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 (V419-007-03)

Summary

EudraCT number	2010-021490-37
Trial protocol	BE FI DE
Global end of trial date	03 March 2013

Results information

Result version number	v2 (current)
This version publication date	15 November 2019
First version publication date	02 August 2015
Version creation reason	

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	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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	03 March 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 March 2013
Global end of trial reached?	Yes
Global end of trial date	03 March 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study determined whether participants who receive the vaccine V419 at 2, 3, 4, and 12 months of age have an acceptable immune response to the vaccine. The study also determined whether the immune response to V419 is similar to that of participants who receive a licensed vaccine control.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

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: 264
Worldwide total number of subjects	1250
EEA total number of subjects	1250

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)	1250
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: -

Pre-assignment

Screening details:

Healthy infants 46 to 74 days old were enrolled in this study.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	PR5I

Arm description:

The PR5I group received V419, Prevenar 13™, and RotaTeq™ at 2, 3, and 4 months; followed by V419 and ProQuad™ at 12 months, and Prevenar 13™ and ProQuad™ at 13 months.

Arm type	Experimental
Investigational medicinal product name	V419
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

V419 (Diphtheria and Tetanus Toxoids and Acellular Pertussis
Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [MeningococcalOuter Membrane Protein Complex], and Hepatitis B [Recombinant] Vaccine) 0.5 mL intramuscular
injection at 2, 3, 4, and 12 months of age.

Investigational medicinal product name	Prevenar 13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Prevenar 13 0.5 mL intramuscular injection at 2, 3, 4,and 13 months of age

Investigational medicinal product name	RotaTeq
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

RotaTeq (pentavalent combination live vaccine of 5 human-bovine reassortant rotavirus strains) 2 mL oral dose at 2, 3, and 4 months of age

Investigational medicinal product name	ProQuad™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ProQuad™ 0.5 mL subcutaneous injection at 12 and 13 months of age

Arm title	INFANRIX™ hexa

Arm description:

The INFANRIX™ hexa group received INFANRIX™ hexa, Prevenar 13™, and RotaTeq™ at 2, 3, and 4 months; followed by INFANRIX™ hexa and ProQuad™ at 12 months; and Prevenar 13™ and ProQuad™ at 13 months.

Arm type	Active comparator
Investigational medicinal product name	INFANRIX™ hexa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

INFANRIX™ hexa 0.5 mL intramuscular injection at 2, 3, 4, and 12 months of age.

Investigational medicinal product name	ProQuad™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ProQuad™ 0.5 mL subcutaneous injection at 12 and 13 months of age

Investigational medicinal product name	RotaTeq
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

RotaTeq (pentavalent combination live vaccine of 5 human-bovine reassortant rotavirus strains) 2 mL oral dose at 2, 3, and 4 months of age

Number of subjects in period 1	PR5I	INFANRIX™ hexa
Started	628	622
Site 0048 Excluded	611	606
Treated	610	605
Completed	599	590
Not completed	29	32
Consent withdrawn by subject	11	8
Not Vaccinated	-	1
Adverse event, non-fatal	-	5
Site 0048 Participants	17	16
Lost to follow-up	-	2

Protocol deviation	1	-

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	PR5I

Arm description:

The PR5I group received V419, Prevenar 13™, and RotaTeq™ at 2, 3, and 4 months; followed by V419 and ProQuad™ at 12 months, and Prevenar 13™ and ProQuad™ at 13 months.

Arm type	Experimental
Investigational medicinal product name	V419
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

V419 (Diphtheria and Tetanus Toxoids and Acellular Pertussis
Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [MeningococcalOuter Membrane Protein Complex], and Hepatitis B [Recombinant] Vaccine) 0.5 mL intramuscular
injection at 2, 3, 4, and 12 months of age.

Investigational medicinal product name	Prevenar 13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Prevenar 13 0.5 mL intramuscular injection at 2, 3, 4,and 13 months of age

Investigational medicinal product name	RotaTeq
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

RotaTeq (pentavalent combination live vaccine of 5 human-bovine reassortant rotavirus strains) 2 mL oral dose at 2, 3, and 4 months of age

Investigational medicinal product name	ProQuad™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection

Routes of administration	Subcutaneous use

Dosage and administration details:

ProQuad™ 0.5 mL subcutaneous injection at 12 and 13 months of age

Arm title	INFANRIX™ hexa

Arm description:

The INFANRIX™ hexa group received INFANRIX™ hexa, Prevenar 13™, and RotaTeq™ at 2, 3, and 4 months; followed by INFANRIX™ hexa and ProQuad™ at 12 months; and Prevenar 13™ and ProQuad™ at 13 months.

Arm type	Active comparator
Investigational medicinal product name	INFANRIX™ hexa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

INFANRIX™ hexa 0.5 mL intramuscular injection at 2, 3, 4, and 12 months of age.

Investigational medicinal product name	ProQuad™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ProQuad™ 0.5 mL subcutaneous injection at 12 and 13 months of age

Investigational medicinal product name	RotaTeq
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

RotaTeq (pentavalent combination live vaccine of 5 human-bovine reassortant rotavirus strains) 2 mL oral dose at 2, 3, and 4 months of age

Number of subjects in period 2	PR5I	INFANRIX™ hexa
Started	599	590
Completed	591	581
Not completed	8	9
Consent withdrawn by subject	6	7
Physician decision	-	1
Lost to follow-up	2	-
Protocol deviation	-	1

Period 3

Period 3 title	Toddler Dose
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	PR5I

Arm description:

The PR5I group received V419, Prevenar 13™, and RotaTeq™ at 2, 3, and 4 months; followed by V419 and ProQuad™ at 12 months, and Prevenar 13™ and ProQuad™ at 13 months.

Arm type	Experimental
Investigational medicinal product name	V419
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

V419 (Diphtheria and Tetanus Toxoids and Acellular Pertussis
Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [MeningococcalOuter Membrane Protein Complex], and Hepatitis B [Recombinant] Vaccine) 0.5 mL intramuscular
injection at 2, 3, 4, and 12 months of age.

Investigational medicinal product name	Prevenar 13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Prevenar 13 0.5 mL intramuscular injection at 2, 3, 4,and 13 months of age

Investigational medicinal product name	RotaTeq
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, Injection
Routes of administration	Intramuscular use

Dosage and administration details:

RotaTeq (pentavalent combination live vaccine of 5 human-bovine reassortant rotavirus strains) 2 mL oral dose at 2, 3, and 4 months of age

Investigational medicinal product name	ProQuad™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ProQuad™ 0.5 mL subcutaneous injection at 12 and 13 months of age

Arm title	INFANRIX™ hexa

Arm description:

The INFANRIX™ hexa group received INFANRIX™ hexa, Prevenar 13™, and RotaTeq™ at 2, 3, and 4 months; followed by INFANRIX™ hexa and ProQuad™ at 12 months; and Prevenar 13™ and ProQuad™ at 13 months.

Arm type	Active comparator

Investigational medicinal product name	INFANRIX™ hexa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

INFANRIX™ hexa 0.5 mL intramuscular injection at 2, 3, 4, and 12 months of age.

Investigational medicinal product name	RotaTeq
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, Injection
Routes of administration	Intramuscular use

Dosage and administration details:

RotaTeq (pentavalent combination live vaccine of 5 human-bovine reassortant rotavirus strains) 2 mL oral dose at 2, 3, and 4 months of age

Investigational medicinal product name	ProQuad™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ProQuad™ 0.5 mL subcutaneous injection at 12 and 13 months of age

Number of subjects in period 3	PR5I	INFANRIX™ hexa
Started	590	582
Completed	539	548
Not completed	51	35
Transferred to other arm/group	1	-
Did not receive ProQuad	50	35
Joined	0	1
Transferred in from other group/arm	-	1

Period 4

Period 4 title	Post-Treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes

Arm title	PR5I

Arm description:

The PR5I group received V419, Prevenar 13™, and RotaTeq™ at 2, 3, and 4 months; followed by V419 and ProQuad™ at 12 months, and Prevenar 13™ and ProQuad™ at 13 months.

Arm type	Experimental
Investigational medicinal product name	V419
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

V419 (Diphtheria and Tetanus Toxoids and Acellular Pertussis
Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [MeningococcalOuter Membrane Protein Complex], and Hepatitis B [Recombinant] Vaccine) 0.5 mL intramuscular
injection at 2, 3, 4, and 12 months of age.

Investigational medicinal product name	Prevenar 13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Prevenar 13 0.5 mL intramuscular injection at 2, 3, 4,and 13 months of age

Investigational medicinal product name	RotaTeq
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, Injection
Routes of administration	Intramuscular use

Dosage and administration details:

RotaTeq (pentavalent combination live vaccine of 5 human-bovine reassortant rotavirus strains) 2 mL oral dose at 2, 3, and 4 months of age

Investigational medicinal product name	ProQuad™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ProQuad™ 0.5 mL subcutaneous injection at 12 and 13 months of age

Arm title	INFANRIX™ hexa

Arm description:

The INFANRIX™ hexa group received INFANRIX™ hexa, Prevenar 13™, and RotaTeq™ at 2, 3, and 4 months; followed by INFANRIX™ hexa and ProQuad™ at 12 months; and Prevenar 13™ and ProQuad™ at 13 months.

Arm type	Active comparator
Investigational medicinal product name	INFANRIX™ hexa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

INFANRIX™ hexa 0.5 mL intramuscular injection at 2, 3, 4, and 12 months of age.

Investigational medicinal product name	RotaTeq
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Inhalation powder, Injection
Routes of administration	Intramuscular use

Dosage and administration details:

RotaTeq (pentavalent combination live vaccine of 5 human-bovine reassortant rotavirus strains) 2 mL oral dose at 2, 3, and 4 months of age

Investigational medicinal product name	ProQuad™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ProQuad™ 0.5 mL subcutaneous injection at 12 and 13 months of age

Number of subjects in period 4	PR5I	INFANRIX™ hexa
Started	539	548
Completed	539	545
Not completed	0	3
Consent withdrawn by subject	-	1
Adverse event, non-fatal	-	2

Baseline characteristics

Subject analysis sets	
Subject analysis set title	PR5I
Subject analysis set type	Per protocol

Subject analysis set description:

The PR5I group received V419, Prevenar 13™, and RotaTeq™ at 2, 3, and 4 months; followed by V419 and ProQuad™ at 12 months, and Prevenar 13™ and ProQuad™ at 13 months. All randomized participants excluding participants from site 0048.

Subject analysis set title	INFANRIX™ hexa
Subject analysis set type	Per protocol

Subject analysis set description:

The INFANRIX™ hexa group received INFANRIX™ hexa, Prevenar 13™, and RotaTeq™ at 2, 3, and 4 months; followed by INFANRIX™ hexa and ProQuad™ at 12 months; and Prevenar 13™ and ProQuad™ at 13 months. All randomized participants excluding participants from site 0048.

Reporting group values	PR5I	INFANRIX™ hexa	
Number of subjects	611	606	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	611	606	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units:			
	62 ± 46	62 ± 46	
Gender Categorical Units: Subjects			
Female	291	290	
Male	320	316	
Age Continuous Units: Days			
arithmetic mean	61.4	61.5	
standard deviation	± 6.9	± 6.9	

End points

End points reporting groups

Reporting group title	PR5I

Reporting group description:

The PR5I group received V419, Prevenar 13™, and RotaTeq™ at 2, 3, and 4 months; followed by V419 and ProQuad™ at 12 months, and Prevenar 13™ and ProQuad™ at 13 months.

Reporting group title	INFANRIX™ hexa

Reporting group description:

The INFANRIX™ hexa group received INFANRIX™ hexa, Prevenar 13™, and RotaTeq™ at 2, 3, and 4 months; followed by INFANRIX™ hexa and ProQuad™ at 12 months; and Prevenar 13™ and ProQuad™ at 13 months.

Reporting group title	PR5I

Reporting group description:

The PR5I group received V419, Prevenar 13™, and RotaTeq™ at 2, 3, and 4 months; followed by V419 and ProQuad™ at 12 months, and Prevenar 13™ and ProQuad™ at 13 months.

Reporting group title	INFANRIX™ hexa

Reporting group description:

The INFANRIX™ hexa group received INFANRIX™ hexa, Prevenar 13™, and RotaTeq™ at 2, 3, and 4 months; followed by INFANRIX™ hexa and ProQuad™ at 12 months; and Prevenar 13™ and ProQuad™ at 13 months.

Reporting group title	PR5I

Reporting group description:

The PR5I group received V419, Prevenar 13™, and RotaTeq™ at 2, 3, and 4 months; followed by V419 and ProQuad™ at 12 months, and Prevenar 13™ and ProQuad™ at 13 months.

Reporting group title	INFANRIX™ hexa

Reporting group description:

The INFANRIX™ hexa group received INFANRIX™ hexa, Prevenar 13™, and RotaTeq™ at 2, 3, and 4 months; followed by INFANRIX™ hexa and ProQuad™ at 12 months; and Prevenar 13™ and ProQuad™ at 13 months.

Reporting group title	PR5I

Reporting group description:

The PR5I group received V419, Prevenar 13™, and RotaTeq™ at 2, 3, and 4 months; followed by V419 and ProQuad™ at 12 months, and Prevenar 13™ and ProQuad™ at 13 months.

Reporting group title	INFANRIX™ hexa

Reporting group description:

The INFANRIX™ hexa group received INFANRIX™ hexa, Prevenar 13™, and RotaTeq™ at 2, 3, and 4 months; followed by INFANRIX™ hexa and ProQuad™ at 12 months; and Prevenar 13™ and ProQuad™ at 13 months.

Reporting group title	PR5I

Reporting group description:

The PR5I group received V419, Prevenar 13™, and RotaTeq™ at 2, 3, and 4 months; followed by V419 and ProQuad™ at 12 months, and Prevenar 13™ and ProQuad™ at 13 months.

Reporting group title	INFANRIX™ hexa

Reporting group description:

The INFANRIX™ hexa group received INFANRIX™ hexa, Prevenar 13™, and RotaTeq™ at 2, 3, and 4 months; followed by INFANRIX™ hexa and ProQuad™ at 12 months; and Prevenar 13™ and ProQuad™ at 13 months.

Subject analysis set title	PR5I
Subject analysis set type	Per protocol

Subject analysis set description:

The PR5I group received V419, Prevenar 13™, and RotaTeq™ at 2, 3, and 4 months; followed by V419 and ProQuad™ at 12 months, and Prevenar 13™ and ProQuad™ at 13 months. All randomized participants excluding participants from site 0048.

Subject analysis set title	INFANRIX™ hexa
Subject analysis set type	Per protocol

Subject analysis set description:

The INFANRIX™ hexa group received INFANRIX™ hexa, Prevenar 13™, and RotaTeq™ at 2, 3, and 4 months; followed by INFANRIX™ hexa and ProQuad™ at 12 months; and Prevenar 13™ and ProQuad™ at 13 months. All randomized participants excluding participants from site 0048.

Primary: Percentage of participants vaccinated with PR5I with acceptable antibody (Ab) response to Haemophilus influenzae type b, diphtheria, tetanus, and poliovirus types 1, 2 & 3, at 5 months

End point title	Percentage of participants vaccinated with PR5I with acceptable antibody (Ab) response to Haemophilus influenzae type b, diphtheria, tetanus, and poliovirus types 1, 2 & 3, at 5 months[1]

End point description:

Antibody titres in the PR5I group were measured by Radioimmunoassay (RIA) for Haemophilus influenzae type b (PRP), Micrometabolic inhibition test (MIT) for diphtheria & poliovirus, and Enzyme-Linked Immunosorbent Assay (ELISA) for tetanus. 95% confidence interval (CI) were calculated based on the exact binomial method by Clopper and Pearson. 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 CI limits for PRP, diphtheria (80%), tetanus (90%), and IPV1, 2 & 3 (90%). The population analyzed was all participants in the PR5I group who met inclusion criteria, were not protocol violators, received vaccinations within acceptable day ranges, and who had serology results within revised windows (RW) of Days 28 to 51 Post-Dose 3. Participants from site 0048 were excluded.

End point type	Primary

End point timeframe:

One month after post-dose 3 of PRI5 (5 months old)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical comparisons between treatment groups were neither planned nor performed for this primary endpoint.

End point values	PR5I			
Subject group type	Subject analysis set			
Number of subjects analysed	550			
Units: Percentage of participants				
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: Percentage of participants vaccinated with PR5I with acceptable Ab response or seroresponse rates to all antigens contained in the PR5I vaccine one month after the toddler dose at 13 months

End point title	Percentage of participants vaccinated with PR5I with acceptable Ab response or seroresponse rates to all antigens contained in the PR5I vaccine one month after the toddler dose at 13 months[2]

End point description:

Antibody titres in the PR5I group were measured by RIA for PRP, MIT for diphtheria & poliovirus, enhanced Chemiluminescence assay (ECi)) for Hepatitis B surface antigen (HBsAg) and ELISA for tetanus, Pertussis toxoid (PT), Filamentous haemagglutinin (FHA), Fimbriae types 2 & 3 (FIM) & Pertactin (PRN). 95% confidence interval (CI) were calculated based on the exact binomial method by Clopper and Pearson. 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 lower CI limits for PRP, PT, FHA, FIM, and PRN (75%); Diphtheria (80%); HBsAG, IPV 1, 2, 3 (90%). The population analyzed was all participants in the PR5I group who met inclusion criteria, were not protocol violators, received vaccinations within acceptable day ranges, and who had serology results within RW of Days 28 to 51 Post-Toddler dose. Participants from site 0048 were excluded.

End point type	Primary

End point timeframe:

One month after toddler dose of PRI5 (13 months old)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical comparisons between treatment groups were neither planned nor performed for this primary endpoint.

End point values	PR5I			
Subject group type	Subject analysis set			
Number of subjects analysed	551			
Units: Percentage of participants				
number (confidence interval 95%)				
Anti-PRP ≥1.0 µg/mL (n=439)	94.99 (92.51 to 96.83)			
Anti-Diphtheria ≥0.1 IU/mL (n=531)	99.81 (98.96 to 100)			
Anti-Tetanus ≥0.1 IU/mL (n=528)	100 (99.30 to 100)			
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)			
Anti-HBsAg ≥10 mIU/mL(n=551)	99.64 (98.70 to 99.96)			
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)	98.90 (97.61 to 99.59)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants vaccinated with PR5I compared with INFANRIX™ hexa with acceptable Ab response to Haemophilus influenzae type b, diphtheria, tetanus, and poliovirus types 1, 2 & 3, at 5 months

End point title	Percentage of participants vaccinated with PR5I compared with

	INFANRIX™ hexa with acceptable Ab response to Haemophilus influenzae type b, diphtheria, tetanus, and poliovirus types 1, 2 & 3, at 5 months

End point description:

Antibody titres were measured by RIA for PRP, MIT for diphtheria & poliovirus, and ELISA for tetanus. Percentage of participants with an Ab titre ≥0.15 µg/mL for Hib) (PRP); ≥0.01 IU/mL; for diphtheria & tetanus; ≥8 (1/dil) for inactivated poliovirus types 1, 2 & 3 (IPV1, 2 & 3) are reported. The estimated response rates are based on the method by Miettinen and Nurminen stratified by country. The population analyzed was all participants who met inclusion criteria, were not protocol violators, received vaccinations within acceptable day ranges, and who had serology results within RW of Days 28 to 51 Post-Dose 3. Participants from site 0048 were excluded.

End point type	Primary

End point timeframe:

One month after post-dose 3 of PRI5 (5 months old)

End point values	PR5I	INFANRIX™ hexa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	550	530		
Units: Percentage of participants				
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	Difference in percentages: PRP
Statistical analysis description:	
PR5I minus INFANRIX™ hexa	
Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1080
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	< 0.001 [4]
Method	Miettinen & Nurminen
Parameter estimate	Difference in percentages
Point estimate	11.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.44
upper limit	14.68

Notes:

[3] - 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.
[4] - 1-sided

Statistical analysis title	Difference in percentages: Diphtheria
Statistical analysis description:	
PR5I minus INFANRIX™ hexa	
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 [6]
Method	Miettinen & Nurminen
Parameter estimate	Difference in percentages
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.95
upper limit	0.96

Notes:

[5] - 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
[6] - 1-sided

Statistical analysis title	Difference in percentages: Tetanus
Statistical analysis description:	
PR5I minus INFANRIX™ hexa	
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 [8]
Method	Miettinen & Nurminen
Parameter estimate	Difference in percentages
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.71
upper limit	0.74

Notes:

[7] - 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.
[8] - 1-sided

Statistical analysis title	Difference in percentages: IPV1
Statistical analysis description:	
PR5I minus INFANRIX™ hexa	
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 [10]
Method	Miettinen & Nurminen
Parameter estimate	Difference in percentages
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	1.07

Notes:

[9] - 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.
[10] - 1-sided

Statistical analysis title	Difference in percentages: IPV2
Statistical analysis description:	
PR5I minus INFANRIX™ hexa	
Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1080
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
P-value	< 0.001 [12]
Method	Miettinen & Nurminen
Parameter estimate	Difference in percentages
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.69
upper limit	1.21

Notes:

[11] - 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.
[12] - 1-sided

Statistical analysis title	Difference in percentages: IPV3
Statistical analysis description:	
PR5I minus INFANRIX™ hexa	
Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1080
Analysis specification	Pre-specified
Analysis type	non-inferiority[13]
P-value	< 0.001 [14]
Method	Miettinen & Nurminen
Parameter estimate	Difference in percentages
Point estimate	0

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

Notes:

[13] - 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.
[14] - 1-sided

Primary: Percentage of participants vaccinated with PR5I compared with INFANRIX™ hexa with acceptable Ab response rates to Hepatitis B and seroresponse to Pertussis antigens Pt, FHA and PRN one month after the toddler dose at 13 months old

End point title	Percentage of participants vaccinated with PR5I compared with INFANRIX™ hexa with acceptable Ab response rates to Hepatitis B and seroresponse to Pertussis antigens Pt, FHA and PRN one month after the toddler dose at 13 months old

End point description:

Antibody titres were measured by ECi for HBsAg and ELISA for PT, FHA, & PRN. Percentage of participants with an Ab titre ≥10 mIU/mL HBsAg; ≥8 (1/dil) for IPV1, 2 & 3, and seroresponse to PT, FHA, and PRN are reported. The estimated response rates are based on the method by Miettinen and Nurminen stratified by country. The population analyzed was all participants who met inclusion criteria, were not protocol violators, received vaccinations within acceptable day ranges, and who had serology results within RW of Days 28 to 51 Post-Toddler dose. Participants from site 0048 were excluded.

End point type	Primary

End point timeframe:

One month after toddler dose of PRI5 (13 months old)

End point values	PR5I	INFANRIX™ hexa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	551	531		
Units: Percentage of participants				
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	Difference in percentages: HBsAg

Statistical analysis description:

PR5I minus INFANRIX™ hexa

Comparison groups	PR5I v INFANRIX™ hexa

Number of subjects included in analysis	1082
Analysis specification	Pre-specified
Analysis type	non-inferiority[15]
P-value	< 0.001 [16]
Method	Miettinen & Nurminen
Parameter estimate	Difference in percentages
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	1.85

Notes:

[15] - 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.
[16] - 1-sided

Statistical analysis title	Difference in percentages: PT
Statistical analysis description:	
PR5I minus INFANRIX™ hexa	
Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1082
Analysis specification	Pre-specified
Analysis type	non-inferiority[17]
P-value	< 0.001 [18]
Method	Miettinen & Nurminen
Parameter estimate	Difference in percentages
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	2.86

Notes:

[17] - 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.
[18] - 1-sided

Statistical analysis title	Difference in percentages: FHA
Statistical analysis description:	
PR5I minus INFANRIX™ hexa	
Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1082
Analysis specification	Pre-specified
Analysis type	non-inferiority[19]
P-value	< 0.001 [20]
Method	Miettinen & Nurminen
Parameter estimate	Difference in percentages
Point estimate	-2.59

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

Notes:

[19] - 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.
[20] - 1-sided

Statistical analysis title	Difference in percentages: PRN

Statistical analysis description:

PR5I minus INFANRIX™ hexa

Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1082
Analysis specification	Pre-specified
Analysis type	non-inferiority[21]
P-value	< 0.001 [22]
Method	Miettinen & Nurminen
Parameter estimate	Difference in percentages
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	1.52

Notes:

[21] - 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.
[22] - 1-sided

Secondary: Percentage of participants vaccinated with PR5I with acceptable Ab response to measles, mumps, rubella and varicella one month after the toddler dose of ProQuad at 13 months old

End point title	Percentage of participants vaccinated with PR5I with acceptable Ab response to measles, mumps, rubella and varicella one month after the toddler dose of ProQuad at 13 months old

End point description:

Ab titres were measured by ELISA, excepting the Ab to varicella which was determined by glycoprotein ELISA. Percentage of participants 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 are reported. 95% CI were calculated based on the exact binomial method by Clopper and Pearson. The immune response to ProQuad 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 CI limits: 90% for measles, mumps & rubella, and 76% for varicella. The population analyzed was all participants in the PR5I group who met inclusion criteria, were not protocol violators, received vaccinations within acceptable day ranges, and who had serology results within RW of Days 28 to 51 Post-Toddler dose. Participants from site 0048 were excluded. Participants in the INFANRIX™ hexa group were not analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

One month after toddler dose of PRI5 (13 months old)

End point values	PR5I			
Subject group type	Subject analysis set			
Number of subjects analysed	467			
Units: Percentage of participants				
number (confidence interval 95%)				
Anti-Measles ≥255 mIU/mL	96.15 (93.98 to 97.70)			
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: Percentage of participants vaccinated with PR5I compared with INFANRIX™ hexa with acceptable Ab response to measles, mumps, rubella and varicella one month after the toddler dose of ProQuad at 13 months old

End point title	Percentage of participants vaccinated with PR5I compared with INFANRIX™ hexa with acceptable Ab response to measles, mumps, rubella and varicella one month after the toddler dose of ProQuad at 13 months old

End point description:

Ab titres were measured by ELISA, excepting the Ab to varicella which was determined by glycoprotein ELISA. Percentage of participants 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 are reported. The estimated response rates are based on the method by Miettinen and Nurminen stratified by country. The population analyzed was all participants who met inclusion criteria, were not protocol violators, received vaccinations within acceptable day ranges, and who had serology results within RW of Days 28 to 51 Post-Toddler dose. Participants from site 0048 were excluded.

End point type	Secondary

End point timeframe:

One month after toddler dose of PRI5 (13 months old)

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

Statistical analyses

Statistical analysis title	Difference in percentages: Measles
Statistical analysis description: PR5I minus INFANRIX™ hexa	
Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	941
Analysis specification	Pre-specified
Analysis type	non-inferiority[23]
P-value	< 0.001 [24]
Method	Miettinen & Nurminen
Parameter estimate	Difference in percentages
Point estimate	-0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.82
upper limit	2.25

Notes:

[23] - 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.
[24] - 1-sided

Statistical analysis title	Difference in percentages: Mumps
Statistical analysis description: PR5I minus INFANRIX™ hexa	
Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	941
Analysis specification	Pre-specified
Analysis type	non-inferiority[25]
P-value	< 0.001 [26]
Method	Miettinen & Nurminen
Parameter estimate	Difference in percentages
Point estimate	3.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	6.4

Notes:

[25] - 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.
[26] - 1-sided

Statistical analysis title	Difference in percentages: Rubella
Statistical analysis description: PR5I minus INFANRIX™ hexa	
Comparison groups	PR5I v INFANRIX™ hexa

Number of subjects included in analysis	941
Analysis specification	Pre-specified
Analysis type	non-inferiority[27]
P-value	< 0.001 [28]
Method	Miettinen & Nurminen
Parameter estimate	Difference in percentages
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	2.34

Notes:

[27] - 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.
[28] - 1-sided

Statistical analysis title	Difference in percentages: Varicella

Statistical analysis description:

PR5I minus INFANRIX™ hexa

Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	941
Analysis specification	Pre-specified
Analysis type	non-inferiority[29]
P-value	< 0.001 [30]
Method	Miettinen & Nurminen
Parameter estimate	Difference in percentages
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.11
upper limit	2.06

Notes:

[29] - 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.
[30] - 1-sided

Secondary: Percentage of participants with injection-site and systemic adverse events (AEs) from Day 1 to Day 15 after any vaccination

End point title	Percentage of participants with injection-site and systemic adverse events (AEs) from Day 1 to Day 15 after any vaccination

End point description:

Global safety was assessed by measuring injection-site and systemic AEs reported daily on the Vaccination Report Card (VRC) by the parent(s) or legal representative from Day 1 to Day 15 (D1-D15) after each hexavalent vaccination. Solicited injection-site and systemic AEs were reported daily from Day 1 to Day 5 (D1-D5) after each hexavalent vaccination. AEs at injection sites were always considered as vaccine-related (Injection-Site Reactions (ISRs)). The investigator assessed whether systemic AEs were related (V-related) or not to the vaccine. All AEs (related and unrelated) are reported. The population analyzed was all randomised participants who received at least 1 vaccination and who had safety follow-up. Participants from site 0048 were excluded.

End point type	Secondary

End point timeframe:

Day 1 to Day 15 after any vaccination

End point values	PR5I	INFANRIX™ hexa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	610	603		
Units: Percentage of participants				
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	91.0		
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)	97.0	98.5		
At least 1 V-related solicited systemic AE (D1-D5)	94.9	96.2		

Statistical analyses

Statistical analysis title	Risk difference: ISRs or systemic AEs
Statistical analysis description:	
PR5I minus INFANRIX™ hexa: Miettinen & Nurminen method	
Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other[31]
Parameter estimate	Risk difference (RD)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	0.4

Notes:

[31] - If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Statistical analysis title	Risk difference: ISRs or V-related sys. AEs
Statistical analysis description:	
PR5I minus INFANRIX™ hexa: Miettinen & Nurminen method	
Comparison groups	PR5I v INFANRIX™ hexa

Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other[32]
Parameter estimate	Risk difference (RD)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	1.1

Notes:

[32] - If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Statistical analysis title	Risk difference: At least 1 ISR

Statistical analysis description:

PR5I minus INFANRIX™ hexa: Miettinen & Nurminen method

Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other[33]
Parameter estimate	Risk difference (RD)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	4.3

Notes:

[33] - If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Statistical analysis title	Risk difference: At least 1 solicited ISR

Statistical analysis description:

PR5I minus INFANRIX™ hexa: Miettinen & Nurminen method

Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other[34]
Parameter estimate	Risk difference (RD)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	4.3

Notes:

[34] - If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Statistical analysis title	Risk difference: At least 1 systemic AE

Statistical analysis description:

PR5I minus INFANRIX™ hexa: Miettinen & Nurminen method

Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other[35]
Parameter estimate	Risk difference (RD)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	0.3

Notes:

[35] - If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Statistical analysis title	Risk difference: At least 1 V-related sys. AE

Statistical analysis description:

PR5I minus INFANRIX™ hexa: Miettinen & Nurminen method

Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other[36]
Parameter estimate	Risk difference (RD)
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	1.3

Notes:

[36] - If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Statistical analysis title	Risk difference: At least 1 solicited systemic AE

Statistical analysis description:

PR5I minus INFANRIX™ hexa: Miettinen & Nurminen method

Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other[37]
Parameter estimate	Risk difference (RD)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	0.2

Notes:

[37] - If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Statistical analysis title	Risk difference: At least 1 V-related sol. sys. AE

Statistical analysis description:	
PR5I minus INFANRIX™ hexa: Miettinen & Nurminen method	
Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other[38]
Parameter estimate	Risk difference (RD)
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	1.1

Notes:

[38] - If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Secondary: Percentage of participants reporting solicited ISRs from Day 1 to Day 5 after any vaccination

End point title	Percentage of participants reporting solicited ISRs from Day 1 to Day 5 after any vaccination

End point description:

Solicited ISRs were defined as injection-site erythema, injection-site pain, and injection-site swelling occurring from Day 1 (D1) to Day 5 (D5) after vaccination. AEs at injection sites were always considered as vaccine-related (Injection-Site Reactions (ISRs)). The population analyzed was all randomised participants who received at least 1 vaccination and who had safety follow-up. Participants from site 0048 were excluded.

End point type	Secondary

End point timeframe:

Day 1 to Day 5 after any vaccination

End point values	PR5I	INFANRIX™ hexa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	610	603		
Units: Percentage of participants				
number (not applicable)				
Injection-site erythema	69.0	64.2		
Injection-site pain	73.6	71.8		
Injection-site swelling	56.9	52.9		

Statistical analyses

Statistical analysis title	Risk difference: Injection-site erythema
Statistical analysis description:	
PR5I minus INFANRIX™ hexa: Miettinen & Nurminen method	
Comparison groups	PR5I v INFANRIX™ hexa

Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other[39]
Parameter estimate	Risk difference (RD)
Point estimate	4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	10.1

Notes:

[39] - If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Statistical analysis title	Risk difference: Injection-site pain

Statistical analysis description:

PR5I minus INFANRIX™ hexa: Miettinen & Nurminen method

Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other[40]
Parameter estimate	Risk difference (RD)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	6.8

Notes:

[40] - If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Statistical analysis title	Risk difference: Injection-site swelling

Statistical analysis description:

PR5I minus INFANRIX™ hexa: Miettinen & Nurminen method

Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other[41]
Parameter estimate	Risk difference (RD)
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	9.6

Notes:

[41] - If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Secondary: Percentage of participants reporting unsolicited ISRs from Day 1 to Day 15 after any vaccination

End point title	Percentage of participants reporting unsolicited ISRs from Day

	1 to Day 15 after any vaccination

End point description:

Unsolicited ISRs with incidence ≥1% after any vaccination were reported daily on the VRC by the parent(s) or legal representative from (D1-D15). AEs at injection sites were always considered as vaccine-related ISRs. The population analyzed was all randomised participants who received at least 1 vaccination and who had safety follow-up. Participants from site 0048 were excluded.

End point type	Secondary

End point timeframe:

Day 1 to Day 15 after any vaccination

End point values	PR5I	INFANRIX™ hexa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	610	603		
Units: Percentage of participants				
number (not applicable)				
Injection-site bruising	2.8	2.7		
Injection-site haematoma	1.5	0.8		
Injection-site haemorrhage	1.3	2.0		
Injection-site induration	14.6	18.2		
Injection-site nodule	1.3	1.5		
Injection-site warmth	3.0	1.8		

Statistical analyses

Statistical analysis title	Risk difference: Injection-site bruising

Statistical analysis description:

PR5I minus INFANRIX™ hexa: Miettinen & Nurminen method

Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other[42]
Parameter estimate	Risk difference (RD)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	2.1

Notes:

[42] - If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Statistical analysis title	Risk difference: Injection-site haematoma

Statistical analysis description:

PR5I minus INFANRIX™ hexa: Miettinen & Nurminen method

Comparison groups	PR5I v INFANRIX™ hexa

Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other[43]
Parameter estimate	Risk difference (RD)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	2.1

Notes:

[43] - If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Statistical analysis title	Risk difference: Injection-site haemorrhage

Statistical analysis description:

PR5I minus INFANRIX™ hexa: Miettinen & Nurminen method

Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other[44]
Parameter estimate	Risk difference (RD)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	0.8

Notes:

[44] - If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Statistical analysis title	Risk difference: Injection-site induration

Statistical analysis description:

PR5I minus INFANRIX™ hexa: Miettinen & Nurminen method

Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other[45]
Parameter estimate	Risk difference (RD)
Point estimate	-3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.8
upper limit	0.5

Notes:

[45] - If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Statistical analysis title	Risk difference: Injection-site nodule

Statistical analysis description:

PR5I minus INFANRIX™ hexa: Miettinen & Nurminen method

Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other[46]
Parameter estimate	Risk difference (RD)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	1.3

Notes:

[46] - If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Statistical analysis title	Risk difference: Injection-site warmth

Statistical analysis description:

PR5I minus INFANRIX™ hexa: Miettinen & Nurminen method

Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other[47]
Parameter estimate	Risk difference (RD)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	3

Notes:

[47] - If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Secondary: Percentage of participants reporting solicited systemic AE from Day 1 to Day 5 after any vaccination

End point title	Percentage of participants reporting solicited systemic AE from Day 1 to Day 5 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 D1 to D5 after vaccination. The investigator assessed whether these systemic AEs were related or not to the vaccines. All (related and unrelated) AEs are reported. The population analyzed was all randomised participants who received at least 1 vaccination and who had safety follow-up. Participants from site 0048 were excluded.

End point type	Secondary

End point timeframe:

Day 1 to Day 5 after any vaccination

End point values	PR5I	INFANRIX™ hexa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	610	603		
Units: Percentage of participants				
number (not applicable)				
Crying	85.4	87.9		
Decreased appetite	63.9	67.0		
Irritability	87.9	85.7		
Pyrexia	71.5	73.1		
Somnolence	76.9	80.1		
Vomiting	31.8	31.0		

Statistical analyses

Statistical analysis title	Risk difference: Crying
Statistical analysis description:	
PR5I minus INFANRIX™ hexa: Miettinen & Nurminen method	
Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other[48]
Parameter estimate	Risk difference (RD)
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	1.4

Notes:

[48] - If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Statistical analysis title	Risk difference: Decreased appetite
Statistical analysis description:	
PR5I minus INFANRIX™ hexa: Miettinen & Nurminen method	
Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other[49]
Parameter estimate	Risk difference (RD)
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	2.3

Notes:

[49] - If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Statistical analysis title	Risk difference: Irritability
Statistical analysis description:	
PR5I minus INFANRIX™ hexa: Miettinen & Nurminen method	
Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other[50]
Parameter estimate	Risk difference (RD)
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	6

Notes:

[50] - If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Statistical analysis title	Risk difference: Pyrexia
Statistical analysis description:	
PR5I minus INFANRIX™ hexa: Miettinen & Nurminen method	
Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other[51]
Parameter estimate	Risk difference (RD)
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	3.4

Notes:

[51] - If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Statistical analysis title	Risk difference: Somnolence
Statistical analysis description:	
PR5I minus INFANRIX™ hexa: Miettinen & Nurminen method	
Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other[52]
Parameter estimate	Risk difference (RD)
Point estimate	-3.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.8
upper limit	1.4

Notes:

[52] - If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Statistical analysis title	Risk difference: Vomiting

Statistical analysis description:

PR5I minus INFANRIX™ hexa: Miettinen & Nurminen method

Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1213
Analysis specification	Pre-specified
Analysis type	other[53]
Parameter estimate	Risk difference (RD)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	6

Notes:

[53] - If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

2 months after toddler dose (up to approximately age 14 months)

Adverse event reporting additional description:

All Treated Participants. Participants from site 0048 were excluded.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	INFANRIX hexa

Reporting group description:

The INFANRIX™ hexa group received INFANRIX™ hexa, Prevenar 13™, and RotaTeq™ at 2, 3, and 4 months; followed by INFANRIX™ hexa and ProQuad™ at 12 months; and Prevenar 13™ and ProQuad™ at 13 months.

Reporting group title	PR5I

Reporting group description:

The P R5I group received V419, Prevenar 13™, and RotaTeq™ at 2, 3, and 4 months; followed by V419 and ProQuad™ at 12 months, and Prevenar 13™ and ProQuad™ at 13 months.

Serious adverse events	INFANRIX hexa	PR5I	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 605 (3.64%)	23 / 610 (3.77%)	
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)			
Prolymphocytic leukaemia			
subjects affected / exposed	0 / 605 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Abdominal injury			
subjects affected / exposed	1 / 605 (0.17%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			

subjects affected / exposed	1 / 605 (0.17%)	3 / 610 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	0 / 605 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 605 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Benign familial neonatal convulsions			
subjects affected / exposed	1 / 605 (0.17%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 605 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile convulsion			
subjects affected / exposed	0 / 605 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 605 (0.33%)	2 / 610 (0.33%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Inguinal hernia			

subjects affected / exposed	0 / 605 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 605 (0.17%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swollen tongue			
subjects affected / exposed	1 / 605 (0.17%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Neuroendocrine cell hyperplasia of infancy			
subjects affected / exposed	1 / 605 (0.17%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 605 (0.17%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	2 / 605 (0.33%)	3 / 610 (0.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 605 (0.17%)	2 / 610 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis viral			

subjects affected / exposed	1 / 605 (0.17%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exanthema subitum			
subjects affected / exposed	0 / 605 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 605 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	1 / 605 (0.17%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 605 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	2 / 605 (0.33%)	2 / 610 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 605 (0.00%)	1 / 610 (0.16%)	
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	7 / 605 (1.16%)	3 / 610 (0.49%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	0 / 605 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 605 (0.17%)	0 / 610 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 605 (0.00%)	1 / 610 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	INFANRIX hexa	PR5I	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	599 / 605 (99.01%)	603 / 610 (98.85%)	
Nervous system disorders			
Somnolence			
subjects affected / exposed	485 / 605 (80.17%)	470 / 610 (77.05%)	
occurrences (all)	1058	1082	
General disorders and administration site conditions			
Crying			
subjects affected / exposed	531 / 605 (87.77%)	523 / 610 (85.74%)	
occurrences (all)	1482	1543	
Injection site erythema			
subjects affected / exposed	430 / 605 (71.07%)	459 / 610 (75.25%)	
occurrences (all)	1517	1745	
Injection site induration			
subjects affected / exposed	127 / 605 (20.99%)	106 / 610 (17.38%)	
occurrences (all)	296	245	
Injection site pain			
subjects affected / exposed	456 / 605 (75.37%)	469 / 610 (76.89%)	
occurrences (all)	1637	1710	
Injection site swelling			

subjects affected / exposed	347 / 605 (57.36%)	384 / 610 (62.95%)	
occurrences (all)	1101	1214	
Irritability			
subjects affected / exposed	518 / 605 (85.62%)	537 / 610 (88.03%)	
occurrences (all)	1570	1639	
Pyrexia			
subjects affected / exposed	472 / 605 (78.02%)	471 / 610 (77.21%)	
occurrences (all)	1065	1072	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	32 / 605 (5.29%)	20 / 610 (3.28%)	
occurrences (all)	36	23	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	84 / 605 (13.88%)	98 / 610 (16.07%)	
occurrences (all)	113	129	
Flatulence			
subjects affected / exposed	39 / 605 (6.45%)	45 / 610 (7.38%)	
occurrences (all)	50	55	
Vomiting			
subjects affected / exposed	194 / 605 (32.07%)	205 / 610 (33.61%)	
occurrences (all)	333	328	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	38 / 605 (6.28%)	35 / 610 (5.74%)	
occurrences (all)	44	39	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	27 / 605 (4.46%)	35 / 610 (5.74%)	
occurrences (all)	32	42	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	35 / 605 (5.79%)	24 / 610 (3.93%)	
occurrences (all)	41	29	
Otitis media			

subjects affected / exposed	26 / 605 (4.30%)	32 / 610 (5.25%)	
occurrences (all)	30	33	
Rhinitis			
subjects affected / exposed	86 / 605 (14.21%)	82 / 610 (13.44%)	
occurrences (all)	101	102	
Upper respiratory tract infection			
subjects affected / exposed	76 / 605 (12.56%)	69 / 610 (11.31%)	
occurrences (all)	83	82	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	408 / 605 (67.44%)	401 / 610 (65.74%)	
occurrences (all)	718	752	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 November 2010	Amendment 1: The protocol template contained an error with respect to AE causality definitions in Table 3-3 of Section 3.4.5 Evaluating Adverse Events. Previously the protocol incorrectly grouped the "Possibly related" definition under the category of "No, there is not a reasonable possibility of vaccine relationship." The protocol was amended to correctly state the "Possibly related" definition under the category of "Yes, there is a reasonable possibility of vaccine relationship."
22 December 2010	Amendment 2: The primary reasons for this amendment were: 1) To revise the timing of when non-study vaccines could be received during the study; 2) the scale for grading injection-site pain and tenderness was revised to more directly reflect pain at the injection site; 3) the definition for a sub-responder to tetanus was redefined from a titer of < 0.01 IU/mL to < 0.1 IU/mL and 4) 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 were added.
08 July 2011	Amendment 3: The primary reason for this amendment was to include administration of a second dose of ProQuad™ at the 13-month visit (Visit 6) in order to complete the series for ProQuad™, in alignment with the EU SmPC. In addition, the telephone contact at the end of the study (Visit 7) was extended to 28 days postvaccination to align with the recommended safety follow-up period for live virus vaccines.
08 February 2012	Amendment 4: The criterion for exclusion from the per-protocol immunogenicity analysis related to vaccine dosing was revised for clarity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported