



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, 4, and 11 to 12 Months

Summary

EudraCT number	2010-021491-28
Trial protocol	FI SE IT
Global end of trial date	09 October 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	V419-008
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01480258
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)	EMA-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	09 October 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 October 2013
Global end of trial reached?	Yes
Global end of trial date	09 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the immunogenicity of PR5I when given at 2, 4, and 11 to 12 months of age.

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 3 doses of the hexavalent PR5I vaccine when given at 2, 4 and 11 to 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	23 November 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	Sweden: 132
Country: Number of subjects enrolled	Finland: 919
Country: Number of subjects enrolled	Italy: 264
Worldwide total number of subjects	1315
EEA total number of subjects	1315

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)	1315
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 23 November 2011 (first subject entered) in 23 active centres in 3 European countries (Finland, Italy, and Sweden).

Pre-assignment

Screening details:

1325 subjects were screened.

1315 subjects were randomised.

1312 subjects were vaccinated.

1300 subjects received the 2 doses of the infant series (period 1).

1281 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	Investigator, Subject

Blinding implementation details:

The parent(s)/legal representative of the subject, the Investigator, laboratory testing personnel, and sponsor/sponsor representative personnel (except for an unblinded sponsor representative) 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 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).

Subjects also received either 1 dose of Rotarix (live human rotavirus RIX4414 strain) at 2 and 4 months of age (in Italy & Sweden) or 1 dose of RotaTaq (pentavalent combination live vaccine of 5 human-bovine reassortant rotavirus strains) at 2, 4, and 5 months of age (in Finland), both 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 2nd 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, separate limb from the concomitant vaccine), one dose at 2 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 and 4 months of age.	
Investigational medicinal product name	Rotarix™
Investigational medicinal product code	Rotarix
Other name	
Pharmaceutical forms	Oral liquid, Oral solution, Powder and solvent for oral solution
Routes of administration	Oral use
Dosage and administration details:	
1.5 mL, oral route, one dose at 2 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, 4 and 5 months of age.	
Note: The 3rd dose of RotaTeq was to be given to subjects at least 4 weeks after the 2nd dose and no later than 26 weeks of age.	

Arm title	INFANRIX hexa
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Arm description:

Subjects received at 2 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).

Subjects also received either 1 dose of Rotarix (live human rotavirus RIX4414 strain) at 2 and 4 months of age (in Italy & Sweden) or 1 dose of RotaTeq (pentavalent combination live vaccine of 5 human-bovine reassortant rotavirus strains) at 2, 4, and 5 months of age (in Finland), both 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 2nd 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, separate limb from the concomitant vaccine), one dose at 2 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 and 4 months of age.

Investigational medicinal product name	Rotarix™
Investigational medicinal product code	Rotarix
Other name	
Pharmaceutical forms	Oral liquid, Oral solution, Powder and solvent for oral solution
Routes of administration	Oral use

Dosage and administration details:

1.5 mL, oral route, one dose at 2 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, 4 and 5 months of age.

Note: The 3rd dose of RotaTeq was to be given to subjects at least 4 weeks after the 2nd dose and no later than 26 weeks of age.

Number of subjects in period 1	PR5I	INFANRIX hexa
Started	656	659
Completed	649	651
Not completed	7	8
Consent withdrawn by subject	1	6
Physician decision	-	1
Adverse event, non-fatal	1	1
Not vaccinated	3	-
Protocol deviation	2	-

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 (except for an unblinded sponsor representative) 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
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Arm title	PR5I
Arm description:	
# Subjects (arm 1 - period 1) received at 11 to 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 Prevenar 13 (PCV-13 = Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)) by IM route (opposite leg).	
# Blood samples were collected at Month 11 or 12 before any Toddler dose and 1 month (28 to 37 days) 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, separate limb from the concomitant vaccine), one dose at 11 to 12 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 11 to 12 months of age.	
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 Prevenar 13 (PCV-13 = Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)) by IM route (opposite leg).	
# Blood samples were collected at Month 11 or 12 before any Toddler dose and 1 month (28 to 37 days) after 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, separate limb from the concomitant vaccine), one dose at 11 to 12 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 11 to 12 months of age.	

Number of subjects in period 2 ^[1]	PR5I	INFANRIX hexa
Started	639	642
Completed	639	642

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, 10 subjects discontinued the study between the Infant Series and Toddler Dose: 1 "physician decision" and 9 "consent withdrawn by subject".

In the INFANRIX hexa arm, 9 subjects discontinued the study between the Infant Series and Toddler Dose: 2 "lost to follow-up", 1 "protocol deviation", and 6 "consent withdrawn by subject".

Baseline characteristics

Reporting groups

Reporting group title	PR5I
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Reporting group description:

Subjects received at 2 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).

Subjects also received either 1 dose of Rotarix (live human rotavirus RIX4414 strain) at 2 and 4 months of age (in Italy & Sweden) or 1 dose of RotaTeq (pentavalent combination live vaccine of 5 human-bovine reassortant rotavirus strains) at 2, 4, and 5 months of age (in Finland), both 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 2nd dose of infant series.

Reporting group title	INFANRIX hexa
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Reporting group description:

Subjects received at 2 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).

Subjects also received either 1 dose of Rotarix (live human rotavirus RIX4414 strain) at 2 and 4 months of age (in Italy & Sweden) or 1 dose of RotaTeq (pentavalent combination live vaccine of 5 human-bovine reassortant rotavirus strains) at 2, 4, and 5 months of age (in Finland), both 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 2nd dose of infant series.

Reporting group values	PR5I	INFANRIX hexa	Total
Number of subjects	656	659	1315
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	656	659	1315
Age continuous			
# Subjects vaccinated: age (in days) at date of vaccination dose 1.			
# Subjects randomised but not vaccinated: age (in days) calculated as date of visit 1 - date of birth.			
Units: days			
arithmetic mean	68	68.1	
standard deviation	± 10.3	± 10.5	-
Gender categorical Units: Subjects			
Female	323	313	636
Male	333	346	679

End points

End points reporting groups

Reporting group title	PR5I
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Reporting group description:

Subjects received at 2 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).

Subjects also received either 1 dose of Rotarix (live human rotavirus RIX4414 strain) at 2 and 4 months of age (in Italy & Sweden) or 1 dose of RotaTeq (pentavalent combination live vaccine of 5 human-bovine reassortant rotavirus strains) at 2, 4, and 5 months of age (in Finland), both 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 2nd dose of infant series.

Reporting group title	INFANRIX hexa
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Reporting group description:

Subjects received at 2 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).

Subjects also received either 1 dose of Rotarix (live human rotavirus RIX4414 strain) at 2 and 4 months of age (in Italy & Sweden) or 1 dose of RotaTeq (pentavalent combination live vaccine of 5 human-bovine reassortant rotavirus strains) at 2, 4, and 5 months of age (in Finland), both 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 2nd dose of infant series.

Reporting group title	PR5I
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Reporting group description:

Subjects (arm 1 - period 1) received at 11 to 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 Prevenar 13 (PCV-13 = Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)) by IM route (opposite leg).

Blood samples were collected at Month 11 or 12 before any Toddler dose and 1 month (28 to 37 days) after Toddler dose.

Reporting group title	INFANRIX hexa
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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 Prevenar 13 (PCV-13 = Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)) by IM route (opposite leg).

Blood samples were collected at Month 11 or 12 before any Toddler dose and 1 month (28 to 37 days) after Toddler dose.

Subject analysis set title	PR5I - Rotarix
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Subjects (arm 1 - period 1 - sub-group Rotarix) received 1 dose of PR5I (DTaP-HB-IPV-Hib) by intramuscular route (IM) + 1 dose of Prevenar 13 (PCV-13) by IM route (opposite leg) + 1 dose of Rotarix (in Italy & Sweden) by oral route at 2 and 4 months of age.

Blood samples were collected on Day 0 (D0) before any vaccination and at Month 5 (M5), i.e. 1 month after the 2nd dose of infant series.

Subject analysis set title	INFANRIX hexa - Rotarix
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Subjects (arm 2 - period 1 - sub-group Rotarix) received 1 dose of INFANRIX hexa (DTaP-HBV-IPV-Hib) by intramuscular route (IM) + 1 dose of Prevenar 13 (PCV-13) by IM route (opposite leg) + 1 dose of Rotarix (in Italy & Sweden) by oral route at 2 and 4 months of age.

Primary: Acceptability of antibody (Ab) response or seroresponse rates to all antigens contained in PR5I vaccine one month after the Toddler dose of PR5I (11 to 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 (11 to 12 months of age) ^[1]
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End point description:

% of subjects with an Ab titre ≥ 1.0 $\mu\text{g/mL}$ for Haemophilus influenzae type b (Hib) (polyribosylribitol phosphate, PRP); ≥ 10 mIU/mL for Hepatitis B (HBsAg); ≥ 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)) 1 month Post-Toddler dose of PR5I.

Seroresponse was defined: (1) If pre-Dose 1 Ab concentration (cc) was $< \text{LLOQ}$ (lower limit of quantitation), postvaccination Ab cc was $\geq \text{LLOQ}$, (2) If pre-Dose 1 Ab cc was $\geq \text{LLOQ}$, postvaccination Ab cc was $\geq$ prevaccination levels.

Ab titres were measured by Radioimmunoassay (RIA) for PRP, enhanced Chemiluminescence assay (ECi) for HBsAg, Micrometabolic inhibition test (MIT) for diphtheria & poliovirus, and Enzyme-Linked Immunosorbent Assay (ELISA) for PT, FHA, FIM, PRN & tetanus.

Analysis was done on the Per Protocol Revised Windows (PP-RW) population.

End point type	Primary
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End point timeframe:

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

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 endpoint includes only one arm.

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: 75% for PRP, PT, FHA, FIM & PRN, 80% for diphtheria, and 90% for HBsAg, tetanus and IPV1, 2 & 3.

Acceptability criteria were met for all PR5I antigens.

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

End point values	PR5I			
Subject group type	Reporting group			
Number of subjects analysed	638			
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-PRP ≥ 1.0 $\mu\text{g/mL}$ (N=454)	89.87 (86.72 to 92.49)			
Anti-HBsAg ≥ 10 mIU/mL (N=377)	98.14 (96.21 to 99.25)			
Anti-Diphtheria ≥ 0.1 IU/mL (N= 590)	98.64 (97.35 to 99.41)			
Anti-Tetanus ≥ 0.1 IU/mL (N=589)	99.83 (99.06 to 100)			
Anti-PT seroresponse (N=566)	99.12 (97.95 to 99.71)			
Anti-FHA seroresponse (N=582)	97.42 (95.78 to 98.55)			
Anti-FIM seroresponse (N=581)	98.28 (96.86 to 99.17)			
Anti-PRN seroresponse (N=582)	96.91 (95.16 to 98.16)			
Anti-IPV1 ≥ 8 (1/dil) (N=591)	99.32 (98.28 to 99.82)			
Anti-IPV2 ≥ 8 (1/dil) (N=591)	99.83 (99.06 to 100)			

Anti-IPV3 ≥ 8 (1/dil) (N=590)	99.49 (98.52 to 99.9)			
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Statistical analyses

No statistical analyses for this end point

Secondary: Non-inferiority of antibody (Ab) response rate to Haemophilus influenzae type b (PRP) one month after the 2nd dose of PR5I (4 months of age) as compared with INFANRIX hexa

End point title	Non-inferiority of antibody (Ab) response rate to Haemophilus influenzae type b (PRP) one month after the 2nd dose of PR5I (4 months of age) as compared with INFANRIX hexa
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End point description:

Percentage of subjects with an Ab titre ≥ 1.0 $\mu\text{g/mL}$ for Hib (polyribosylribitol phosphate, PRP) measured by RIA 1 month Post-Dose 2 of PR5I or INFANRIX hexa.

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 2 or Post-Toddler dose.

Note: (N=***, ***) represents the number of assessed subjects in the PR5I and INFANRIX hexa groups, respectively.

End point type	Secondary
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End point timeframe:

1 month after the 2nd dose of PR5I or INFANRIX hexa (Post-Dose 2).

End point values	PR5I	INFANRIX hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	649	651		
Units: Percentage of subjects				
number (not applicable)				
Anti-PRP ≥ 1.0 $\mu\text{g/mL}$ (N=609, 592)	72.86	26.66		

Statistical analyses

Statistical analysis title	Non-inferiority for PRP
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Statistical analysis description:

The estimate of the difference between PR5I & INFANRIX hexa groups in PRP response rate (based on Ab titre ≥ 1.0 $\mu\text{g/mL}$) 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=609, 592 (PR5I group, INFANRIX hexa group).

Comparison groups	PR5I v INFANRIX hexa
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Number of subjects included in analysis	1300
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
P-value	< 0.001
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages of subjects
Point estimate	46.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	41.05
upper limit	51.06

Notes:

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

Secondary: Superiority of antibody (Ab) response rates to Haemophilus influenzae type b (PRP) one month after the 2nd dose of PR5I (4 months of age) as compared with INFANRIX hexa

End point title	Superiority of antibody (Ab) response rates to Haemophilus influenzae type b (PRP) one month after the 2nd dose of PR5I (4 months of age) as compared with INFANRIX hexa
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End point description:

Percentage of subjects with an Ab titre ≥ 1.0 $\mu\text{g/mL}$ for Hib (polyribosylribitol phosphate, PRP) measured by RIA 1 month Post-Dose 2 of PR5I or INFANRIX hexa.

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
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End point timeframe:

1 month after the 2nd dose of PR5I or INFANRIX hexa (Post-Dose 2).

End point values	PR5I	INFANRIX hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	649	651		
Units: Percentage of subjects				
number (not applicable)				
Anti-PRP ≥ 1.0 $\mu\text{g/mL}$ (N=609, 592)	72.86	26.66		

Statistical analyses

Statistical analysis title	Superiority for PRP
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Statistical analysis description:

The estimate of the difference between PR5I & INFANRIX hexa groups in PRP response rate (based on Ab titre ≥ 1.0 $\mu\text{g/mL}$) 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 0, it was concluded that PR5I group response rate was superior to INFANRIX hexa group response rate.

Analysis was done on the PP-RW population: N=609, 592 (PR5I group, INFANRIX hexa group).

Comparison groups	PR5I v INFANRIX hexa
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Number of subjects included in analysis	1300
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	< 0.001
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages of subjects
Point estimate	46.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	41.05
upper limit	51.06

Notes:

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

Secondary: Non-inferiority of antibody (Ab) response rates to PR5I antigens one month after the Toddler dose of PR5I (11 to 12 months of age) as compared with INFANRIX hexa

End point title	Non-inferiority of antibody (Ab) response rates to PR5I antigens one month after the Toddler dose of PR5I (11 to 12 months of age) as compared with INFANRIX hexa
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End point description:

% of subjects with an Ab titre ≥ 1.0 $\mu\text{g/mL}$ for Hib (PRP); ≥ 10 mIU/mL for Hepatitis B (HBsAg); ≥ 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) & Pertactin (PRN)) 1 month Post-Toddler dose of PR5I.

Seroresponse was defined: (1) If pre-Dose 1 Ab concentration (cc) was <LLOQ (lower limit of quantitation), postvaccination Ab cc was $\geq$ LLOQ, (2) If pre-Dose 1 Ab cc was $\geq$ LLOQ, postvaccination Ab cc was $\geq$ prevaccination levels.

Ab titres were measured by RIA for PRP, Eci for HBsAg, MIT for diphtheria & poliovirus, and ELISA for PT, FHA, PRN & 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	Secondary
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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	638	642		
Units: Percentage of subjects				
number (not applicable)				
Anti-PRP ≥ 1.0 $\mu\text{g/mL}$ (N=454, 478)	89.8	91.06		
Anti-HBsAg ≥ 10 mIU/mL (N=377, 391)	98.14	98.73		
Anti-Diphtheria ≥ 0.1 IU/mL (N= 590, 578)	98.62	99.83		
Anti-Tetanus ≥ 0.1 IU/mL (N=589, 577)	99.83	100		
Anti-PT seroresponse (N=566, 561)	99.11	99.64		
Anti-FHA seroresponse (N=582, 571)	97.4	99.13		
Anti-PRN seroresponse (N=582, 572)	96.86	98.28		
Anti-IPV1 ≥ 8 (1/dil) (N=591, 580)	99.32	99.83		

Anti-IPV2 ≥ 8 (1/dil) (N=591, 579)	99.83	100		
Anti-IPV3 ≥ 8 (1/dil) (N=590, 579)	99.49	99.65		

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 ≥ 1.0 $\mu\text{g/mL}$) 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=454, 478 (PR5I group, INFANRIX hexa group).	
Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1280
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	-1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.13
upper limit	2.52

Notes:

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

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=377, 391 (PR5I group, INFANRIX hexa group).	
Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1280
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	-0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.66
upper limit	1.35

Notes:

[5] - 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 ≥ 0.1 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=590, 578 (PR5I group, INFANRIX hexa group).	
Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1280
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	-1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.54
upper limit	-0.22

Notes:

[6] - 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 ≥ 0.1 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=589, 577 (PR5I group, INFANRIX hexa group).	
Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1280
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	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.95
upper limit	0.5

Notes:

[7] - 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=566, 561 (PR5I group, INFANRIX hexa group).

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1280
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	-0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.75
upper limit	0.49

Notes:

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

Statistical analysis title	Non-inferiority for FHA
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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=582, 571 (PR5I group, INFANRIX hexa group).

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1280
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	-1.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.47
upper limit	-0.26

Notes:

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

Statistical analysis title	Non-inferiority for PRN
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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=582, 572 (PR5I group, INFANRIX hexa group).

Comparison groups	PR5I v INFANRIX hexa
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Number of subjects included in analysis	1280
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	-1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.42
upper limit	0.39

Notes:

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

Statistical analysis title	Non-inferiority for IPV1
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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=591, 580 (PR5I group, INFANRIX hexa group).

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1280
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	-0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.59
upper limit	0.34

Notes:

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

Statistical analysis title	Non-inferiority for IPV2
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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=591, 579 (PR5I group, INFANRIX hexa group).

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1280
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	-0.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.96
upper limit	0.49

Notes:

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

Statistical analysis title	Non-inferiority for IPV3
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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=590, 579 (PR5I group, INFANRIX hexa group).

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1280
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	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	0.82

Notes:

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

Secondary: Non-inferiority of Rotavirus response (geometric mean titer, GMT) one month after the 2nd dose of Rotarix (4 months of age) administered concomitantly with PR5I versus INFANRIX hexa

End point title	Non-inferiority of Rotavirus response (geometric mean titer, GMT) one month after the 2nd dose of Rotarix (4 months of age) administered concomitantly with PR5I versus INFANRIX hexa
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End point description:

Antibody titres expressed in units/mL were measured for Rotavirus IgA by Enzyme Immunoassay (EIA), 1 month after the 2nd dose of Rotarix, administered concomitantly with PR5I or INFANRIX hexa (Post-Dose 2).

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

End point type	Secondary
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End point timeframe:

1 month after the 2nd dose of Rotarix, administered concomitantly with PR5I or INFANRIX hexa (Post-Dose 2).

End point values	PR5I - Rotarix	INFANRIX hexa - Rotarix		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	160	171		
Units: Titre				
geometric mean (confidence interval 95%)				
Rotavirus IgA GMT (N=160, 171)	96.41 (71.69 to 129.65)	122.24 (92.48 to 161.58)		

Statistical analyses

Statistical analysis title	Non-inferiority for Rotavirus IgA
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Statistical analysis description:

The estimate for anti-rotavirus IgA GMT ratio (PR5I group/INFANRIX hexa group) was calculated with its 1-sided P-value and 2-sided 95% CI. If the lower bound of the 95% CI for GMT ratio was greater than 0.50 (non-inferiority margin), it was concluded that the Rotarix antigen response in the PR5I group was not inferior to the Rotarix antigen response in the INFANRIX hexa group.

Analysis was done on the PP-RW population, Subgroups Rotarix: N=160, 171 (PR5I group, INFANRIX hexa group).

Comparison groups	PR5I - Rotarix v INFANRIX hexa - Rotarix
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[14]
P-value	= 0.011
Method	ANCOVA
Parameter estimate	Geometric Mean Titer (GMT) ratio
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.2

Notes:

[14] - Statistical analysis was based on an ANCOVA model.

Secondary: Global safety from D1 to D15 after any vaccination

End point title	Global safety from D1 to D15 after any vaccination
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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 vaccination. Solicited injection-site and systemic AEs were reported daily from D1 to D5 after each vaccination. AEs at injection sites were always considered as vaccine-related (V-related) (Injection-Site Reactions (ISRs)).

The investigator had to assess whether systemic AEs were 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=1312) who received at least 1 vaccination and who had safety follow-up.

End point type	Secondary
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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	653	659		
Units: Percentage of subjects				
number (not applicable)				
At least 1 ISR or systemic AE (D1-D15)	99.5	99.2		
At least 1 ISR or V-related systemic AE (D1-D15)	99.5	98.8		
At least 1 ISR (D1-D15)	90.8	88.2		
At least 1 solicited ISR (D1-D5)	90.4	87.9		
At least 1 systemic AE (D1-D15)	99.1	98.9		
At least 1 V-related systemic AE (D1-D15)	99.1	98.3		
At least 1 solicited systemic AE (D1-D5)	99.1	98.3		
At least 1 V-related solicited systemic AE (D1-D5)	99.1	98.2		

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 an overall trend and not any specific difference. If 0.0 was excluded from the 95% CI, the trend could not be ruled out. Analysis was done on the All Subjects as Treated (ASaT) population.	
Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1312
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	-0.7
upper limit	1.4

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 an overall trend and not any specific difference. If 0.0 was excluded from the 95% CI, the trend could not be ruled out. Analysis was done on the All Subjects as Treated (ASaT) population.	
Comparison groups	PR5I v INFANRIX hexa

Number of subjects included in analysis	1312
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	-0.3
upper limit	2

Statistical analysis title	At least 1 ISR
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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 an overall trend and not any specific difference. If 0.0 was excluded from the 95% CI, the trend could not be ruled out. Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	6

Statistical analysis title	At least 1 solicited ISR
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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 an overall trend and not any specific difference. If 0.0 was excluded from the 95% CI, the trend could not be ruled out. Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1312
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	-0.9
upper limit	5.9

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 an overall trend and not any specific difference. If 0.0 was excluded from the 95% CI, the trend could not be ruled out. Analysis was done on the All Subjects as Treated (ASaT) population.	
Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1312
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	-1.1
upper limit	1.4

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 an overall trend and not any specific difference. If 0.0 was excluded from the 95% CI, the trend could not be ruled out. Analysis was done on the All Subjects as Treated (ASaT) population.	
Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1312
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	-0.5
upper limit	2.2

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 an overall trend and not any specific difference. If 0.0 was excluded from the 95% CI, the trend could not be ruled out. Analysis was done on the All Subjects as Treated (ASaT) population.	
Comparison groups	PR5I v INFANRIX hexa

Number of subjects included in analysis	1312
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	-0.5
upper limit	2.2

Statistical analysis title	At least 1 vaccine-related solicited systemic AE
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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 an overall trend and not any specific difference. If 0.0 was excluded from the 95% CI, the trend could not be ruled out. Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1312
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	-0.4
upper limit	2.3

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
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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=1312) who received at least 1 vaccination and who had safety follow-up.

End point type	Secondary
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End point timeframe:

From Day 1 (D1) to D5 after vaccination.

End point values	PR5I	INFANRIX hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	653	659		
Units: Percentage of subjects				
number (not applicable)				
Injection-site erythema	68.6	60.4		
Injection-site pain	73.4	70		
Injection-site swelling	56.8	49.3		

Statistical analyses

Statistical analysis title	Injection-site erythema
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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	1312
Analysis specification	Pre-specified
Analysis type	other ^[15]
Parameter estimate	Risk difference (RD)
Point estimate	8.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	3
upper limit	13.3

Notes:

[15] - Injection-site erythema: the 95% CI of the difference between the PR5I and INFANRIX™ hexa groups excluded 0 and was therefore statistically significant. The difference was not considered to be clinically significant as none of these events were considered serious or led to study discontinuation, and the majority were mild or moderate in intensity.

Statistical analysis title	Injection-site pain
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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	1312
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	3.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	8.3

Statistical analysis title	Injection-site swelling
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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	1312
Analysis specification	Pre-specified
Analysis type	other ^[16]
Parameter estimate	Risk difference (RD)
Point estimate	7.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.1
upper limit	12.9

Notes:

[16] - Injection-site swelling: the 95% CI of the difference between the PR5I and INFANRIX™ hexa groups excluded 0 and was therefore statistically significant. The difference was not considered to be clinically significant as none of these events were considered serious or led to study discontinuation, and the majority were mild or moderate in intensity.

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
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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 $\geq 1\%$ are reported below.

Analysis was done on the All Subjects as Treated (ASaT) population, i.e. all randomised subjects (N=1312) who received at least 1 vaccination and who had safety follow-up.

End point type	Secondary
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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	653	659		
Units: Percentage of subjects				
number (not applicable)				
Injection-site bruising	0.9	2		
Injection-site haemorrhage	1.8	1.8		
Injection-site induration	15.8	13.2		
Injection-site nodule	1.1	0.8		
Injection-site warmth	2.3	1.2		

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 an overall trend and not any specific difference. If 0.0 was excluded from the 95% CI, the trend could not be ruled out. Analysis was done on the All Subjects as Treated (ASaT) population.	
Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1312
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	-2.5
upper limit	0.3

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 an overall trend and not any specific difference. If 0.0 was excluded from the 95% CI, the trend could not be ruled out. Analysis was done on the All Subjects as Treated (ASaT) population.	
Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	1.6

Statistical analysis title	Injection-site induration
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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 an overall trend and not any specific difference. If 0.0 was excluded from the 95% CI, the trend could not be ruled out.

Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	6.4

Statistical analysis title	Injection-site nodule
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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 an overall trend and not any specific difference. If 0.0 was excluded from the 95% CI, the trend could not be ruled out.

Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1312
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	-0.8
upper limit	1.5

Statistical analysis title	Injection-site warmth
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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 an overall trend and not any specific difference. If 0.0 was excluded from the 95% CI, the trend could not be ruled out.

Analysis was done on the All Subjects as Treated (ASaT) population.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1312
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	-0.4
upper limit	2.7

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
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End point description:

Solicited systemic AEs were defined as crying, decreased appetite, irritability, pyrexia (rectal temperature $\geq 38.0^{\circ}\text{C}$), 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=1312) who received at least 1 vaccination and who had safety follow-up.

End point type	Secondary
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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	653	659		
Units: Percentage of subjects				
number (not applicable)				
Crying	89.3	87.1		
Decreased appetite	65.8	62.2		
Irritability	91.6	89.4		
Pyrexia	73.8	67.4		
Somnolence	86.1	80.3		
Vomiting	32.8	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.	
Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	5.7

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.	
Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	8.8

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.	
Comparison groups	PR5I v INFANRIX hexa

Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	5.4

Statistical analysis title	Pyrexia
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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.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other ^[17]
Parameter estimate	Risk difference (RD)
Point estimate	6.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.5
upper limit	11.3

Notes:

[17] - Pyrexia: the 95% CI of the difference between PR5I and INFANRIX™ hexa groups excluded 0 and was statistically significant. The difference was not considered to be clinically significant as the majority were of mild to moderate intensity and did not result in any study discontinuations.

Statistical analysis title	Somnolence
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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.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other ^[18]
Parameter estimate	Risk difference (RD)
Point estimate	5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	9.8

Notes:

[18] - The 95% CI of the difference between PR5I and INFANRIX™ hexa groups excluded 0 and was statistically significant. The difference was not considered to be clinically significant as the majority were of mild to moderate intensity and did not result in any study discontinuations.

Statistical analysis title	Vomiting
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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.

Comparison groups	PR5I v INFANRIX hexa
Number of subjects included in analysis	1312
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	6.9

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=1312) who received at least 1 vaccination and who had safety follow-up.

Unsolicited non-serious systemic AEs (vaccine-related or not) with incidence $\geq 2.5\%$ are presented hereafter.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	PR5I
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Reporting group description:

Subjects received 1 dose of PR5I (DTaP-HB-IPV-Hib) by intramuscular route (IM) + 1 dose of Prevenar 13 (PCV-13) by IM route (opposite leg) at 2 and 4 months of age.

Subjects also received either 1 dose of Rotarix at 2 and 4 months of age (in Italy & Sweden) or 1 dose of RotaTeq at 2, 4, and 5 months of age (in Finland), both by oral route.

Respectively, 342 (52.4%) subjects reported at least 1 unsolicited non-serious systemic AE, and 172 (26.3%) subjects reported at least 1 vaccine-related unsolicited non-serious systemic AE within 15 days after any vaccination.

Reporting group title	INFANRIX hexa
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Reporting group description:

Subjects received 1 dose of INFANRIX hexa (DTaP-HBV-IPV-Hib) by intramuscular route (IM) + 1 dose of Prevenar 13 (PCV-13) by IM route (opposite leg) at 2 and 4 months of age.

Subjects also received either 1 dose of Rotarix at 2 and 4 months of age (in Italy & Sweden) or 1 dose of RotaTeq at 2, 4, and 5 months of age (in Finland), both by oral route.

Respectively, 319 (48.4%) subjects reported at least 1 unsolicited non-serious systemic AE, and 149 (22.6%) 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	5 / 653 (0.77%)	7 / 659 (1.06%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Congenital, familial and genetic disorders			
Heart disease congenital			
subjects affected / exposed	1 / 653 (0.15%)	0 / 659 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitello-intestinal duct remnant			

subjects affected / exposed	0 / 653 (0.00%)	1 / 659 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Kawasaki's disease			
subjects affected / exposed	0 / 653 (0.00%)	1 / 659 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 653 (0.00%)	1 / 659 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Idiopathic thrombocytopenic purpura			
subjects affected / exposed	1 / 653 (0.15%)	0 / 659 (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			
Pyrexia			
subjects affected / exposed	0 / 653 (0.00%)	1 / 659 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection-site abscess			
subjects affected / exposed	0 / 653 (0.00%)	1 / 659 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 653 (0.15%)	0 / 659 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	0 / 653 (0.00%)	1 / 659 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 653 (0.00%)	1 / 659 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 653 (0.15%)	1 / 659 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 653 (0.15%)	0 / 659 (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	342 / 653 (52.37%)	319 / 659 (48.41%)	
General disorders and administration site conditions			
Crying			
subjects affected / exposed	19 / 653 (2.91%)	16 / 659 (2.43%)	
occurrences (all)	19	16	
Irritability			
subjects affected / exposed	14 / 653 (2.14%)	20 / 659 (3.03%)	
occurrences (all)	14	20	
Pyrexia			
subjects affected / exposed	32 / 653 (4.90%)	28 / 659 (4.25%)	
occurrences (all)	32	28	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed occurrences (all)	20 / 653 (3.06%) 20	10 / 659 (1.52%) 10	
Constipation subjects affected / exposed occurrences (all)	22 / 653 (3.37%) 22	16 / 659 (2.43%) 16	
Diarrhoea subjects affected / exposed occurrences (all)	76 / 653 (11.64%) 76	70 / 659 (10.62%) 70	
Flatulence subjects affected / exposed occurrences (all)	29 / 653 (4.44%) 29	25 / 659 (3.79%) 25	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	30 / 653 (4.59%) 30	24 / 659 (3.64%) 24	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	35 / 653 (5.36%) 35	36 / 659 (5.46%) 36	
Otitis media subjects affected / exposed occurrences (all)	24 / 653 (3.68%) 24	15 / 659 (2.28%) 15	
Rhinitis subjects affected / exposed occurrences (all)	34 / 653 (5.21%) 34	41 / 659 (6.22%) 41	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	42 / 653 (6.43%) 42	44 / 659 (6.68%) 44	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 April 2011	Protocol Amendment submitted to the regulatory authority in Finland only. # This amendment was in response to the change in Rotarix™ availability in some EU countries. This amendment allowed for subsets of subjects to receive 1 of 2 available rotavirus vaccines, either Rotarix™ or RotaTeq™. The specific primary changes were as follows: 1. Designation that a subset of subjects were to receive Rotarix™ concomitantly with PR5I or INFANRIX™ hexa, while another subset of subjects were to receive RotaTeq™ concomitantly with PR5I or INFANRIX™ hexa. Vaccine designation was to be site specific. 2. Revision of the power statement for the secondary hypothesis for Rotarix™ immunogenicity since Rotarix™ was to be administered to a subset of subjects, and not the entire study population as the original protocol indicated. 3. Indication that RotaTeq™ was to be administered at 2, 4, and 5 months of age. This dosing schedule was consistent with the product label. # In addition, the text in all relevant sections was updated to reflect a change in timing of when non-study vaccines could be received during the study; non-study licensed pediatric vaccines were not to be administered within 30 days before or after any dose of study vaccine, except for inactivated influenza vaccine, which was not to be administered within 14 days before or after any dose of study vaccine.
13 May 2011	Protocol Amendment submitted to the regulatory authority in Finland, Italy and Sweden. This amendment stated that RotaTeq™, a vaccine administered concomitantly with PR5I that was not evaluated for immunogenicity, was to be supplied centrally by the Sponsor Representative (it was originally planned to be sourced locally by study sites, but local sourcing was not operationally feasible). This was also to have the additional benefit of greater control over vaccine accountability and cold-chain.
20 January 2012	Country-specific protocol amendment for Finland. This amendment allowed the 1st dose of RotaTeq™ to be given in Finland prior to Visit 1 outside the study, as RotaTeq™ is recommended to be given as early as 6 weeks of age in the Finnish pediatric vaccination schedule. This amendment was to allow for flexibility for study entry within the full prespecified age range (46 to 89 days), even if a subject had received RotaTeq™ through the Finnish national vaccine program.
25 April 2013	Country-specific protocol amendment for Finland. # Section 2.7.1, Immunogenicity of PR5I: - Addition of a new primary statistical analysis method for all GMT analyses (i.e., MI ANCOVA) to account for missing baseline titers due to limited serum volumes obtained from 2-month old infant subjects at study entry. - Addition of a second PP population (referred to as PP-RW) in addition to the existing PP population (referred to as PP-OW) to account for subjects who received study vaccinations and/or blood draws outside of narrow protocol-defined visit windows. The success of the hypothesis test will be based on the results from the PP-RW population. PP-RW is defined as the PP population using a blood draw sample window of Days 28 to 51 following Dose 2 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 2 or the Toddler dose. The change to the SAP was introduced into all 4 Phase III studies (V419-005, V419-006, V419-007, and V419-008). # Section 3.5, SAP: - Addition of 2 sensitivity analyses: (1) analysis of GMT endpoints with no baseline adjustment and (2) analysis of GMT endpoints based on data from subjects with both baseline and postvaccination titers to support the ANCOVA MI primary analysis for GMT endpoints.

26 April 2013	Protocol Amendment applicable only to Italy and Sweden. Same as Protocol Amendment 4 (issued on 25 April 2013) which was only applicable to Finland.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported