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	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	V419-008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01480258
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	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:

This study will determine whether participants who receive V419 (PR5I) at 2, 4, and 11 to 12 months of age have an acceptable response to the vaccine. This study will also determine whether the immune response to V419 is similar to that of participants who received a licensed vaccine control. The primary hypothesis is that participants who receive PR5I at 2, 4, and 11 to 12 months have an acceptable response rate to all PR5I-contained antigens at one month after the toddler dose of PR5I.

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.

The following additional measures defined for this individual study were in place for the protection of trial subjects: After each vaccination, participants 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: -

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	Finland: 919
Country: Number of subjects enrolled	Italy: 264
Country: Number of subjects enrolled	Sweden: 132
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	1315

months)	
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:

Participants from Italy and Sweden were randomized to Rotavirus Vaccine Subset 1 (Rotarix™).
Participants from Finland were randomized to Rotavirus Vaccine Subset 2 (RotaTeq™).

Pre-assignment

Screening details:

1325 participants were screened.
1315 participants were randomised.
1312 participants were vaccinated.
1300 participants received the 2 doses of the infant series (period 1).
1281 participants received the toddler dose (period 2).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	PR5I

Arm description:

Infant series: PR5I 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 2 and 4 months of age, and rotavirus vaccine (either Rotarix™ 1.5 mL oral dose at 2 and 4 months of age [subset 1] or RotaTeq™ 2 mL oral dose at 2, 4 and 5 months of age [subset 2]). Toddler dose: PR5I 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 11 to 12 months of age.

Arm type	Experimental
Investigational medicinal product name	PR5I
Investigational medicinal product code	
Other name	V419 Vaxelis®
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

DTaP-HB-IPV-Hib (Diphtheria, tetanus, pertussis [acellular, component], hepatitis B [recombinant DNA], polio virus [inactivated], and Haemophilus influenza type b conjugate vaccine [adsorbed]) Vaccine 0.5 mL intramuscular injection at 2 and 4 months of age.
Injection is to be administered in the upper anterolateral thigh, separate limb from the concomitant vaccine. PR5I is a liquid suspension hexavalent vaccine.

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 and 4 months of age.
Injection is to be administered in the upper anterolateral thigh, separate limb from the concomitant vaccine.

Investigational medicinal product name	Rotavirus vaccine
Investigational medicinal product code	
Other name	Rotarix™ RotaTeq™
Pharmaceutical forms	Oral solution

Routes of administration	Oral use

Dosage and administration details:

Rotarix™ 1.5 mL oral dose at 2 and 4 months of age (subset 1,
Italy and Sweden) or RotaTeq™ 2 mL oral dose at 2, 4 and 5 months of age (subset 2, Finland)

Arm title	INFANRIX™ hexa

Arm description:

Infant series: INFANRIX™ hexa 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 2 and 4 months of age, and rotavirus vaccine (either Rotarix™ 1.5 mL oral dose at 2 and 4 months of age [subset 1] or RotaTeq™ 2 mL oral dose at 2, 4 and 5 months of age [subset 2]). Toddler dose: INFANRIX™ hexa 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 11 to 12 months of age.

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:

Combined Diphtheria-Tetanus-acellular Pertussis [DTaP],
Hepatitis B [HepB], Poliovirus [IPV] and Haemophilus influenzae type b [Hib] Vaccine 0.5 mL intramuscular injection at 2 and 4 months of age.
Injection is to be administered in the upper anterolateral thigh, separate limb from the concomitant vaccine.
INFANRIX™ hexa is provided as 2 components (lyophilized Hib and liquid DTaP, IPV, and HepB). Prior to administration, the vaccine must be reconstituted by adding the liquid DTaPHepB-IPV component to the vial containing the Hib pellet.

Investigational medicinal product name	Rotavirus vaccine
Investigational medicinal product code	
Other name	Rotarix™ RotaTeq™
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Rotarix™ 1.5 mL oral dose at 2 and 4 months of age (subset 1,
Italy and Sweden) or RotaTeq™ 2 mL oral dose at 2, 4 and 5 months of age (subset 2, Finland)

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 and 4 months of age.
Injection is to be administered in the upper anterolateral thigh, separate limb from the concomitant vaccine.

Number of subjects in period 1	PR5I	INFANRIX™ hexa
Started	656	659
Vaccinated	653	659
Completed	649	651
Not completed	7	8
Consent withdrawn by subject	1	6

Physician decision	-	1
Not Vaccinated	3	-
Adverse event, non-fatal	1	1
Protocol deviation	2	-

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	PR5I

Arm description:

Infant series: PR5I 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 2 and 4 months of age, and rotavirus vaccine (either Rotarix™ 1.5 mL oral dose at 2 and 4 months of age [subset 1] or RotaTeq™ 2 mL oral dose at 2, 4 and 5 months of age [subset 2]). Toddler dose: PR5I 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 11 to 12 months of age.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	INFANRIX™ hexa

Arm description:

Infant series: INFANRIX™ hexa 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 2 and 4 months of age, and rotavirus vaccine (either Rotarix™ 1.5 mL oral dose at 2 and 4 months of age [subset 1] or RotaTeq™ 2 mL oral dose at 2, 4 and 5 months of age [subset 2]). Toddler dose: INFANRIX™ hexa 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 11 to 12 months of age.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	PR5I	INFANRIX™ hexa
Started	649	651
Completed	639	642
Not completed	10	9
Physician decision	1	-
Consent withdrawn by subject	9	6
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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	PR5I

Arm description:

Infant series: PR5I 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 2 and 4 months of age, and rotavirus vaccine (either Rotarix™ 1.5 mL oral dose at 2 and 4 months of age [subset 1] or RotaTeq™ 2 mL oral dose at 2, 4 and 5 months of age [subset 2]). Toddler dose: PR5I 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 11 to 12 months of age.

Arm type	Experimental
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 11 to 12 months of age.
Injection is to be administered in the upper anterolateral thigh, separate limb from the concomitant vaccine.

Investigational medicinal product name	PR5I
Investigational medicinal product code	
Other name	V419 Vaxelis®
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

DTaP-HB-IPV-Hib (Diphtheria, tetanus, pertussis [acellular, component], hepatitis B [recombinant DNA], polio virus [inactivated], and Haemophilus influenza type b conjugate vaccine [adsorbed]) Vaccine 0.5 mL intramuscular injection at 11 to 12 months of age.
Injection is to be administered in the upper anterolateral thigh, separate limb from the concomitant vaccine. PR5I is a liquid suspension hexavalent vaccine.

Arm title	INFANRIX™ hexa

Arm description:

Infant series: INFANRIX™ hexa 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 2 and 4 months of age, and rotavirus vaccine (either Rotarix™ 1.5 mL oral dose at 2 and 4 months of age [subset 1] or RotaTeq™ 2 mL oral dose at 2, 4 and 5 months of age [subset 2]). Toddler dose: INFANRIX™ hexa 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 11 to 12 months of age.

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:

Combined Diphtheria-Tetanus-acellular Pertussis [DTaP],

Hepatitis B [HepB], Poliovirus [IPV] and Haemophilus influenzae type b [Hib] Vaccine 0.5 mL intramuscular injection at 11 to 12 months of age.
Injection is to be administered in the upper anterolateral thigh, separate limb from the concomitant vaccine.
INFANRIX™ hexa is provided as 2 components (lyophilized Hib and liquid DTaP, IPV, and HepB). Prior to administration, the vaccine must be reconstituted by adding the liquid DTaPHepB-IPV component to the vial containing the Hib pellet.

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 11 to 12 months of age.
Injection is to be administered in the upper anterolateral thigh, separate limb from the concomitant vaccine.

Number of subjects in period 3	PR5I	INFANRIX™ hexa
Started	639	642
Completed	639	642

Baseline characteristics

Reporting groups	
Reporting group title	PR5I
Reporting group description:	
Infant series: PR5I 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 2 and 4 months of age, and rotavirus vaccine (either Rotarix™ 1.5 mL oral dose at 2 and 4 months of age [subset 1] or RotaTeq™ 2 mL oral dose at 2, 4 and 5 months of age [subset 2]). Toddler dose: PR5I 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 11 to 12 months of age.	
Reporting group title	INFANRIX™ hexa
Reporting group description:	
Infant series: INFANRIX™ hexa 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 2 and 4 months of age, and rotavirus vaccine (either Rotarix™ 1.5 mL oral dose at 2 and 4 months of age [subset 1] or RotaTeq™ 2 mL oral dose at 2, 4 and 5 months of age [subset 2]). Toddler dose: INFANRIX™ hexa 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 11 to 12 months of age.	

Reporting group values	PR5I	INFANRIX™ hexa	Total
Number of subjects	656	659	1315
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	656	659	1315
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: Days			
arithmetic mean	68	68.1	
standard deviation	± 10.3	± 10.5	-
Sex: Female, Male Units: Subjects			
Female	323	313	636
Male	333	346	679
Region of Enrollment Units: Subjects			
Finland	459	460	919
Italy	132	132	264
Sweden	65	67	132

End points

End points reporting groups

Reporting group title	PR5I

Reporting group description:

Infant series: PR5I 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 2 and 4 months of age, and rotavirus vaccine (either Rotarix™ 1.5 mL oral dose at 2 and 4 months of age [subset 1] or RotaTeq™ 2 mL oral dose at 2, 4 and 5 months of age [subset 2]). Toddler dose: PR5I 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 11 to 12 months of age.

Reporting group title	INFANRIX™ hexa

Reporting group description:

Infant series: INFANRIX™ hexa 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 2 and 4 months of age, and rotavirus vaccine (either Rotarix™ 1.5 mL oral dose at 2 and 4 months of age [subset 1] or RotaTeq™ 2 mL oral dose at 2, 4 and 5 months of age [subset 2]). Toddler dose: INFANRIX™ hexa 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 11 to 12 months of age.

Reporting group title	PR5I

Reporting group description:

Infant series: PR5I 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 2 and 4 months of age, and rotavirus vaccine (either Rotarix™ 1.5 mL oral dose at 2 and 4 months of age [subset 1] or RotaTeq™ 2 mL oral dose at 2, 4 and 5 months of age [subset 2]). Toddler dose: PR5I 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 11 to 12 months of age.

Reporting group title	INFANRIX™ hexa

Reporting group description:

Infant series: INFANRIX™ hexa 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 2 and 4 months of age, and rotavirus vaccine (either Rotarix™ 1.5 mL oral dose at 2 and 4 months of age [subset 1] or RotaTeq™ 2 mL oral dose at 2, 4 and 5 months of age [subset 2]). Toddler dose: INFANRIX™ hexa 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 11 to 12 months of age.

Reporting group title	PR5I

Reporting group description:

Infant series: PR5I 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 2 and 4 months of age, and rotavirus vaccine (either Rotarix™ 1.5 mL oral dose at 2 and 4 months of age [subset 1] or RotaTeq™ 2 mL oral dose at 2, 4 and 5 months of age [subset 2]). Toddler dose: PR5I 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 11 to 12 months of age.

Reporting group title	INFANRIX™ hexa

Reporting group description:

Infant series: INFANRIX™ hexa 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 2 and 4 months of age, and rotavirus vaccine (either Rotarix™ 1.5 mL oral dose at 2 and 4 months of age [subset 1] or RotaTeq™ 2 mL oral dose at 2, 4 and 5 months of age [subset 2]). Toddler dose: INFANRIX™ hexa 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 11 to 12 months of age.

Subject analysis set title	PR51
Subject analysis set type	Safety analysis

Subject analysis set description:

Infant series: PR5I 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 2 and 4 months of age, and rotavirus vaccine (either Rotarix™ 1.5 mL oral dose at 2 and 4 months of age [subset 1] or RotaTeq™ 2 mL oral dose at 2, 4 and 5 months of age [subset 2]). Toddler dose: PR5I 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 11 to 12 months of age.

Subject analysis set title	INFANRIX™ hexa
Subject analysis set type	Safety analysis

Subject analysis set description:

Infant series: INFANRIX™ hexa 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 2 and 4 months of age, and rotavirus vaccine (either Rotarix™ 1.5 mL oral dose at 2 and 4 months of age [subset 1] or RotaTeq™ 2 mL oral dose at 2, 4 and 5 months of age [subset 2]). Toddler dose: INFANRIX™ hexa 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 11 to 12 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]

End point description:

Acceptability response rates: Ab titre ≥1.0 µg/mL for Hib (polyribosylribitol phosphate, PRP); ≥10 mIU/mL for HBsAg; ≥0.1 IU/mL for diphtheria and tetanus; ≥8 (1/dil) for IPV type 1, 2 & 3, and percentage of pertussis seroresponder participants (Pertussis toxoid [PT], Filamentous haemagglutinin [FHA], Fimbriae types 2 & 3 [FIM] and Pertactin [PRN]) 1 month Post-Toddler PR51 dose. Seroresponse: (1) If pre-Dose 1 Ab concentration (cc) was <LLOQ (lower limit of quantitation), postvaccination Ab cc was ≥LLOQ, (2) If pre-Dose 1 Ab cc was ≥LLOQ, postvaccination Ab cc was ≥prevaccination levels. Analysis population: participants who met the inclusion criteria, were not protocol violators, received PR51 vaccinations within acceptable day ranges, and had a blood draw sample window of Days 28 to 51 following the Toddler dose. The analysis populations may not have been identical for each antigen-specific analysis at each post-vaccination visit.

End point type	Primary

End point timeframe:

1 month after Toddler dose of PR51 (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: No between-group statistical analyses were performed for this endpoint. Single-sided analyses are presented on ClinicalTrials.gov NCT01480258.

End point values	PR5I	INFANRIX™ hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	638	0[2]		
Units: Percentage of participants				
number (confidence interval 95%)				
Anti-PRP ≥1.0 µg/mL; n=454	89.87 (86.72 to 92.49)	(to)		
Anti-HBsAg ≥10 mIU/mL; n=377	98.14 (96.21 to 99.25)	(to)		
Anti-Diphtheria ≥0.1 IU/mL; n=590	98.64 (97.35 to 99.41)	(to)		
Anti-Tetanus ≥0.1 IU/mL; n=589	99.83 (99.06 to 100.00)	(to)		
Anti-PT seroresponse; n=566	99.12 (97.95 to 99.71)	(to)		
Anti-FHA seroresponse; n=582	97.42 (95.78 to 98.55)	(to)		
Anti-FIM seroresponse; n=581	98.28 (96.86 to 99.17)	(to)		
Anti-PRN seroresponse; n=582	96.91 (95.16 to 98.16)	(to)		
Anti-IPV1 ≥1:8 dilution; n=591	99.32 (98.28 to 99.82)	(to)		
Anti-IPV2 ≥1:8 dilution; n=591	99.83 (99.06 to 100.00)	(to)		
Anti-IPV3 ≥1:8 dilution; n=590	99.49 (98.52 to 99.90)	(to)		

Notes:

[2] - Participants receiving INFANRIX™ hexa were excluded from the acceptability analyses.

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

End point description:

Percentage of participants with an Ab titre ≥1.0 µg/mL for Hib (polyribosylribitol phosphate, PRP) measured by radioimmunoassay (RIA) 1 month post-infant dose 2 of PR5I or INFANRIX hexa. Analysis population: participants who received 2nd dose in the Infant series and had a blood draw sample window of Days 28 to 51 post-infant dose 2.

End point type	Secondary

End point timeframe:

1 month after the 2nd dose (post-infant dose 2)

End point values	PR5I	INFANRIX™ hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	609	592		
Units: Percentage of participants				
number (not applicable)	72.86	26.66		

Statistical analyses

Statistical analysis title	Between group comparison
Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1201
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	< 0.001 [4]
Method	Miettinen & Nurminen
Parameter estimate	Difference in percentages
Point estimate	46.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	41.05
upper limit	51.06

Notes:

[3] - If the lower bound of the 95% confidence interval (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] - Stratification 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

End point description:

Percentage of participants with an Ab titre ≥1.0 µg/mL for Hib (polyribosylribitol phosphate, PRP) measured by RIA 1 month post-infant dose 2 of PR5I or INFANRIX hexa. Analysis population: participants who received 2nd dose in the Infant series and had a blood draw sample window of Days 28 to 51 post-infant dose 2.

End point type	Secondary

End point timeframe:

1 month after the 2nd dose (post-infant dose 2)

End point values	PR5I	INFANRIX™ hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	609	592		
Units: Percentage of participants				
number (not applicable)	72.86	26.66		

Statistical analyses

Statistical analysis title	Between group comparison
Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1201
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.001
Method	Miettinen & Nurminen
Parameter estimate	Difference in percentages
Point estimate	46.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	41.05
upper limit	51.06

Notes:

[5] - 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.

Secondary: Non-inferiority 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 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 description:

Percentage of participants with pre-specified Ab titre for PRP, HBsAg, diphtheria, tetanus, IPV1, 2 & 3, and percentage of pertussis seroresponder participants (PT, FHA, FIM and PRN) 1 month post-toddler dose were calculated based on the method by Miettinen and Nurminen stratified by country. Seroresponse was defined: (1) If pre-Dose 1 Ab cc was <LLOQ, post-vaccination Ab cc was ≥LLOQ, (2) If pre-Dose 1 Ab cc was ≥LLOQ, post-vaccination Ab cc was ≥pre-vaccination levels. Due to the timing of the occurrence of protocol violation or the availability of each antigen serology testing result, the

analysis populations may not have been identical for each antigen-specific analysis at each post-vaccination visit. Analysis population: participants who met the inclusion criteria, were not protocol violators, received vaccinations within acceptable day ranges, and had a blood draw sample window of Days 28 to 51 following the Toddler dose.

End point type	Secondary

End point timeframe:

1 month after Toddler dose (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 participants				
number (not applicable)				
Anti-PRP ≥1.0 µg/mL; n=454, n=478	89.80	91.06		
Anti-HBsAg ≥10 mIU/mL; n=377, n=391	98.14	98.73		
Anti-Diphtheria ≥0.1 IU/mL; n=590, n=578	98.62	99.83		
Anti-Tetanus ≥0.1 IU/mL; n=589, n=577	99.83	100.00		
Anti-PT seroresponse; n=566, n=561	99.11	99.64		
Anti-FHA seroresponse; n=582, n=571	97.40	99.13		
Anti-PRN seroresponse; n=582, n=572	96.86	98.28		
Anti-IPV1 ≥1:8 dilution; n=591, n=580	99.32	99.83		
Anti-IPV2 ≥1:8 dilution; n=591, n=579	99.83	100.00		
Anti-IPV3 ≥1:8 dilution; n=590, n=579	99.49	99.65		

Statistical analyses

Statistical analysis title	Between group comparison
Statistical analysis description:	
Between group comparison of PRP	
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 [7]
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages
Point estimate	-1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.13
upper limit	2.52

Notes:

[6] - The estimate of the difference between PR5I & INFANRIX hexa groups in PRP response rate (based on Ab titre ≥1.0 µg/mL) was calculated with its 1-sided P-value & 2-sided 95% 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.

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

Statistical analysis title	Between group comparison
Statistical analysis description:	
Between group comparison of HBsAg	
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 [9]
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages
Point estimate	-0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.66
upper limit	1.35

Notes:

[8] - 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% 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.

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

Statistical analysis title	Between group comparison
Statistical analysis description:	
Between group comparison of diptheria	
Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1280
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
P-value	< 0.001 [11]
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages
Point estimate	-1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.54
upper limit	-0.22

Notes:

[10] - 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% 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.

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

Statistical analysis title	Between group comparison

Statistical analysis description:	
Between group comparison of tetanus	
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 [13]
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.95
upper limit	0.5

Notes:

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

Statistical analysis title	Between group comparison
Statistical analysis description:	
Between group comparison of PT	
Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1280
Analysis specification	Pre-specified
Analysis type	non-inferiority[14]
P-value	< 0.001 [15]
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages
Point estimate	-0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.75
upper limit	0.49

Notes:

[14] - The estimate of the difference between PR5I & INFANRIX hexa groups in the percentage of seroresponder participants for PT was calculated with its 1-sided P-value & 2-sided 95% 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.
[15] - Statistical method was based on the Miettinen & Nurminen method stratified by country.

Statistical analysis title	Between group comparison
Statistical analysis description:	
Between group comparison of FHA	
Comparison groups	PR5I v INFANRIX™ hexa

Number of subjects included in analysis	1280
Analysis specification	Pre-specified
Analysis type	non-inferiority[16]
P-value	< 0.001 [17]
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages
Point estimate	-1.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.47
upper limit	-0.26

Notes:

[16] - The estimate of the difference between PR5I & INFANRIX hexa groups in the percentage of seroresponder participants for FHA was calculated with its 1-sided P-value & 2-sided 95% 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.
[17] - Statistical method was based on the Miettinen & Nurminen method stratified by country.

Statistical analysis title	Between group comparison
Statistical analysis description:	
Between group comparison of PRN	
Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1280
Analysis specification	Pre-specified
Analysis type	non-inferiority[18]
P-value	< 0.001 [19]
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages
Point estimate	-1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.42
upper limit	0.39

Notes:

[18] - The estimate of the difference between PR5I & INFANRIX hexa groups in the percentage of seroresponder participants for PRN was calculated with its 1-sided P-value & 2-sided 95% 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.
[19] - Statistical method was based on the Miettinen & Nurminen method stratified by country.

Statistical analysis title	Between group comparison
Statistical analysis description:	
Between group comparison of IPV1	
Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1280
Analysis specification	Pre-specified
Analysis type	non-inferiority[20]
P-value	< 0.001 [21]
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages
Point estimate	-0.51

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.59
upper limit	0.34

Notes:

[20] - 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% 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.
[21] - Statistical method was based on the Miettinen & Nurminen method stratified by country.

Statistical analysis title	Between group comparison
Statistical analysis description:	
Between group comparison of IPV2	
Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1280
Analysis specification	Pre-specified
Analysis type	non-inferiority[22]
P-value	< 0.001 [23]
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.96
upper limit	0.49

Notes:

[22] - 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% 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.
[23] - Statistical method was based on the Miettinen & Nurminen method stratified by country.

Statistical analysis title	Between group comparison
Statistical analysis description:	
Between group comparison of IPV3	
Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	1280
Analysis specification	Pre-specified
Analysis type	non-inferiority[24]
P-value	< 0.001 [25]
Method	Miettinen & Nurminen with stratification
Parameter estimate	Difference in percentages
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	0.82

Notes:

[24] - 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% 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.

[25] - Statistical method 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

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). The 95% CI for GMT was based on the t-distribution of the natural log-transformed antibody titer. Analysis population: participants who received dose 2 of Rotarix.

End point type	Secondary

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	INFANRIX™ hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	171		
Units: Titre (units/mL)				
geometric mean (confidence interval 95%)	96.41 (71.69 to 129.65)	122.24 (92.48 to 161.58)		

Statistical analyses

Statistical analysis title	Between group comparison
Comparison groups	PR5I v INFANRIX™ hexa
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	non-inferiority[26]
P-value	= 0.011
Method	ANCOVA
Parameter estimate	Geometric Mean Titre (GMT) ratio
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.2

Notes:

[26] - 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.

Secondary: Number of participants who experienced an adverse event (AE) from Day 1 to Day 15 after any vaccination

End point title	Number of participants who experienced an adverse event (AE) from Day 1 to Day 15 after any vaccination

End point description:

Injection-site and systemic 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 population: all randomized participants who received at least 1 vaccination and who had safety follow-up.

End point type	Secondary

End point timeframe:

Solicited AEs: up to 5 days (Days 1-5 after any vaccination); unsolicited AEs: up to 15 days (Day 1-15 after any vaccination)

End point values	PR51	INFANRIX™ hexa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	653	659		
Units: Percentage of participants				
number (not applicable)				
At least 1 ISR or systemic AE (D1-D15)	99.5	99.2		
At least 1 V-related ISR or 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	Between group comparison

Statistical analysis description:

Between group comparison of ISR or systemic AE

Comparison groups	PR51 v INFANRIX™ hexa

Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other[27]
Parameter estimate	Risk difference (RD)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	1.4

Notes:

[27] - The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% 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.

Statistical analysis title	Between group comparison

Statistical analysis description:

Between group comparison of V-related ISR or systemic AE

Comparison groups	PR51 v INFANRIX™ hexa
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other[28]
Parameter estimate	Risk difference (RD)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	2

Notes:

[28] - The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% 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.

Statistical analysis title	Between group comparison

Statistical analysis description:

Between group comparison of at least 1 ISR

Comparison groups	PR51 v INFANRIX™ hexa
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other[29]
Parameter estimate	Risk difference (RD)
Point estimate	2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	6

Notes:

[29] - The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% 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.

Statistical analysis title	Between group comparison
Statistical analysis description:	
Between group comparison of at least 1 solicited ISR	
Comparison groups	PR51 v INFANRIX™ hexa
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other[30]
Parameter estimate	Risk difference (RD)
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	5.9

Notes:

[30] - The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% 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.

Statistical analysis title	Between group comparison
Statistical analysis description:	
Between group comparison of at least 1 systemic AE	
Comparison groups	PR51 v INFANRIX™ hexa
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other[31]
Parameter estimate	Risk difference (RD)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	1.4

Notes:

[31] - The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% 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.

Statistical analysis title	Between group comparison
Statistical analysis description:	
Between group comparison of at least 1 vaccine-related systemic AE	
Comparison groups	PR51 v INFANRIX™ hexa

Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other[32]
Parameter estimate	Risk difference (RD)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	2.2

Notes:

[32] - The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% 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.

Statistical analysis title	Between group comparison

Statistical analysis description:

Between group comparison of at least 1 solicited systemic AE

Comparison groups	PR51 v INFANRIX™ hexa
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other[33]
Parameter estimate	Risk difference (RD)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	2.2

Notes:

[33] - The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% 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.

Statistical analysis title	Between group comparison

Statistical analysis description:

Between group comparison of at least 1 vaccine-related solicited systemic AE

Comparison groups	PR51 v INFANRIX™ hexa
Number of subjects included in analysis	1312
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	-0.4
upper limit	2.3

Notes:

[34] - The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% 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.

Secondary: Percentage of participants reporting solicited ISRs from D1 to D5 after any vaccination

End point title	Percentage of participants reporting solicited ISRs from D1 to D5 after any vaccination

End point description:

Adverse events at injection sites were always considered as related to vaccine (Injection-Site Reactions [ISRs]). Solicited ISRs were defined as injection-site erythema, injection-site pain, and injection-site swelling occurring from D1 to D5 after vaccination. Analysis population: all randomised participants who received at least 1 vaccination and who had safety follow-up.

End point type	Secondary

End point timeframe:

Up to 5 days (Day 1 to Day 5 following vaccination)

End point values	PR51	INFANRIX™ hexa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	653	659		
Units: Percentage of participants				
number (not applicable)				
Injection-site erythema	68.6	60.4		
Injection-site pain	73.4	70.0		
Injection-site swelling	56.8	49.3		

Statistical analyses

Statistical analysis title	Between group comparison

Statistical analysis description:

Between group comparison of injection-site erythema

Comparison groups	PR51 v INFANRIX™ hexa
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other[35]
Parameter estimate	Risk difference (RD)
Point estimate	8.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	3
upper limit	13.3

Notes:

[35] - The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% 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.

Statistical analysis title	Between group comparison

Statistical analysis description:

Between group comparison of injection-site pain

Comparison groups	PR51 v INFANRIX™ hexa
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other[36]
Parameter estimate	Risk difference (RD)
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	8.3

Notes:

[36] - The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% 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.

Statistical analysis title	Between group comparison

Statistical analysis description:

Between group comparison of injection-site swelling

Comparison groups	PR51 v INFANRIX™ hexa
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other[37]
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:

[37] - The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% 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.

Secondary: Percentage of participants reporting unsolicited ISRs from D1 to D15 after any vaccination

End point title	Percentage of participants reporting unsolicited ISRs from D1 to D15 after any vaccination

End point description:

Adverse events at injection sites were always considered as related to vaccine (Injection-Site Reactions [ISRs]). Unsolicited ISRs occurring from Day 1 (D1) to D15 after any vaccination were reported daily on the VRC by the parent(s) or legal representative. Unsolicited ISRs with incidence ≥1% are reported below. Analysis population: all randomised participants who received at least 1 vaccination and who had safety follow-up.

End point type	Secondary

End point timeframe:

From D1 to D15 after any vaccination

End point values	PR51	INFANRIX™ hexa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	653	659		
Units: Percentage of participants				
number (not applicable)				
Injection-site bruising	0.9	2.0		
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	Between group comparison
Statistical analysis description:	
Between group comparison of injection-site bruising	
Comparison groups	PR51 v INFANRIX™ hexa
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other[38]
Parameter estimate	Risk difference (RD)
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	0.3

Notes:

[38] - The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% 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.

Statistical analysis title	Between group comparison
Statistical analysis description:	
Between group comparison of injection-site haemorrhage	
Comparison groups	PR51 v INFANRIX™ hexa
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other[39]
Parameter estimate	Risk difference (RD)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	1.6

Notes:

[39] - The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% 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.

Statistical analysis title	Between group comparison
Statistical analysis description:	
Between group comparison of injection-site induration	
Comparison groups	PR51 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	Between group comparison
Statistical analysis description:	
Between group comparison of injection-site nodule	
Comparison groups	PR51 v INFANRIX™ hexa
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other[40]
Parameter estimate	Risk difference (RD)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	1.5

Notes:

[40] - The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% 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.

Statistical analysis title	Between group comparison
Statistical analysis description:	
Between group comparison of injection-site warmth	
Comparison groups	PR51 v INFANRIX™ hexa

Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other[41]
Parameter estimate	Risk difference (RD)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	2.7

Notes:

[41] - The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% 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.

Secondary: Percentage of participants reporting solicited adverse events (AEs) from D1 to D5 after any vaccination

End point title	Percentage of participants reporting solicited adverse events (AEs) from D1 to D5 after any vaccination

End point description:

Solicited systemic AEs were defined as crying, decreased appetite, irritability, pyrexia (rectal temperature ≥38.0°C), somnolence, and vomiting occurring from 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 population: all randomised participants who received at least 1 vaccination and who had safety follow-up.

End point type	Secondary

End point timeframe:

Up to 5 days (from D1 to D5 after any vaccination)

End point values	PR51	INFANRIX™ hexa		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	653	659		
Units: Percentage of participants				
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	31.0		

Statistical analyses

Statistical analysis title	Between group comparison

Statistical analysis description:

Between group comparison of crying

Comparison groups	PR51 v INFANRIX™ hexa

Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other[42]
Parameter estimate	Risk difference (RD)
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	5.7

Notes:

[42] - The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% 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.

Statistical analysis title	Between group comparison
Statistical analysis description:	
Between group comparison of decreased appetite	
Comparison groups	PR51 v INFANRIX™ hexa
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other[43]
Parameter estimate	Risk difference (RD)
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	8.8

Notes:

[43] - The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% CI were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Statistical analysis title	Between group comparison
Statistical analysis description:	
Between group comparison of irritability	
Comparison groups	PR51 v INFANRIX™ hexa
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other[44]
Parameter estimate	Risk difference (RD)
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	5.4

Notes:

[44] - The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% CI were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Statistical analysis title	Between group comparison
Statistical analysis description:	
Between group comparison of pyrexia	
Comparison groups	PR51 v INFANRIX™ hexa
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other[45]
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:

[45] - The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% CI were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. If the 95% CI for the risk differences included 0.0, the numerical differences were not considered significant.

Statistical analysis title	Between group comparison
Statistical analysis description:	
Between group comparison of somnolence	
Comparison groups	PR51 v INFANRIX™ hexa
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other[46]
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:

[46] - The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% 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.

Statistical analysis title	Between group comparison
Statistical analysis description:	
Between group comparison of vomiting	
Comparison groups	PR51 v INFANRIX™ hexa
Number of subjects included in analysis	1312
Analysis specification	Pre-specified
Analysis type	other[47]
Parameter estimate	Risk difference (RD)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	6.9

Notes:

[47] - The risk differences between groups (PR5I group – INFANRIX hexa group) and their 2-sided 95% CI were calculated for the above criteria based on the unstratified Miettinen & Nurminen method. 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:

Up to approximately 11 months. Serious AEs and deaths were collected for the duration of the study; unsolicited AEs were collected from D1 to D15 after each hexavalent vaccination, solicited AEs were collected D1 to D5 after each hexavalent vaccination

Adverse event reporting additional description:

Analysis population includes all randomised participants who received at least 1 vaccination and had safety follow-up.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	PR5I

Reporting group description:

Infant series: PR5I 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 2 and 4 months of age, and rotavirus vaccine (either Rotarix™ 1.5 mL oral dose at 2 and 4 months of age [subset 1] or RotaTeq™ 2 mL oral dose at 2, 4 and 5 months of age [subset 2]). Toddler dose: PR5I 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 11 to 12 months of age.

Reporting group title	INFANRIX™ hexa

Reporting group description:

Infant series: INFANRIX™ hexa 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 2 and 4 months of age, and rotavirus vaccine (either Rotarix™ 1.5 mL oral dose at 2 and 4 months of age [subset 1] or RotaTeq™ 2 mL oral dose at 2, 4 and 5 months of age [subset 2]). Toddler dose: INFANRIX™ hexa 0.5 mL injection + Prevenar 13™ 0.5 mL injection administered at 11 to 12 months of age.

Serious adverse events	PR5I	INFANRIX™ hexa	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 653 (0.92%)	10 / 659 (1.52%)	
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	1 / 653 (0.15%)	1 / 659 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
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	
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	
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	
Pneumonia respiratory syncytial viral			

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	
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	
Pyelonephritis acute			
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	
Streptococcal infection			
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	650 / 653 (99.54%)	653 / 659 (99.09%)	
Nervous system disorders			
Somnolence			
subjects affected / exposed	562 / 653 (86.06%)	529 / 659 (80.27%)	
occurrences (all)	1168	1118	
General disorders and administration site conditions			
Crying			
subjects affected / exposed	583 / 653 (89.28%)	574 / 659 (87.10%)	
occurrences (all)	1422	1305	
Injection site bruising			
subjects affected / exposed	13 / 653 (1.99%)	23 / 659 (3.49%)	
occurrences (all)	15	24	
Injection site erythema			
subjects affected / exposed	485 / 653 (74.27%)	450 / 659 (68.29%)	
occurrences (all)	1625	1490	
Injection site haemorrhage			
subjects affected / exposed	17 / 653 (2.60%)	17 / 659 (2.58%)	
occurrences (all)	21	20	
Injection site induration			
subjects affected / exposed	119 / 653 (18.22%)	107 / 659 (16.24%)	
occurrences (all)	266	246	
Injection site pain			
subjects affected / exposed	496 / 653 (75.96%)	493 / 659 (74.81%)	
occurrences (all)	1778	1656	
Injection site swelling			
subjects affected / exposed	406 / 653 (62.17%)	373 / 659 (56.60%)	
occurrences (all)	1179	1083	
Irritability			
subjects affected / exposed	598 / 653 (91.58%)	589 / 659 (89.38%)	
occurrences (all)	1518	1446	
Pyrexia			
subjects affected / exposed	490 / 653 (75.04%)	452 / 659 (68.59%)	
occurrences (all)	875	768	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	20 / 653 (3.06%)	10 / 659 (1.52%)	
occurrences (all)	23	11	
Constipation			
subjects affected / exposed	22 / 653 (3.37%)	16 / 659 (2.43%)	
occurrences (all)	25	18	
Diarrhoea			
subjects affected / exposed	76 / 653 (11.64%)	70 / 659 (10.62%)	
occurrences (all)	95	84	
Flatulence			
subjects affected / exposed	29 / 653 (4.44%)	25 / 659 (3.79%)	
occurrences (all)	32	29	
Vomiting			
subjects affected / exposed	220 / 653 (33.69%)	211 / 659 (32.02%)	
occurrences (all)	324	319	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	30 / 653 (4.59%)	24 / 659 (3.64%)	
occurrences (all)	31	29	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	35 / 653 (5.36%)	36 / 659 (5.46%)	
occurrences (all)	39	39	
Otitis media			
subjects affected / exposed	24 / 653 (3.68%)	15 / 659 (2.28%)	
occurrences (all)	26	15	
Rhinitis			
subjects affected / exposed	34 / 653 (5.21%)	41 / 659 (6.22%)	
occurrences (all)	39	44	
Upper respiratory tract infection			
subjects affected / exposed	41 / 653 (6.28%)	43 / 659 (6.53%)	
occurrences (all)	45	48	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	431 / 653 (66.00%)	411 / 659 (62.37%)	
occurrences (all)	731	694	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 April 2011	Amendment 1:The primary reasons for this amendment was (1) to designate that a subset of participants would receive Rotarix™ concomitantly with PR5I or INFANRIX hexa, while another subset of participants would receive RotaTeq™ concomitantly with PR5I or INFANRIX hexa; (2) revise the power statement for the secondary hypothesis for Rotarix™ immunogenicity; and (3) indicate that RotaTeq™ was to be administered at 2, 4, and 5 months of age.
13 May 2011	Amendment 2: The primary reason for this amendment was to designate that RotaTeq™ was to be supplied centrally by Merck.
20 January 2012	Amendment 3: The primary reason for this amendment was to allow the first dose of RotaTeq™ to be given in Finland prior to Visit 1 outside the study.
26 April 2013	Amendment 5: The primary reason for this amendment was to revise the statistical analysis plan.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported