Clinical trial results:
Open, Randomised, Comparative, Multicentre Study of the Immunogenicity and Safety of Concomitant versus Separate administration of a combined measles, mumps, rubella and varicella live vaccine (ProQuad®) and a Booster dose of Infanrix® hexa in Healthy Children 12 to 23 months of age

Summary

EudraCT number	2006-004129-27
Trial protocol	DE IT
Global end of trial date	27 March 2008

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	22 July 2015

Trial information

Trial identification

Sponsor protocol code	X06-MMRV-302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00432042
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 March 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 March 2008
Global end of trial reached?	Yes
Global end of trial date	27 March 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that ProQuad® can be administered concomitantly with a booster dose of Infanrix® hexa to healthy children of 12 to 23 months of age without impairing neither the antibody response rates to measles, mumps, rubella, varicella, hepatitis B, and Haemophilus influenzae type b, or to the 3 pertussis antibody titres measured at 42 days following vaccination.

Protection of trial subjects:

Healthy subjects with prior known sensitivity/allergy to any component of the vaccine including neomycin, sorbitol or gelatine were excluded.
Vaccines were administered by qualified study personnel.
After each vaccination, subjects were kept under observation for at least 20 minutes to ensure their safety.
Appropriate medical treatment and supervision were always readily available in case of a rare anaphylactic reaction following the administration of the vaccine.

Background therapy:

For Italy, primary vaccination with the combined diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and Haemophilus influenzae type b vaccine Infanrix hexa as a 2-dose schedule, with receipt of the 2nd dose ≥6 months prior to inclusion.
For Germany, primary vaccination with the combined diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and Haemophilus influenzae type b vaccine Infanrix hexa as a 3-dose schedule, with receipt of the 3rd dose ≥6 months prior to inclusion.

Evidence for comparator:

The immunisation schedule of hexavalent vaccines consists of a primary series followed by a booster dose given at the same age as ProQuad. The rationale of the study was to generate immunogenicity and safety data for ProQuad when administered concomitantly either with the 3rd dose of Infanrix hexa (Italian schedule) or with the 4th dose of Infanrix hexa (German schedule) given in the 2nd year of life. Therefore, concomitant administration of ProQuad and Infanrix hexa was compared to administration of each of these vaccines alone.

Actual start date of recruitment	12 January 2007
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	Germany: 728
Country: Number of subjects enrolled	Italy: 227
Worldwide total number of subjects	955
EEA total number of subjects	955

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)	954
Children (2-11 years)	1
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled between 12 January 2007 and 13 February 2008 in 51 active centres: 6 vaccination centres in Italy, and 45 private paediatricians in Germany.

Pre-assignment

Screening details:

963 subjects were screened.
955 subjects were randomised (14 subjects randomised in 1 centre in Germany were excluded from analyses due to a major Good Clinical Practice (GCP) non compliance (non reliability of vaccination history)).
952 subjects received at least 1 vaccine dose.
945 subjects completed the study.

Period 1

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

Blinding implementation details:

Not applicable as this study was open-label.
For immunogenicity data, serology tests were performed by laboratory staffs who were blinded to which vaccine each subject received.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1: ProQuad + Infanrix hexa

Arm description:

Subjects received ProQuad (measles, mumps, rubella and varicella (live attenuated)) vaccine dose 1 by subcutaneous route concomitantly with Infanrix hexa (DTaP-HBV-IPV-Hib = Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), and Haemophilus influenzae type b conjugate vaccine (adsorbed)) booster dose by intramuscular route at 12-23 months of age.
Subjects were blood sampled at (i) Day -7 (D-7) to D0 before vaccination = pre-vaccination, and (ii) 6 weeks (D42 to D56) after vaccination = post-vaccination.

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

Dosage and administration details:

0.5 mL, subcutaneous route (deltoid region), 1 dose at 12-23 months of age.
ProQuad had to be administered in the contralateral arm than the one for Infanrix hexa.

Investigational medicinal product name	Infanrix® hexa
Investigational medicinal product code	DTaP-HBs-IPV//Hib
Other name	Infanrix hexa
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular route (deltoid region), 1 dose at 12-23 months of age.
Infanrix hexa had to be administered in the contralateral arm than the one for ProQuad.

Arm title	Group 2: ProQuad

Arm description:

Subjects received ProQuad (measles, mumps, rubella and varicella (live attenuated)) vaccine dose 1 by subcutaneous route at 12-23 months of age.
Subjects were blood sampled at (i) Day -7 (D-7) to D0 before vaccination = pre-vaccination, and (ii) 6 weeks (D42 to D56) after vaccination = post-vaccination.

Arm type	Active comparator
Investigational medicinal product name	ProQuad®
Investigational medicinal product code	MMRV
Other name	ProQuad
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL, subcutaneous route (deltoid region), 1 dose at 12-23 months of age.

Arm title	Group 3: Infanrix hexa

Arm description:

Subjects received Infanrix hexa (DTaP-HBV-IPV-Hib = Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), and Haemophilus influenzae type b conjugate vaccine (adsorbed)) booster dose by intramuscular route at 12-23 months of age.
Subjects were blood sampled at (i) Day -7 (D-7) to D0 before vaccination = pre-vaccination, and (ii) 6 weeks (D42 to D56) after vaccination = post-vaccination.

Arm type	Active comparator
Investigational medicinal product name	Infanrix® hexa
Investigational medicinal product code	DTaP-HBs-IPV//Hib
Other name	Infanrix hexa
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular route (deltoid region), 1 dose at 12-23 months of age.

Number of subjects in period 1	Group 1: ProQuad + Infanrix hexa	Group 2: ProQuad	Group 3: Infanrix hexa
Started	479	235	241
Completed	472	234	239
Not completed	7	1	2
Personal reason	-	-	2
Lost to follow-up	5	1	-
Protocol deviation	2	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Group 1: ProQuad + Infanrix hexa
Reporting group description:	
# Subjects received ProQuad (measles, mumps, rubella and varicella (live attenuated)) vaccine dose 1 by subcutaneous route concomitantly with Infanrix hexa (DTaP-HBV-IPV-Hib = Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), and Haemophilus influenzae type b conjugate vaccine (adsorbed)) booster dose by intramuscular route at 12-23 months of age. # Subjects were blood sampled at (i) Day -7 (D-7) to D0 before vaccination = pre-vaccination, and (ii) 6 weeks (D42 to D56) after vaccination = post-vaccination.	
Reporting group title	Group 2: ProQuad
Reporting group description:	
# Subjects received ProQuad (measles, mumps, rubella and varicella (live attenuated)) vaccine dose 1 by subcutaneous route at 12-23 months of age. # Subjects were blood sampled at (i) Day -7 (D-7) to D0 before vaccination = pre-vaccination, and (ii) 6 weeks (D42 to D56) after vaccination = post-vaccination.	
Reporting group title	Group 3: Infanrix hexa
Reporting group description:	
# Subjects received Infanrix hexa (DTaP-HBV-IPV-Hib = Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), and Haemophilus influenzae type b conjugate vaccine (adsorbed)) booster dose by intramuscular route at 12-23 months of age. # Subjects were blood sampled at (i) Day -7 (D-7) to D0 before vaccination = pre-vaccination, and (ii) 6 weeks (D42 to D56) after vaccination = post-vaccination.	

Reporting group values	Group 1: ProQuad + Infanrix hexa	Group 2: ProQuad	Group 3: Infanrix hexa
Number of subjects	479	235	241
Age categorical			
Age at vaccination.			
Units: Subjects			
≥12 and <24 months	474	234	238
<12 or ≥24 months	5	1	3
Age continuous			
Age at vaccination (3 missing values: N=477, 235, 240 respectively)			
Units: months			
arithmetic mean	13.6	13.4	13.5
standard deviation	± 1.9	± 1.5	± 1.7
Gender categorical			
Units: Subjects			
Female	222	112	114
Male	257	123	127

Reporting group values	Total		
Number of subjects	955		
Age categorical			
Age at vaccination.			
Units: Subjects			
≥12 and <24 months	946		
<12 or ≥24 months	9		

Age continuous			
Age at vaccination (3 missing values: N=477, 235, 240 respectively)			
Units: months			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	448		
Male	507		

End points

End points reporting groups

Reporting group title	Group 1: ProQuad + Infanrix hexa

Reporting group description:

Subjects received ProQuad (measles, mumps, rubella and varicella (live attenuated)) vaccine dose 1 by subcutaneous route concomitantly with Infanrix hexa (DTaP-HBV-IPV-Hib = Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), and Haemophilus influenzae type b conjugate vaccine (adsorbed)) booster dose by intramuscular route at 12-23 months of age.
Subjects were blood sampled at (i) Day -7 (D-7) to D0 before vaccination = pre-vaccination, and (ii) 6 weeks (D42 to D56) after vaccination = post-vaccination.

Reporting group title	Group 2: ProQuad

Reporting group description:

Subjects received ProQuad (measles, mumps, rubella and varicella (live attenuated)) vaccine dose 1 by subcutaneous route at 12-23 months of age.
Subjects were blood sampled at (i) Day -7 (D-7) to D0 before vaccination = pre-vaccination, and (ii) 6 weeks (D42 to D56) after vaccination = post-vaccination.

Reporting group title	Group 3: Infanrix hexa

Reporting group description:

Subjects received Infanrix hexa (DTaP-HBV-IPV-Hib = Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), and Haemophilus influenzae type b conjugate vaccine (adsorbed)) booster dose by intramuscular route at 12-23 months of age.
Subjects were blood sampled at (i) Day -7 (D-7) to D0 before vaccination = pre-vaccination, and (ii) 6 weeks (D42 to D56) after vaccination = post-vaccination.

Primary: Antibody (Ab) response rates to Measles, Mumps, Rubella, and Varicella 6 weeks after ProQuad dose 1, administered concomitantly or not with Infanrix hexa booster dose (Group 1 vs Group 2)

End point title	Antibody (Ab) response rates to Measles, Mumps, Rubella, and Varicella 6 weeks after ProQuad dose 1, administered concomitantly or not with Infanrix hexa booster dose (Group 1 vs Group 2)[1]

End point description:

Percentage of subjects with an Ab titre ≥255 mIU/mL for Measles, ≥10 ELISA Ab units/mL for Mumps, ≥10 IU/mL for Rubella, and ≥5 gpELISA units/mL for Varicella 6 weeks after ProQuad dose 1, administered concomitantly or not with Infanrix hexa booster dose.
All Ab titres were measured by Enzyme-Linked Immunosorbent Assay (ELISA), except Ab to Varicella determined by glycoprotein ELISA (gpELISA).
Analysis was done on the Antigen-Specific Per Protocol Set (PPS), i.e. all randomised subjects initially seronegative for those antigens (Measles Ab titre <255 mIU/mL, Mumps Ab titre <10 ELISA Ab units/mL, Rubella Ab titre <10 IU/mL, and Varicella Ab titre <1.25 gpELISA units/mL) excluding subjects with protocol violations which may interfere with the immunogenicity evaluation.
Note: (N=***, ***) represents the number of assessed subjects in the "ProQuad + Infanrix hexa" and "ProQuad" groups, respectively.

End point type	Primary

End point timeframe:

6 weeks after ProQuad dose 1, administered concomitantly or not with Infanrix hexa booster dose.

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The objective of this endpoint was to evaluate the antibody response rates to Measles, Mumps, Rubella, and Varicella 6 weeks after ProQuad dose 1, administered concomitantly or not with Infanrix hexa booster dose. So this endpoint did not concern subjects of the "Infanrix hexa" arm.

End point values	Group 1: ProQuad + Infanrix hexa	Group 2: ProQuad		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	431	215		
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-Measles ≥255 mIU/mL (N=421, 215)	97.4 (95.4 to 98.7)	96.3 (92.8 to 98.4)		
Anti-Mumps ≥10 ELISA Ab units/mL (N=427, 212)	96.7 (94.6 to 98.2)	98.6 (95.9 to 99.7)		
Anti-Rubella ≥10 IU/mL (N=431, 215)	97.9 (96.1 to 99)	99.1 (96.7 to 99.9)		
Anti-Varicella ≥5 gpELISA units/mL (N=394, 205)	97.7 (95.7 to 99)	95.1 (91.2 to 97.6)		

Statistical analyses

Statistical analysis title	Non-inferiority for Measles

Statistical analysis description:

The estimates of the differences between Group 1 (ProQuad + Infanrix hexa) & Group 2 (ProQuad) response rates were calculated with their 2-sided 95% confidence interval (CI). If the lower bounds of the 95% CI were greater than the non-inferiority margin, it was concluded that Group 1 response rates were non-inferior to Group 2 response rates.
Statistical analysis was based on the Miettinen & Nurminen method with stratification by region.
Analysis was done on the Antigen-specific PPS.

Comparison groups	Group 1: ProQuad + Infanrix hexa v Group 2: ProQuad
Number of subjects included in analysis	646
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Difference in percentage of subjects
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.62
upper limit	4.82

Notes:

[2] - For Measles: # Antigen-specific PPS, N=421, 215 (Groups 1 & 2) # Response rate based on Ab titre ≥255 mIU/mL # Non-inferiority margin, -10%.

Statistical analysis title	Non-inferiority for Mumps

Statistical analysis description:

The estimates of the differences between Group 1 (ProQuad + Infanrix hexa) & Group 2 (ProQuad) response rates were calculated with their 2-sided 95% confidence interval (CI). If the lower bounds of the 95% CI were greater than the non-inferiority margin, it was concluded that Group 1 response rates were non-inferior to Group 2 response rates.
Statistical analysis was based on the Miettinen & Nurminen method with stratification by region.
Analysis was done on the Antigen-specific PPS.

Comparison groups	Group 1: ProQuad + Infanrix hexa v Group 2: ProQuad

Number of subjects included in analysis	646
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Difference in percentage of subjects
Point estimate	-1.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.21
upper limit	1.1

Notes:

[3] - For Mumps: # Antigen-specific PPS, N=427, 212 (Groups 1 & 2) # Response rate based on Ab titre ≥10 ELISA Ab units/mL # Non-inferiority margin, -10%.

Statistical analysis title	Non-inferiority for Rubella

Statistical analysis description:

The estimates of the differences between Group 1 (ProQuad + Infanrix hexa) & Group 2 (ProQuad) response rates were calculated with their 2-sided 95% confidence interval (CI). If the lower bounds of the 95% CI were greater than the non-inferiority margin, it was concluded that Group 1 response rates were non-inferior to Group 2 response rates.
Statistical analysis was based on the Miettinen & Nurminen method with stratification by region.
Analysis was done on the Antigen-specific PPS.

Comparison groups	Group 1: ProQuad + Infanrix hexa v Group 2: ProQuad
Number of subjects included in analysis	646
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	Difference in percentage of subjects
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.19
upper limit	1.35

Notes:

[4] - For Rubella: # Antigen-specific PPS, N=431, 215 (Groups 1 & 2) # Response rate based on Ab titre ≥10 IU/mL # Non-inferiority margin, -10%.

Statistical analysis title	Non-inferiority for Varicella

Statistical analysis description:

The estimates of the differences between Group 1 (ProQuad + Infanrix hexa) & Group 2 (ProQuad) response rates were calculated with their 2-sided 95% confidence interval (CI). If the lower bounds of the 95% CI were greater than the non-inferiority margin, it was concluded that Group 1 response rates were non-inferior to Group 2 response rates.
Statistical analysis was based on the Miettinen & Nurminen method with stratification by region.
Analysis was done on the Antigen-specific PPS.

Comparison groups	Group 1: ProQuad + Infanrix hexa v Group 2: ProQuad
Number of subjects included in analysis	646
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	Difference in percentage of subjects
Point estimate	2.53

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	6.58

Notes:

[5] - For Varicella: # Antigen-specific PPS, N=394, 205 (Groups 1 & 2) # Response rate based on Ab titre ≥5 gpELISA units/mL # Non-inferiority margin, -10%.

Primary: Antibody (Ab) response rates to Hepatitis B and Haemophilus influenzae type b (PRP) 6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1 (Group 1 vs Group 3)

End point title	Antibody (Ab) response rates to Hepatitis B and Haemophilus influenzae type b (PRP) 6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1 (Group 1 vs Group 3)[6]

End point description:

Percentage of subjects with an Ab titre ≥10 IU/mL for Hepatitis B, and ≥1 µg/mL for Haemophilus influenzae type b (polyribosylribitol phosphate, PRP) 6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1.
Ab titres were measured by enhanced chemiluminescence (ECi) assay for Hepatitis B and Farr-type radioimmunoassay for PRP.
Analysis was done on the Per Protocol Set (PPS), i.e. all randomised subjects excluding those with protocol violations which may interfere with the immunogenicity evaluation.
Note: (N=***, ***) represents the number of assessed subjects in the "ProQuad + Infanrix hexa" and "Infanrix hexa" groups, respectively.

End point type	Primary

End point timeframe:

6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The objective of this endpoint was to evaluate the antibody response rates to Hepatitis B and Haemophilus influenzae type b (PRP) 6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1. So this endpoint did not concern subjects of the "ProQuad" arm.

End point values	Group 1: ProQuad + Infanrix hexa	Group 3: Infanrix hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	215		
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-Hepatitis B ≥10 IU/mL (N=411, 215)	99.5 (98.3 to 99.9)	98.1 (95.3 to 99.5)		
Anti-PRP ≥1 µg/mL (N=387, 211)	98.2 (96.3 to 99.3)	95.3 (91.5 to 97.7)		

Statistical analyses

Statistical analysis title	Non-inferiority for Hepatitis B

Statistical analysis description:

The estimates of the differences between Group 1 (ProQuad + Infanrix hexa) & Group 3 (Infanrix hexa) response rates were calculated with their 2-sided 95% confidence interval (CI). If the lower bounds of the 95% CI were greater than the non-inferiority margin, it was concluded that Group 1 response rates were non-inferior to Group 3 response rates.

Statistical analysis was based on the Miettinen & Nurminen method with stratification by region. Analysis was done on the PPS.

Comparison groups	Group 1: ProQuad + Infanrix hexa v Group 3: Infanrix hexa
Number of subjects included in analysis	626
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Parameter estimate	Difference in percentage of subjects
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	4.24

Notes:

[7] - For Hepatitis B: # PPS, N=411, 215 (Groups 1 & 3) # Response rate based on Ab titre ≥10 IU/mL # Non-inferiority margin, -5%.

Statistical analysis title	Non-inferiority for PRP

Statistical analysis description:

The estimates of the differences between Group 1 (ProQuad + Infanrix hexa) & Group 3 (Infanrix hexa) response rates were calculated with their 2-sided 95% confidence interval (CI). If the lower bounds of the 95% CI were greater than the non-inferiority margin, it was concluded that Group 1 response rates were non-inferior to Group 3 response rates.
Statistical analysis was based on the Miettinen & Nurminen method with stratification by region. Analysis was done on the PPS.

Comparison groups	Group 1: ProQuad + Infanrix hexa v Group 3: Infanrix hexa
Number of subjects included in analysis	626
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Parameter estimate	Difference in percentage of subjects
Point estimate	2.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	6.89

Notes:

[8] - For PRP: # PPS, N=387, 211 (Groups 1 & 3) # Response rate based on Ab titre ≥1 µg/mL # Non-inferiority margin, -5%.

Primary: Geometric Mean Titres (GMT) for the 3 pertussis antigens (PT, FHA & PRN) 6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1 (Group 1 vs Group 3)

End point title	Geometric Mean Titres (GMT) for the 3 pertussis antigens (PT, FHA & PRN) 6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1 (Group 1 vs Group 3)[9]

End point description:

Antibody titres expressed in EU/mL were measured for the 3 pertussis antigens (Pertussis toxoid (PT), Filamentous haemagglutinin (FHA) & Pertactin (PRN)) by Enzyme-Linked Immunosorbent Assay (ELISA) 6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1. Analysis was done on the Per Protocol Set (PPS), i.e. all randomised subjects excluding those with protocol violations which may interfere with the immunogenicity evaluation.
Note: (N=***, ***) represents the number of assessed subjects in the "ProQuad + Infanrix hexa" and "Infanrix hexa" groups, respectively.

End point type	Primary

End point timeframe:

6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1.

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The objective of this endpoint was to evaluate the Geometric Mean Titres (GMT) for the 3 pertussis antigens (PT, FHA & PRN) 6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1. So this endpoint did not concern subjects of the "ProQuad" arm.

End point values	Group 1: ProQuad + Infanrix hexa	Group 3: Infanrix hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	386	211		
Units: Titres				
geometric mean (confidence interval 95%)				
Anti-PT GMT (N=379, 209)	132.6 (123.8 to 142)	139.1 (126.7 to 152.8)		
Anti-FHA GMT (N=386, 211)	210.9 (195.7 to 227.2)	189.9 (170.2 to 211.8)		
Anti-PRN GMT (N=385, 211)	310 (282.2 to 340.7)	259.7 (226.3 to 298.1)		

Statistical analyses

Statistical analysis title	Non-inferiority for PT

Statistical analysis description:

The estimates of the post-vaccination GMT ratios Group 1 (ProQuad + Infanrix hexa) / Group 3 (Infanrix hexa) were calculated with their 2-sided 95% confidence interval (CI) and adjusted for pre-vaccination titres, Infanrix hexa primary vaccination & region. If the lower bounds of the 95% CI were greater than the non-inferiority margin, it was concluded that Group 1 GMT were non-inferior to Group 3 GMT. Analysis was done on the PPS.

Comparison groups	Group 3: Infanrix hexa v Group 1: ProQuad + Infanrix hexa
Number of subjects included in analysis	597
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
Parameter estimate	GMT ratio
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.08

Notes:

[10] - For PT: # PPS, N=379, 209 (Groups 1 & 3) # Non-inferiority margin, 0.5.
Statistical analysis was based on an ANCOVA model with the log-transformed post-vaccination titres as response, the log-transformed baseline titres as covariate, the Infanrix hexa primary vaccination, the Region (nested effect) and the Group as fixed effects.

Statistical analysis title	Non-inferiority for FHA

Statistical analysis description:

The estimates of the post-vaccination GMT ratios Group 1 (ProQuad + Infanrix hexa) / Group 3 (Infanrix hexa) were calculated with their 2-sided 95% confidence interval (CI) and adjusted for pre-vaccination

titres, Infanrix hexa primary vaccination & region. If the lower bounds of the 95% CI were greater than the non-inferiority margin, it was concluded that Group 1 GMT were non-inferior to Group 3 GMT. Analysis was done on the PPS.

Comparison groups	Group 1: ProQuad + Infanrix hexa v Group 3: Infanrix hexa
Number of subjects included in analysis	597
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
Parameter estimate	GMT ratio
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.23

Notes:

[11] - For FHA: # PPS, N=386, 211 (Groups 1 & 3) # Non-inferiority margin, 0.5.
Statistical analysis was based on an ANCOVA model with the log-transformed post-vaccination titres as response, the log-transformed baseline titres as covariate, the Infanrix hexa primary vaccination, the Region (nested effect) and the Group as fixed effects.

Statistical analysis title	Non-inferiority for PRN

Statistical analysis description:

The estimates of the post-vaccination GMT ratios Group 1 (ProQuad + Infanrix hexa) / Group 3 (Infanrix hexa) were calculated with their 2-sided 95% confidence interval (CI) and adjusted for pre-vaccination titres, Infanrix hexa primary vaccination & region. If the lower bounds of the 95% CI were greater than the non-inferiority margin, it was concluded that Group 1 GMT were non-inferior to Group 3 GMT. Analysis was done on the PPS.

Comparison groups	Group 1: ProQuad + Infanrix hexa v Group 3: Infanrix hexa
Number of subjects included in analysis	597
Analysis specification	Pre-specified
Analysis type	non-inferiority[12]
Parameter estimate	GMT ratio
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	1.36

Notes:

[12] - For PRN: # PPS, N=385, 211 (Groups 1 & 3) # Non-inferiority margin, 0.5.
Statistical analysis was based on an ANCOVA model with the log-transformed post-vaccination titres as response, the log-transformed baseline titres as covariate, the Infanrix hexa primary vaccination, the Region (nested effect) and the Group as fixed effects.

Secondary: Geometric Mean Titres (GMT) for Measles, Mumps, Rubella, and Varicella 6 weeks after ProQuad dose 1, administered concomitantly or not with Infanrix hexa booster dose (Group 1 vs Group 2)

End point title	Geometric Mean Titres (GMT) for Measles, Mumps, Rubella, and Varicella 6 weeks after ProQuad dose 1, administered concomitantly or not with Infanrix hexa booster dose (Group 1 vs Group 2)[13]

End point description:

Antibody (Ab) titres were measured for Measles, Mumps & Rubella by ELISA, and for Varicella by gpELISA 6 weeks after ProQuad dose 1, administered concomitantly or not with Infanrix hexa booster dose.
Ab titres are expressed in ELISA mIU/mL for Measles, ELISA Ab units/mL for Mumps, IU/mL for Rubella, & gpELISA units /mL for Varicella.
Analysis was done on the Antigen-Specific Per Protocol Set (PPS), i.e. all randomised subjects initially

seronegative for those antigens (Measles Ab titre <255 mIU/mL, Mumps Ab titre <10 ELISA Ab units/mL, Rubella Ab titre <10 IU/mL, and Varicella Ab titre <1.25 gpELISA units/mL) excluding subjects with protocol violations which may interfere with the immunogenicity evaluation.
Note: (N=***, ***) represents the number of assessed subjects in the "ProQuad + Infanrix hexa" and "ProQuad" groups, respectively.

End point type	Secondary

End point timeframe:

6 weeks after ProQuad dose 1, administered concomitantly or not with Infanrix hexa booster dose.

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The objective of this endpoint was to evaluate the Geometric Mean Titres (GMT) for Measles, Mumps, Rubella, and Varicella 6 weeks after ProQuad dose 1, administered concomitantly or not with Infanrix hexa booster dose. So this endpoint did not concern subjects of the "Infanrix hexa" arm.

End point values	Group 1: ProQuad + Infanrix hexa	Group 2: ProQuad		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	431	215		
Units: Titres				
geometric mean (confidence interval 95%)				
Anti-Measles GMT (N=421, 215)	4581 (4148 to 5061)	4056 (3520 to 4672)		
Anti-Mumps GMT (N=427, 212)	116 (107 to 127)	126 (113 to 139)		
Anti-Rubella GMT (N=431, 215)	90 (83 to 97)	90 (81 to 99)		
Anti-Varicella GMT (N=394, 205)	16.64 (15.61 to 17.75)	15.31 (13.91 to 16.86)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with anti-Varicella antibody (Ab) titre ≥1.25 gpELISA units/mL 6 weeks after ProQuad dose 1, administered concomitantly or not with Infanrix hexa booster dose (Group 1 vs Group 2)

End point title	Percentage of subjects with anti-Varicella antibody (Ab) titre ≥1.25 gpELISA units/mL 6 weeks after ProQuad dose 1, administered concomitantly or not with Infanrix hexa booster dose (Group 1 vs Group 2)[14]

End point description:

Percentage of subjects with anti-Varicella Ab titre ≥1.25 gpELISA units/mL measured by glycoprotein ELISA (gpELISA) 6 weeks after ProQuad dose 1, administered concomitantly or not with Infanrix hexa booster dose.
Analysis was done on the Varicella-Specific Per Protocol Set (PPS), i.e. all randomised subjects initially seronegative for Varicella (Ab titre <1.25 gpELISA units/mL) excluding subjects with protocol violations which may interfere with the immunogenicity evaluation.
Note: (N=***, ***) represents the number of assessed subjects in the "ProQuad + Infanrix hexa" and "ProQuad" groups, respectively.

End point type	Secondary

End point timeframe:

6 weeks after ProQuad dose 1, administered concomitantly or not with Infanrix hexa booster dose.

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The objective of this endpoint was to evaluate the of subjects with anti-Varicella antibody (Ab) titre ≥1.25 gpELISA units/mL 6 weeks after ProQuad dose 1, administered concomitantly or not with Infanrix hexa booster dose. So this endpoint did not concern subjects of the "Infanrix hexa" arm.

End point values	Group 1: ProQuad + Infanrix hexa	Group 2: ProQuad		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	394	205		
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-Varicella ≥1.25 gpELISA units/mL (N=394, 205)	98.5 (96.7 to 99.4)	98.5 (95.8 to 99.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Antibody (Ab) response rates to Diphtheria, Tetanus, and Poliomyelitis types 1, 2 & 3, 6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1 (Group 1 vs Group 3)

End point title	Antibody (Ab) response rates to Diphtheria, Tetanus, and Poliomyelitis types 1, 2 & 3, 6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1 (Group 1 vs Group 3)[15]

End point description:

Percentage of subjects with an Ab titre ≥0.1 IU/mL for Diphtheria & Tetanus, and ≥8 (1/dil) for Poliomyelitis types 1, 2 & 3, 6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1.
Ab titres were measured by a toxin neutralization test for Diphtheria, by ELISA for Tetanus, and by seroneutralisation (SN) for Poliomyelitis types 1, 2 & 3.
Analysis was done on the Per Protocol Set (PPS), i.e. all randomised subjects excluding those with protocol violations which may interfere with the immunogenicity evaluation.
Note: (N=***, ***) represents the number of assessed subjects in the “ProQuad + Infanrix hexa” and “Infanrix hexa” groups, respectively.

End point type	Secondary

End point timeframe:

6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1.

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The objective of this endpoint was to evaluate the antibody response rates to Diphtheria, Tetanus, and Poliomyelitis types 1, 2 & 3, 6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1. So this endpoint did not concern subjects of the "ProQuad" arm.

End point values	Group 1: ProQuad + Infanrix hexa	Group 3: Infanrix hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	375	208		
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-Diphtheria ≥0.1 IU/mL (N=375, 206)	99.7 (98.5 to 100)	100 (98.2 to 100)		
Anti-Tetanus ≥0.1 IU/mL (N=375, 208)	100 (99 to 100)	100 (98.2 to 100)		
Anti-Poliomyelitis type 1 ≥8 (1/dil) (N=360, 203)	100 (99 to 100)	99.5 (97.3 to 100)		
Anti-Poliomyelitis type 2 ≥8 (1/dil) (N=361, 200)	100 (99 to 100)	100 (98.2 to 100)		
Anti-Poliomyelitis type 3 ≥8 (1/dil) (N=358, 201)	100 (99 to 100)	99.5 (97.3 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titres (GMT) for Diphtheria, Tetanus, Poliomyelitis types 1, 2 & 3, Hepatitis B and Haemophilus influenzae type b 6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1 (Group 1 vs Group 3)

End point title	Geometric Mean Titres (GMT) for Diphtheria, Tetanus, Poliomyelitis types 1, 2 & 3, Hepatitis B and Haemophilus influenzae type b 6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1 (Group 1 vs Group 3)[16]

End point description:

Antibody (Ab) titres were measured for Diphtheria by a toxin neutralization test, for Tetanus by ELISA, for Poliomyelitis types 1, 2 & 3 by SN, for Hepatitis B by ECi assay, and for Haemophilus influenzae type b (PRP) by Farr-type radioimmunoassay 6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1.
Ab titres are expressed in IU/mL for Diphtheria & Tetanus, 1/dil for Poliomyelitis types 1, 2 & 3, mIU/mL for Hepatitis B, and µg/mL for PRP.
Analysis was done on the Per Protocol Set (PPS), i.e. all randomised subjects excluding those with protocol violations which may interfere with the immunogenicity evaluation.
Note: (N=***, ***) represents the number of assessed subjects in the "ProQuad + Infanrix hexa" and "Infanrix hexa" groups, respectively.

End point type	Secondary

End point timeframe:

6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1.

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The objective of this endpoint was to evaluate the Geometric Mean Titres (GMT) for Diphtheria, Tetanus, Poliomyelitis types 1, 2 & 3, Hepatitis B and Haemophilus influenzae type b 6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1. So this endpoint did not concern subjects of the "ProQuad" arm.

End point values	Group 1: ProQuad + Infanrix hexa	Group 3: Infanrix hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411	215		
Units: Titres				
geometric mean (confidence interval 95%)				
Anti-Diphtheria GMT (N=375, 206)	3.11 (2.8 to 3.45)	2.83 (2.46 to 3.26)		
Anti-Tetanus GMT (N=375, 208)	4.8 (4.4 to 5.24)	4.04 (3.6 to 4.53)		
Anti-Poliomyelitis type 1 GMT (N=360, 203)	8161 (7085 to 9399)	5494 (4492 to 6720)		
Anti-Poliomyelitis type 2 GMT (N=361, 200)	9841 (8590 to 11274)	6439 (5195 to 7981)		
Anti-Poliomyelitis type 3 GMT (N=358, 201)	11070 (9603 to 12762)	7956 (6436 to 9834)		
Anti-Hepatitis B GMT (N=411, 215)	2662 (2240 to 3163)	1809 (1424 to 2298)		
Anti-PRP GMT (N=387, 211)	34.3 (29.8 to 39.6)	20.9 (17.2 to 25.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Antibody (Ab) response rates to the 3 pertussis antigens (PT, FHA & PRN) 6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1 (Group 1 vs Group 3)

End point title	Antibody (Ab) response rates to the 3 pertussis antigens (PT, FHA & PRN) 6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1 (Group 1 vs Group 3)[17]

End point description:

Percentage of subjects with pertussis Ab titres for the 3 pertussis antigens (Pertussis toxoid (PT), Filamentous haemagglutinin (FHA) & Pertactin (PRN)) ≥Lower Limit of Quantification (LLOQ) in subjects with baseline Ab titres <LLOQ, or with Ab titres equal or greater than the baseline titres in subjects with baseline Ab titres ≥LLOQ 6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1.
Ab titres were measured by Enzyme-Linked Immunosorbent Assay (ELISA).
Analysis was done on the Per Protocol Set (PPS), i.e. all randomised subjects excluding those with protocol violations which may interfere with the immunogenicity evaluation.
Note: (N=***, ***) represents the number of assessed subjects in the "ProQuad + Infanrix hexa" and "Infanrix hexa" groups, respectively.

End point type	Secondary

End point timeframe:

6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1.

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The objective of this endpoint was to evaluate the antibody response rates to the 3 pertussis antigens (PT, FHA & PRN) 6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1. So this endpoint did not concern subjects of the "ProQuad" arm.

End point values	Group 1: ProQuad + Infanrix hexa	Group 3: Infanrix hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354	205		
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-PT (N=345, 199)	99.7 (98.4 to 100)	99.5 (97.2 to 100)		
Anti-FHA (N=354, 205)	99.2 (97.5 to 99.8)	98 (95.1 to 99.5)		
Anti-PRN (N=354, 205)	99.4 (98 to 99.9)	99.5 (97.3 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titres Ratios (GMTR) for the 3 Pertussis antigens (PT, FHA & PRN) 6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1 (Group 1 vs Group 3)

End point title	Geometric Mean Titres Ratios (GMTR) for the 3 Pertussis antigens (PT, FHA & PRN) 6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1 (Group 1 vs Group 3)[18]

End point description:

Study participants were blood sampled between Day -7 (D-7) and D0 before vaccination (pre-vaccination) and 6 weeks (D42 to D56) after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1 (post-vaccination).
Antibody (Ab) titres were measured by ELISA for the 3 Pertussis antigens (Pertussis toxoid (PT), Filamentous haemagglutinin (FHA) & Pertactin (PRN)).
Individual post- / pre-vaccination anti-Pertussis Ab titres ratios were calculated for the 3 Pertussis antigens (PT, FHA & PRN).
Analysis was done on the Per Protocol Set (PPS), i.e. all randomised subjects excluding those with protocol violations which may interfere with the immunogenicity evaluation.
Note: (N=***, ***) represents the number of assessed subjects in the "ProQuad + Infanrix hexa" and "Infanrix hexa" groups, respectively.

End point type	Secondary

End point timeframe:

6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1.

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The objective of this endpoint was to evaluate the Geometric Mean Titres Ratios (GMTR) of individual post-/pre-vaccination anti-Pertussis antibody (Ab) titres for the 3 Pertussis antigens (PT, FHA & PRN) 6 weeks after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1. So this endpoint did not concern subjects of the "ProQuad" arm.

End point values	Group 1: ProQuad + Infanrix hexa	Group 3: Infanrix hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354	205		
Units: Not applicable				
geometric mean (confidence interval 95%)				

Anti-PT GMTR (N=345, 199)	6.9 (6.4 to 7.5)	6.9 (6.2 to 7.7)		
Anti-FHA GMTR (N=354, 205)	7.5 (6.9 to 8.2)	7.1 (6.3 to 8)		
Anti-PRN GMTR (N=354, 205)	16 (14.6 to 17.7)	14 (12.2 to 16.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Global summary of safety from D0 to D28 after vaccination with ProQuad dose 1 and Infanrix hexa booster dose, administered concomitantly or alone

End point title	Global summary of safety from D0 to D28 after vaccination with ProQuad dose 1 and Infanrix hexa booster dose, administered concomitantly or alone

End point description:

Adverse events (AEs) occurring after vaccination with ProQuad and Infanrix hexa, administered concomitantly or alone, were recorded as follows:
1/ From D0 to D4: solicited injection-site adverse reactions (ISRs: erythema, pain, and swelling).
2/ From D0 to D28: # unsolicited ISRs (including erythema, pain, and swelling from D5 to D28), # AEs of interest (a/ injection-site rashes of interest, b/ non-injection site rashes of interest (Measles-like rash, Rubella-like rash, Varicella-like rash and Herpes zoster-like rash), c/ Mumps-like illness), # rectal or equivalent temperature, and # unsolicited systemic AEs.
AEs at injection sites were always considered as related to ProQuad or Infanrix hexa vaccines (ISRs).
The investigator had to assess whether systemic AEs were vaccine-related systemic AEs or not.
Analysis was done on the Safety Analysis Set, i.e. all subjects who received at least 1 of the study vaccine(s) and who had safety follow-up data.
Note: "0" means not applicable.

End point type	Secondary

End point timeframe:

From Day 0 (D0) to D28 after administration of ProQuad dose 1 and Infanrix hexa booster dose, administered concomitantly or alone.

End point values	Group 1: ProQuad + Infanrix hexa	Group 2: ProQuad	Group 3: Infanrix hexa	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	474	234	239	
Units: Percentage of subjects				
number (not applicable)				
At least 1 AE (ISR or systemic AE) (D0-D28)	90.5	72.6	84.1	
At least 1 ProQuad-related AE (D0-D28)	54.4	46.6	0	
At least 1 Infanrix hexa-related AE (D0-D28)	71.9	0	69.5	
At least 1 ISR (D0-D28)	73.4	26.5	65.3	
At least 1 ISR to ProQuad (D0-D28)	36.3	26.5	0	
At least 1 solicited ISR to ProQuad (D0-D4)	31.6	19.7	0	
At least 1 ISR to Infanrix hexa (D0-D28)	65.8	0	65.3	
At least 1 solicited ISR to Infanrix hexa (D0-D4)	65.4	0	65.3	
At least 1 systemic AE (D0-D28)	70	65	62.3	

At least 1 ProQuad-related systemic AE (D0-D28)	32.1	29.5	0	
At least 1 Infanrix hexa-related syst. AE (D0-D28)	21.1	0	16.7	
At least 1 rectal temperature ≥38°C (D0-D28)	69.3	61.1	57.3	
At least 1 rectal temperature ≥39.4°C (D0-D28)	22.6	20.5	15.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Solicited injection-site reactions (ISRs) to ProQuad from D0 to D4 after ProQuad dose 1, administered concomitantly or not with Infanrix hexa booster dose (Group 1 vs Group 2)

End point title	Solicited injection-site reactions (ISRs) to ProQuad from D0 to D4 after ProQuad dose 1, administered concomitantly or not with Infanrix hexa booster dose (Group 1 vs Group 2)[19]

End point description:

Solicited injection-site adverse reactions (ISRs) to ProQuad were recorded from D0 to D4 after ProQuad dose 1, administered concomitantly or not with Infanrix hexa booster dose.
AEs at ProQuad injection site were always considered as related to ProQuad (ISRs).
Percentage of subjects presenting at least once the considered ISRs are presented here.
Analysis was done on the Safety Analysis Set, i.e. all subjects who received at least 1 of the study vaccine(s) and who had safety follow-up data.

End point type	Secondary

End point timeframe:

From Day 0 (D0) to D4 after ProQuad dose 1, administered concomitantly or not with Infanrix hexa booster dose.

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The objective of this endpoint was to evaluate the solicited ISRs to ProQuad vaccine. So this endpoint did not include the "Infanrix hexa" arm.

End point values	Group 1: ProQuad + Infanrix hexa	Group 2: ProQuad		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	474	234		
Units: Percentage of subjects				
number (not applicable)				
Injection-site erythema	16.7	10.7		
Injection-site pain	20.9	14.1		
Injection-site swelling	9.7	2.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Solicited injection-site reactions (ISRs) to Infanrix hexa from D0 to D4 after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1 (Group 1 vs Group 3)

End point title	Solicited injection-site reactions (ISRs) to Infanrix hexa from D0 to D4 after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1 (Group 1 vs Group 3)[20]

End point description:

Solicited injection-site adverse reactions (ISRs) to Infanrix hexa were recorded from D0 to D4 after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1.
AEs at Infanrix hexa injection site were always considered as related to Infanrix hexa (ISRs).
Percentage of subjects presenting at least once the considered ISRs are presented here.
Analysis was done on the Safety Analysis Set, i.e. all subjects who received at least 1 of the study vaccine(s) and who had safety follow-up data.

End point type	Secondary

End point timeframe:

From Day 0 (D0) to D4 after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1.

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The objective of this endpoint was to evaluate the solicited ISRs to Infanrix hexa. So this endpoint did not include the "ProQuad" arm.

End point values	Group 1: ProQuad + Infanrix hexa	Group 3: Infanrix hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	474	239		
Units: Percentage of subjects				
number (not applicable)				
Injection-site erythema	49.8	52.7		
Injection-site pain	39	35.1		
Injection-site swelling	38	38.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Unsolicited injection-site reactions (ISRs) to ProQuad from D0 to D28 after ProQuad dose 1, administered concomitantly or not with Infanrix hexa booster dose (Group 1 vs Group 2)

End point title	Unsolicited injection-site reactions (ISRs) to ProQuad from D0 to D28 after ProQuad dose 1, administered concomitantly or not with Infanrix hexa booster dose (Group 1 vs Group 2)[21]

End point description:

Unsolicited injection-site adverse reactions (ISRs) to ProQuad occurring from D0 to D28, including erythema, pain, and swelling from D5 to D28 after ProQuad dose 1, administered concomitantly or not with Infanrix hexa booster dose, were reported.
AEs at ProQuad injection site were always considered as related to ProQuad (ISRs).
Percentage of subjects presenting at least once the considered ISRs are presented here.
Analysis was done on the Safety Analysis Set, i.e. all subjects who received at least 1 of the study vaccine(s) and who had safety follow-up data.

End point type	Secondary

End point timeframe:

From Day 0 (D0) to D28 after ProQuad dose 1, administered concomitantly or not with Infanrix hexa booster dose.

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The objective of this endpoint was to evaluate the unsolicited ISRs to ProQuad vaccine. So this endpoint did not include the "Infanrix hexa" arm.

End point values	Group 1: ProQuad + Infanrix hexa	Group 2: ProQuad		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	474	234		
Units: Percentage of subjects				
number (not applicable)				
Injection-site bruising	0.4	0		
Injection-site dryness	0	0.4		
Injection-site erythema	3.8	2.6		
Injection-site haematoma	0.4	1.3		
Injection-site induration	0.4	0.4		
Injection-site nodule	0.2	0		
Injection-site papule	0	0.4		
Injection-site pustule	0.4	0		
Injection-site rash	2.7	4.3		
Injection-site swelling	0.8	0.4		
Injection-site warmth	0.2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Unsolicited injection-site reactions (ISRs) to Infanrix hexa from D0 to D28 after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1 (Group 1 vs Group 3)

End point title	Unsolicited injection-site reactions (ISRs) to Infanrix hexa from D0 to D28 after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1 (Group 1 vs Group 3)[22]

End point description:

Unsolicited injection-site adverse reactions (ISRs) to Infanrix hexa occurring from D0 to D28, including erythema, pain, and swelling from D5 to D28 after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1, were reported.
AEs at Infanrix hexa injection site were always considered as related to Infanrix hexa (ISRs).
Percentage of subjects presenting at least once the considered ISRs are presented here.
Analysis was done on the Safety Analysis Set, i.e. all subjects who received at least 1 of the study vaccine(s) and who had safety follow-up data.

End point type	Secondary

End point timeframe:

From Day 0 (D0) to D28 after Infanrix hexa booster dose, administered concomitantly or not with ProQuad dose 1.

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The objective of this endpoint was to evaluate the unsolicited ISRs to Infanrix hexa. So this endpoint did not include the "ProQuad" arm.

End point values	Group 1: ProQuad + Infanrix hexa	Group 3: Infanrix hexa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	474	239		
Units: Percentage of subjects				
number (not applicable)				
Injection-site erythema	0.6	0		
Injection-site haemorrhage	0.2	0		
Injection-site haematoma	1.1	0.4		
Injection-site hypersensitivity	0	0.4		
Injection-site induration	2.1	1.7		
Injection-site pain	0.2	0		
Injection-site pruritus	0.2	0		
Injection-site rash	0.2	0.8		
Injection-site reaction	0.2	0		
Injection-site swelling	0.4	0		
Injection-site warmth	1.3	0.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects reporting adverse events of interest from D0 to D28 after vaccination with ProQuad dose 1 and Infanrix hexa booster dose, administered concomitantly or alone

End point title	Percentage of subjects reporting adverse events of interest from D0 to D28 after vaccination with ProQuad dose 1 and Infanrix hexa booster dose, administered concomitantly or alone

End point description:

Injection-site rashes of interest, non-injection site rashes of interest (Measles-like rash, Rubella-like rash, Varicella-like rash and Herpes zoster-like rash), and Mumps-like illness were reported from D0 to D28 after vaccination with ProQuad dose 1 and Infanrix hexa booster dose, administered concomitantly or alone.
Percentage of subjects presenting at least once the considered events are presented here.
Analysis was done on the Safety Analysis Set, i.e. all subjects who received at least 1 of the study vaccine(s) and who had safety follow-up data.

End point type	Secondary

End point timeframe:

From Day 0 (D0) to D28 after vaccination with ProQuad dose 1 and Infanrix hexa booster dose, administered concomitantly or alone.

End point values	Group 1: ProQuad + Infanrix hexa	Group 2: ProQuad	Group 3: Infanrix hexa	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	474	234	239	
Units: Percentage of subjects				
number (not applicable)				
At least 1 injection-site rash of interest	3	4.3	0.8	
At least 1 non-injection-site rash of interest	13.5	10.3	3.8	
Measles / Measles-like rash	7	6.8	2.1	
Rubella / Rubella-like rash	3.8	2.6	0.4	
Varicella / Varicella-like rash	3.2	0.9	1.3	
Herpes zoster / Herpes zoster-like rash	0.2	0.4	0	
Mumps / mumps-like illness	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Unsolicited non-serious systemic adverse events (AEs) were collected from D0 to D28 following vaccination.
Serious AEs and deaths were collected throughout the study.

Adverse event reporting additional description:

Analysis of AEs was performed on the Safety Analysis Set, i.e. all subjects who received at least 1 of the study vaccine(s) and who had safety follow-up data.
Unsolicited non-serious systemic AEs (vaccine-related or not) with incidence ≥1% in at least 1 reporting group are presented hereafter.
None of the serious AEs were vaccine-related.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Group 1: ProQuad + Infanrix hexa

Reporting group description:

Subjects received ProQuad dose 1 by subcutaneous route concomitantly with Infanrix hexa (DTaP-HBV-IPV-Hib) booster dose by intramuscular route at 12-23 months of age.
Respectively, 332 (70.0%) subjects reported at least 1 non-serious unsolicited systemic AE, 152 (32.1%) subjects reported at least 1 ProQuad-related non-serious unsolicited systemic AE, and 100 (21.1%) subjects reported at least 1 Infanrix hexa-related non-serious unsolicited systemic AE within 28 days after ProQuad dose 1 administered concomitantly with Infanrix hexa booster dose.

Reporting group title	Group 2: ProQuad

Reporting group description:

Subjects received ProQuad dose 1 by subcutaneous route at 12-23 months of age.
Respectively, 152 (65.0%) subjects reported at least 1 non-serious unsolicited systemic AE, and 69 (29.5%) subjects reported at least 1 ProQuad-related non-serious unsolicited systemic AE within 28 days after ProQuad dose 1.

Reporting group title	Group 3: Infanrix hexa

Reporting group description:

Subjects received Infanrix hexa (DTaP-HBV-IPV-Hib) booster dose by intramuscular route at 12-23 months of age.
Respectively, 149 (62.3%) subjects reported at least 1 non-serious unsolicited systemic AE, and 40 (16.7%) subjects reported at least 1 Infanrix hexa-related non-serious unsolicited systemic AE within 28 days after Infanrix hexa booster dose.

Serious adverse events	Group 1: ProQuad + Infanrix hexa	Group 2: ProQuad	Group 3: Infanrix hexa
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 474 (1.48%)	6 / 234 (2.56%)	4 / 239 (1.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Electric shock			

subjects affected / exposed	0 / 474 (0.00%)	0 / 234 (0.00%)	1 / 239 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Febrile convulsion			
subjects affected / exposed	2 / 474 (0.42%)	0 / 234 (0.00%)	0 / 239 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 474 (0.00%)	3 / 234 (1.28%)	1 / 239 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	1 / 474 (0.21%)	1 / 234 (0.43%)	0 / 239 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Conjunctivitis bacterial			
subjects affected / exposed	0 / 474 (0.00%)	1 / 234 (0.43%)	0 / 239 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 234 (0.00%)	0 / 239 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 474 (0.21%)	1 / 234 (0.43%)	1 / 239 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 474 (0.00%)	0 / 234 (0.00%)	1 / 239 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			

subjects affected / exposed	1 / 474 (0.21%)	0 / 234 (0.00%)	0 / 239 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 474 (0.00%)	1 / 234 (0.43%)	0 / 239 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 474 (0.21%)	0 / 234 (0.00%)	0 / 239 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 474 (0.21%)	0 / 234 (0.00%)	0 / 239 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Group 1: ProQuad + Infanrix hexa	Group 2: ProQuad	Group 3: Infanrix hexa
Total subjects affected by non-serious adverse events			
subjects affected / exposed	332 / 474 (70.04%)	152 / 234 (64.96%)	149 / 239 (62.34%)
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 474 (0.21%)	1 / 234 (0.43%)	3 / 239 (1.26%)
occurrences (all)	1	1	3
Head injury			
subjects affected / exposed	3 / 474 (0.63%)	0 / 234 (0.00%)	5 / 239 (2.09%)
occurrences (all)	3	0	5
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	184 / 474 (38.82%)	80 / 234 (34.19%)	68 / 239 (28.45%)
occurrences (all)	263	104	91
Irritability			

subjects affected / exposed	7 / 474 (1.48%)	3 / 234 (1.28%)	3 / 239 (1.26%)
occurrences (all)	13	3	3
Eye disorders			
Conjunctivitis			
subjects affected / exposed	9 / 474 (1.90%)	6 / 234 (2.56%)	4 / 239 (1.67%)
occurrences (all)	9	7	4
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	22 / 474 (4.64%)	14 / 234 (5.98%)	14 / 239 (5.86%)
occurrences (all)	23	14	14
Teething			
subjects affected / exposed	14 / 474 (2.95%)	9 / 234 (3.85%)	6 / 239 (2.51%)
occurrences (all)	21	12	6
Constipation			
subjects affected / exposed	1 / 474 (0.21%)	3 / 234 (1.28%)	1 / 239 (0.42%)
occurrences (all)	1	3	1
Enteritis			
subjects affected / exposed	10 / 474 (2.11%)	2 / 234 (0.85%)	5 / 239 (2.09%)
occurrences (all)	10	3	5
Vomiting			
subjects affected / exposed	14 / 474 (2.95%)	2 / 234 (0.85%)	14 / 239 (5.86%)
occurrences (all)	15	2	15
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	31 / 474 (6.54%)	13 / 234 (5.56%)	11 / 239 (4.60%)
occurrences (all)	32	15	11
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	20 / 474 (4.22%)	6 / 234 (2.56%)	10 / 239 (4.18%)
occurrences (all)	20	6	10
Rash morbilliform			
subjects affected / exposed	33 / 474 (6.96%)	16 / 234 (6.84%)	5 / 239 (2.09%)
occurrences (all)	36	16	6
Rash rubelliform			
subjects affected / exposed	17 / 474 (3.59%)	6 / 234 (2.56%)	1 / 239 (0.42%)
occurrences (all)	17	6	1

Rash vesicular			
subjects affected / exposed	14 / 474 (2.95%)	3 / 234 (1.28%)	3 / 239 (1.26%)
occurrences (all)	15	3	3
Dermatitis			
subjects affected / exposed	7 / 474 (1.48%)	1 / 234 (0.43%)	4 / 239 (1.67%)
occurrences (all)	7	1	4
Eczema			
subjects affected / exposed	9 / 474 (1.90%)	2 / 234 (0.85%)	1 / 239 (0.42%)
occurrences (all)	9	2	1
Erythema			
subjects affected / exposed	5 / 474 (1.05%)	0 / 234 (0.00%)	1 / 239 (0.42%)
occurrences (all)	6	0	1
Rash			
subjects affected / exposed	7 / 474 (1.48%)	4 / 234 (1.71%)	2 / 239 (0.84%)
occurrences (all)	7	4	2
Psychiatric disorders			
Crying			
subjects affected / exposed	3 / 474 (0.63%)	3 / 234 (1.28%)	0 / 239 (0.00%)
occurrences (all)	3	3	0
Restlessness			
subjects affected / exposed	10 / 474 (2.11%)	3 / 234 (1.28%)	2 / 239 (0.84%)
occurrences (all)	11	3	2
Infections and infestations			
Bronchitis			
subjects affected / exposed	27 / 474 (5.70%)	15 / 234 (6.41%)	12 / 239 (5.02%)
occurrences (all)	28	15	12
Gastroenteritis			
subjects affected / exposed	17 / 474 (3.59%)	4 / 234 (1.71%)	4 / 239 (1.67%)
occurrences (all)	18	4	4
Influenza			
subjects affected / exposed	6 / 474 (1.27%)	7 / 234 (2.99%)	6 / 239 (2.51%)
occurrences (all)	6	8	8
Nasopharyngitis			
subjects affected / exposed	48 / 474 (10.13%)	14 / 234 (5.98%)	18 / 239 (7.53%)
occurrences (all)	50	16	18
Rhinitis			

subjects affected / exposed	27 / 474 (5.70%)	20 / 234 (8.55%)	9 / 239 (3.77%)
occurrences (all)	28	23	10
Upper respiratory tract infection			
subjects affected / exposed	14 / 474 (2.95%)	9 / 234 (3.85%)	7 / 239 (2.93%)
occurrences (all)	16	10	7
Ear infection			
subjects affected / exposed	2 / 474 (0.42%)	3 / 234 (1.28%)	1 / 239 (0.42%)
occurrences (all)	2	3	1
Exanthema subitum			
subjects affected / exposed	5 / 474 (1.05%)	2 / 234 (0.85%)	2 / 239 (0.84%)
occurrences (all)	6	2	2
Otitis media			
subjects affected / exposed	10 / 474 (2.11%)	4 / 234 (1.71%)	2 / 239 (0.84%)
occurrences (all)	10	4	2
Pharyngitis			
subjects affected / exposed	3 / 474 (0.63%)	4 / 234 (1.71%)	4 / 239 (1.67%)
occurrences (all)	3	4	4
Respiratory tract infection			
subjects affected / exposed	5 / 474 (1.05%)	3 / 234 (1.28%)	1 / 239 (0.42%)
occurrences (all)	5	3	1
Tonsillitis			
subjects affected / exposed	6 / 474 (1.27%)	0 / 234 (0.00%)	5 / 239 (2.09%)
occurrences (all)	6	0	5
Viral infection			
subjects affected / exposed	4 / 474 (0.84%)	3 / 234 (1.28%)	5 / 239 (2.09%)
occurrences (all)	5	3	5
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	3 / 474 (0.63%)	3 / 234 (1.28%)	2 / 239 (0.84%)
occurrences (all)	3	3	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 September 2007	Update of study calendar due to the extension of the subject recruitment period, and the changes in the distribution of subjects between Germany and Italy (competitive recruitment) implemented to ensure the best recruitment rate and the achievement of the global targeted included population. (This change was not expected to impact the primary objective of the study since both Infanrix hexa primary vaccination schedules provide similar protection to the subjects. In addition, the statistical models include stratification by country.)
26 November 2007	Further updated study calendar required in order to ensure the planned sample size, and the labelling of the new lot of ProQuad which was sourced from commercial product.
11 March 2008	Changes implemented concerning polio testing (Vero cells replacing Hep-2 cells).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported