the product descriptions table in Section 3.6.1 (Product Descriptions).
08 July 2011	# Addition of the administration of a 2nd dose of ProQuad at the 13-month visit in order to complete the series for ProQuad, in alignment with the EU SmPC, and extension of the telephone contact at the end of the study (Visit 7) to 28 days postvaccination to align with the recommended safety follow-up period for live virus vaccines. # Other changes in the amendment: 1. Change of the recommended injection site of ProQuad. 2. Remove of the text reiterating that serum was to be tested for responses to all PR5I/Control antigens and that ProQuad antigens were to be tested from serum drawn at Visit 6 from Section 1.4 (Summary of Study Design), Section 2.4.1 (Summary of Study Design), and Section 3.2.4.10 (Treatment/Vaccination/Evaluation/Follow-Up). 3. Remove of the word 'SPONSOR' throughout Section 3.6 to indicate that only Merck, the SPONSOR Representative, was to supply and handle the clinical supplies. 4. Addition of text to Section 3.2.4.11.1 (Blinding) to clarify that all safety and immunogenicity assessments were to be performed by blinded site personnel. 5. Replacement of the abbreviation of 'PCV 13' with 'Prevenar 13™'. 6. Correction of the planned enrollment period to 'approximately 10 months' in Section 1.4 (Summary of Study Design) and Section 2.4.1 (Summary of Study Design). 7. Addition of text in Section 3.4.7 (Pharmacovigilance Regulatory Requirements) to clarify that the expectedness of serious adverse events for all licensed vaccines used during the study was based on the vaccine's SmPC. 8. Addition of text in Section 3.4.7 (Pharmacovigilance Regulatory Requirements) to clarify that any unexpected serious adverse event assessed as possibly, probably or definitely related to the study vaccine was to be reported to concerned Health Authorities in accordance with all applicable local laws and regulations. 9. Addition of updated SmPCs for Prevenar 13™, RotaTeq™ and INFANRIX™ hexa to Section 7 (Attachments).

08 February 2012	# Revision (for clarity) of the criterion for exclusion from the PP immunogenicity analysis related to vaccine dosing in Section 3.5.10. + changes and updates in Sections 1.4 (Summary of Study Design), 2.4.1 (Summary of Study Design), and 3.5.10 (Description of Protocol Violations) to reflect the clarification. # Other changes in the amendment: 1. Update of Table 3-1 in Section 3.2.4.10 (Treatment/Vaccination/Evaluation/Follow-Up) to change the recommendation to administer ProQuad™ in the right upper thigh at Visits 5 and 6 instead of the original recommendation to administer in the right lower thigh (in alignment with the SmPC for ProQuad™). Because of this change, the last dose of Prevenar 13™ at Visit 6 (administered concomitantly with ProQuad™) was to be administered in the right lower thigh (in alignment with the SmPC for Prevenar 13™). 2. Update of the paragraph on vaccine supplies in Section 3.6.4 (Storage and Handling Requirements – Vaccine Product) to reflect that new shippers were to be used to provide all clinical supplies to the sites. 3. Addition of updated SmPCs for Prevenar 13™, INFANRIX™ hexa and ProQuad™ to Section 7 Attachments.
13 March 2013	# Amendement date: 24 April 2013 (written after the global end of trial dated 13 March 2013) # Addition of a 2nd PP population (referred to as PP-RW) in addition to the existing PP population (referred to as PP-OW) to account for subjects who had blood draws outside of narrow protocol-defined visit windows. PP-RW is defined as the PP population using a blood draw sample window of Days 28 to 51 following Dose 3 or the Toddler dose. PP-OW is defined as the PP population using a blood draw sample window of Days 28 to 44 following Dose 3 or the Toddler dose. # Other changes in the amendment: 1. Update of the footnote in Section 1.4 (Summary of Study Design), regarding Prevenar 13™. 2. Revision of the criteria for systemic corticosteroid use resulting in exclusion from the PP analysis populations in Section 3.2.1 (Concomitant Medication(s)/Treatment(s)) to align with national vaccine policy and professional practice guidelines. 3. Revision of the assay descriptions for Poliovirus and detection of IgG antibodies to measles and rubella in Section 3.3.1 (Clinical and Laboratory Measurements for Immunogenicity). 4. Remove of the Summary of Product Characteristics for INFANRIX™ hexa, RotaTeq™, PREVENAR 13™ and ProQuad™ from Section 7 (Attachments). 5. Implementation of other general text changes throughout the protocol to improve clarity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported