Clinical trial results:
An open-label, randomised, comparative, multi-centre study of the immunogenicity and safety of a 2-dose regimen of ProQuad® manufactured with rHA administered to healthy children from 9 months of age

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2007-002468-88
Trial protocol	FR DE FI
Global end of trial date	29 December 2008

Results information

Result version number	v2 (current)
This version publication date	11 May 2016
First version publication date	11 June 2015
Version creation reason	• Correction of full data set Correction of data in the "Adverse Events" section.

Trial information

Trial identification

Sponsor protocol code	MRV02C

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00566527
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	29 December 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 December 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1st primary objective: to demonstrate that a 2-dose regimen of ProQuad administered at a 3-month interval to healthy children of 11 months of age at the time of Dose 1 was as immunogenic as in healthy children of 12 months of age at the time of Dose 1, in terms of antibody response rates to measles, mumps, rubella and varicella at Day 42 following Dose 2.
2nd primary objective (only if the 1st primary objective was reached): similar to the 1st one at 9 months of age.
3rd primary objective: to demonstrate that a 2-dose regimen of ProQuad administered at a 3-month interval to healthy children of 11 months of age and 9 months of age at the time of Dose 1 is well tolerated compared to healthy children of 12 months of age at the time of Dose 1.
Note: "ProQuad® manufactured with rHA" (recombinant Human Albumin) was referred to "ProQuad" to facilitate the reading.

Protection of trial subjects:

Subjects with prior known sensitivity or allergy to any component of the vaccine (including neomycin, sorbitol or gelatin) or true allergy to egg proteins (anaphylactic or anaphylactoid reaction after ingesting eggs) were not vaccinated.
Vaccines were administered by qualified study personnel.
After each vaccination, subjects were kept under observation for at least 20 minutes to ensure their safety.

Background therapy: -

Evidence for comparator:

The objective of this study was to provide sufficient data for a change in the indication of the Dose 1 of ProQuad from 12 months of age to the lowest possible age (11 months or 9 months). Therefore, subjects receiving ProQuad Dose 1 at 12 months of age constituted the "active comparator" arm of this study. In the experimental arms, subjects received ProQuad Dose 1 at 11 or 9 months of age.

Actual start date of recruitment	29 November 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	Finland: 1290
Country: Number of subjects enrolled	France: 140
Country: Number of subjects enrolled	Germany: 190
Worldwide total number of subjects	1620
EEA total number of subjects	1620

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)	1620
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled between 29 November 2007 and 14 April 2008 in 48 active centres in 3 European countries (Finland, France and Germany).

Pre-assignment

Screening details:

1626 subjects were screened out.
1620 subjects were randomised and constituted the population of the study.
1483 subjects received at least 1 dose of ProQuad.
1465 subjects received the 2 doses of ProQuad.
1459 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:

This was an open-label study. Therefore, neither blinding procedure nor emergency identification of investigational vaccine was necessary.

Arms

Are arms mutually exclusive?	Yes
Arm title	ProQuad - 9 months

Arm description:

Subjects received 2 doses of ProQuad (measles, mumps, rubella and varicella (live attenuated)) vaccine: the 1st dose was administered at 9 months of age, and the 2nd dose 90 days later.

Arm type	Experimental
Investigational medicinal product name	ProQuad® manufactured with rHA
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, upper arm), 2 doses with a 3-month interval.
Both doses had to be administered in the opposite arm to the blood sampling.

Arm title	ProQuad - 11 months

Arm description:

Subjects received 2 doses of ProQuad (measles, mumps, rubella and varicella (live attenuated)) vaccine: the 1st dose was administered at 11 months of age, and the 2nd dose 90 days later.

Arm type	Experimental
Investigational medicinal product name	ProQuad® manufactured with rHA
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, upper arm), 2 doses with a 3-month interval.
Both doses had to be administered in the opposite arm to the blood sampling.

Arm title	ProQuad - 12 months

Arm description:

Subjects received 2 doses of ProQuad (measles, mumps, rubella and varicella (live attenuated)) vaccine: the 1st dose was administered at 12 months of age, and the 2nd dose 90 days later.

Arm type	Active comparator
Investigational medicinal product name	ProQuad® manufactured with rHA
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, upper arm), 2 doses with a 3-month interval.
Both doses had to be administered in the opposite arm to the blood sampling.

Number of subjects in period 1	ProQuad - 9 months	ProQuad - 11 months	ProQuad - 12 months
Started	541	540	539
Completed	524	474	461
Not completed	17	66	78
Allergic reaction to EMLA patch	-	-	1
Physician decision	3	8	20
Consent withdrawn by subject	6	43	43
Family moved away	-	1	3
Adverse event, non-fatal	2	-	1
Patient in vacation during last visit timeframe	-	1	-
Blood sample could not be drawn	3	9	6
Lost to follow-up	3	4	4

Baseline characteristics

Reporting groups	
Reporting group title	ProQuad - 9 months
Reporting group description:	
Subjects received 2 doses of ProQuad (measles, mumps, rubella and varicella (live attenuated)) vaccine: the 1st dose was administered at 9 months of age, and the 2nd dose 90 days later.	
Reporting group title	ProQuad - 11 months
Reporting group description:	
Subjects received 2 doses of ProQuad (measles, mumps, rubella and varicella (live attenuated)) vaccine: the 1st dose was administered at 11 months of age, and the 2nd dose 90 days later.	
Reporting group title	ProQuad - 12 months
Reporting group description:	
Subjects received 2 doses of ProQuad (measles, mumps, rubella and varicella (live attenuated)) vaccine: the 1st dose was administered at 12 months of age, and the 2nd dose 90 days later.	

Reporting group values	ProQuad - 9 months	ProQuad - 11 months	ProQuad - 12 months
Number of subjects	541	540	539
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	541	540	539
Age continuous			
Age in months at inclusion			
Units: months			
arithmetic mean	9.47	9.48	9.47
standard deviation	± 0.29	± 0.3	± 0.3
Gender categorical Units: Subjects			
Female	282	281	258
Male	259	259	281

Reporting group values	Total		
Number of subjects	1620		
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	1620		
Age continuous			
Age in months at inclusion			
Units: months			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	821		
Male	799		

End points

End points reporting groups

Reporting group title	ProQuad - 9 months
Reporting group description:	
Subjects received 2 doses of ProQuad (measles, mumps, rubella and varicella (live attenuated)) vaccine: the 1st dose was administered at 9 months of age, and the 2nd dose 90 days later.	

Reporting group title	ProQuad - 11 months
Reporting group description:	
Subjects received 2 doses of ProQuad (measles, mumps, rubella and varicella (live attenuated)) vaccine: the 1st dose was administered at 11 months of age, and the 2nd dose 90 days later.	

Reporting group title	ProQuad - 12 months
Reporting group description:	
Subjects received 2 doses of ProQuad (measles, mumps, rubella and varicella (live attenuated)) vaccine: the 1st dose was administered at 12 months of age, and the 2nd dose 90 days later.	

Primary: #1st# Immunogenicity at 11 vs 12 months of age: Antibody (Ab) response rates to measles, mumps, rubella and varicella 42 days after the 2nd dose of ProQuad

End point title	#1st# Immunogenicity at 11 vs 12 months of age: Antibody (Ab) response rates to measles, mumps, rubella and varicella 42 days after the 2nd dose of ProQuad[1]

End point description:

Percentage of subjects with an anti-measles Ab titre ≥255 mIU/mL, an anti-mumps Ab titre ≥10.0 ELISA Ab units/mL, an anti-rubella Ab titre ≥10.0 IU/mL, and an anti-varicella Ab titre ≥5 gpELISA units/mL 42 days after injection of the 2nd dose of ProQuad.
All Ab titres were measured by Enzyme-Linked Immunosorbent Assay (ELISA), except Ab to varicella determined by glycoprotein ELISA.
Analysis was done on the Post-Dose 2 Antigen-specific Per Protocol set (PPS): i.e., all subjects initially seronegative for those antigens (Measles Ab titre <255 mIU/mL, Mumps Ab titre <10.0 ELISA Ab units/mL, Rubella Ab titre <10.0 IU/mL, and Varicella Ab titre <1.25 gpELISA units/mL) and with post-dose immunogenicity evaluation for those antigens.
Note: (N=***, ***) represents the number of assessed subjects in the "11 months" and "12 months" groups, respectively.

End point type	Primary

End point timeframe:

42 days after injection of the 2nd dose of ProQuad.

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: This endpoint corresponds to the 1st primary objective of the study, i.e. comparison of the immunogenicity induced by a 2-dose regimen of ProQuad administered to children of 11 months of age at the time of Dose 1 (arm 2) versus children of 12 months of age at the time of Dose 1 (arm 3), in terms of antibody response rates to measles, mumps, rubella and varicella at Day 42 following Dose 2.

End point values	ProQuad - 11 months	ProQuad - 12 months		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	540	539		
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-Measles ≥255 mIU/mL (N= 440, 434)	98 (96.2 to 99.1)	98.8 (97.3 to 99.6)		
Anti-Mumps ≥10 ELISA Ab units/mL (N= 436, 414)	99.5 (98.4 to 99.9)	99.5 (98.3 to 99.9)		

Anti-Rubella ≥10 IU/mL (N= 445, 443)	99.3 (98 to 99.9)	99.5 (98.4 to 99.9)		
Anti-Varicella ≥5 gpELISA (N= 299, 347)	100 (98.8 to 100)	100 (98.9 to 100)		

Statistical analyses

Statistical analysis title	Non-inferiority for Measles

Statistical analysis description:

The estimates of the differences between Group 2 (11 months) & Group 3 (12 months) response rates were calculated with their 2-sided 95% confidence interval (CI). If all lower bounds of the 95% CI were greater than the non-inferiority margin, it was concluded that Group 2 response rates were non-inferior to Group 3 response rates.
Statistical analysis was based on the Miettinen & Nurminen method using a stratification by country.
Analysis was done on the Post-Dose 2 Antigen-specific PPS.

Comparison groups	ProQuad - 11 months v ProQuad - 12 months
Number of subjects included in analysis	1079
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Difference in percentages of subjects
Point estimate	-0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.82
upper limit	0.87

Notes:

[2] - For Measles: # Post-Dose 2 Antigen-specific PPS, N=440, 434 (Groups 2 & 3) # Response rate based on Ab titre ≥255 mIU/mL # Non-inferiority margin, -5%.

Statistical analysis title	Non-inferiority for Mumps

Statistical analysis description:

The estimates of the differences between Group 2 (11 months) & Group 3 (12 months) response rates were calculated with their 2-sided 95% confidence interval (CI). If all lower bounds of the 95% CI were greater than the non-inferiority margin, it was concluded that Group 2 response rates were non-inferior to Group 3 response rates.
Statistical analysis was based on the Miettinen & Nurminen method using a stratification by country.
Analysis was done on the Post-Dose 2 Antigen-specific PPS.

Comparison groups	ProQuad - 11 months v ProQuad - 12 months
Number of subjects included in analysis	1079
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Difference in percentages of subjects
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	1.32

Notes:

[3] - For Mumps: # Post-Dose 2 Antigen-specific PPS, N=436, 414 (Groups 2 & 3) # Response rate based on Ab titre ≥10 ELISA Ab units/mL # Non-inferiority margin, -5%.

Statistical analysis title	Non-inferiority for Rubella

Statistical analysis description:

The estimates of the differences between Group 2 (11 months) & Group 3 (12 months) response rates were calculated with their 2-sided 95% confidence interval (CI). If all lower bounds of the 95% CI were greater than the non-inferiority margin, it was concluded that Group 2 response rates were non-inferior to Group 3 response rates.
Statistical analysis was based on the Miettinen & Nurminen method using a stratification by country.
Analysis was done on the Post-Dose 2 Antigen-specific PPS.

Comparison groups	ProQuad - 12 months v ProQuad - 11 months
Number of subjects included in analysis	1079
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	Difference in percentages of subjects
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.55
upper limit	1.03

Notes:

[4] - For Rubella: # Post-Dose 2 Antigen-specific PPS, N=445, 443 (Groups 2 & 3) # Response rate based on Ab titre ≥10 IU/mL # Non-inferiority margin, -5%.

Statistical analysis title	Non-inferiority for Varicella

Statistical analysis description:

The estimates of the differences between Group 2 (11 months) & Group 3 (12 months) response rates were calculated with their 2-sided 95% confidence interval (CI). If all lower bounds of the 95% CI were greater than the non-inferiority margin, it was concluded that Group 2 response rates were non-inferior to Group 3 response rates.
Statistical analysis was based on the Miettinen & Nurminen method using a stratification by country.
Analysis was done on the Post-Dose 2 Antigen-specific PPS.

Comparison groups	ProQuad - 11 months v ProQuad - 12 months
Number of subjects included in analysis	1079
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	Difference in percentages of subjects
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.28
upper limit	1.1

Notes:

[5] - For Varicella: # Post-Dose 2 Antigen-specific PPS, N=299, 347 (Groups 2 & 3) # Response rate based on Ab titre ≥5 gpELISA units/mL # Non-inferiority margin, -10%.

Primary: #2nd# Immunogenicity at 9 vs 12 months of age: Antibody (Ab) response rates to measles, mumps, rubella and varicella 42 days after the 2nd dose of ProQuad

End point title	#2nd# Immunogenicity at 9 vs 12 months of age: Antibody (Ab) response rates to measles, mumps, rubella and varicella 42 days after the 2nd dose of ProQuad[6]

End point description:

Percentage of subjects with an anti-measles Ab titre ≥255 mIU/mL, an anti-mumps Ab titre ≥10.0 ELISA Ab units/mL, an anti-rubella Ab titre ≥10.0 IU/mL, and an anti-varicella Ab titre ≥5 gpELISA units/mL 42 days after injection of the 2nd dose of ProQuad.
All Ab titres were measured by Enzyme-Linked Immunosorbent Assay (ELISA), except Ab to varicella

determined by glycoprotein ELISA.
Analysis was done on the Post-Dose 2 Antigen-specific Per Protocol set (PPS): i.e., all subjects initially seronegative for those antigens (Measles Ab titre <255 mIU/mL, Mumps Ab titre <10.0 ELISA Ab units/mL, Rubella Ab titre <10.0 IU/mL, and Varicella Ab titre <1.25 gpELISA units/mL) and with post-dose immunogenicity evaluation for those antigens.
Note: (N=***, ***) represents the number of assessed subjects in the "9 months" and "12 months" groups, respectively.

End point type	Primary

End point timeframe:

42 days after injection of the 2nd dose of ProQuad.

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: This endpoint corresponds to the 2nd primary objective of the study (similar to the 1st one) at 9 months of age (i.e. arm 1 versus arm 3), only assessed if the 1st primary objective was reached.

End point values	ProQuad - 9 months	ProQuad - 12 months		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	541	539		
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-Measles ≥255 mIU/mL (N= 490, 434)	94.9 (92.6 to 96.7)	98.8 (97.3 to 99.6)		
Anti-Mumps ≥10 ELISA Ab units/mL (N= 481, 414)	99.2 (97.9 to 99.8)	99.5 (98.3 to 99.9)		
Anti-Rubella ≥10 IU/mL (N= 500, 443)	99.4 (98.3 to 99.9)	99.5 (98.4 to 99.9)		
Anti-Varicella ≥5 gpELISA (N= 208, 347)	100 (98.2 to 100)	100 (98.9 to 100)		

Statistical analyses

Statistical analysis title	Non-inferiority for Measles

Statistical analysis description:

The estimates of the differences between Group 1 (9 months) & Group 3 (12 months) response rates were calculated with their 2-sided 95% confidence interval (CI). If all 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 using a stratification by country.
Analysis was done on the Post-Dose 2 Antigen-specific PPS.

Comparison groups	ProQuad - 9 months v ProQuad - 12 months
Number of subjects included in analysis	1080
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Parameter estimate	Difference in percentages of subjects
Point estimate	-3.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.44
upper limit	-1.87

Notes:

[7] - For Measles: # Post-Dose 2 Antigen-specific PPS, N=490, 434 (Groups 1 & 3) # Response rate based on Ab titre ≥255 mIU/mL # Non-inferiority margin, -5%.

Statistical analysis title	Non-inferiority for Mumps

Statistical analysis description:

The estimates of the differences between Group 1 (9 months) & Group 3 (12 months) response rates were calculated with their 2-sided 95% confidence interval (CI). If all 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 using a stratification by country.
Analysis was done on the Post-Dose 2 Antigen-specific PPS.

Comparison groups	ProQuad - 9 months v ProQuad - 12 months
Number of subjects included in analysis	1080
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Parameter estimate	Difference in percentages of subjects
Point estimate	-0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.71
upper limit	1.01

Notes:

[8] - For Mumps: # Post-Dose 2 Antigen-specific PPS, N=481, 414 (Groups 1 & 3) # Response rate based on Ab titre ≥10 ELISA Ab units/mL # Non-inferiority margin, -5%.

Statistical analysis title	Non-inferiority for Rubella

Statistical analysis description:

The estimates of the differences between Group 1 (9 months) & Group 3 (12 months) response rates were calculated with their 2-sided 95% confidence interval (CI). If all 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 using a stratification by country.
Analysis was done on the Post-Dose 2 Antigen-specific PPS.

Comparison groups	ProQuad - 9 months v ProQuad - 12 months
Number of subjects included in analysis	1080
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
Parameter estimate	Difference in percentages of subjects
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.34
upper limit	1.09

Notes:

[9] - For Rubella: # Post-Dose 2 Antigen-specific PPS, N=500, 443 (Groups 1 & 3) # Response rate based on Ab titre ≥10 IU/mL # Non-inferiority margin, -5%.

Statistical analysis title	Non-inferiority for Varicella

Statistical analysis description:

The estimates of the differences between Group 1 (9 months) & Group 3 (12 months) response rates were calculated with their 2-sided 95% confidence interval (CI). If all 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 using a stratification by country.

Analysis was done on the Post-Dose 2 Antigen-specific PPS.

Comparison groups	ProQuad - 9 months v ProQuad - 12 months
Number of subjects included in analysis	1080
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
Parameter estimate	Difference in percentages of subjects
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.83
upper limit	1.1

Notes:

[10] - For Varicella: # Post-Dose 2 Antigen-specific PPS, N=208, 347 (Groups 1 & 3) # Response rate based on Ab titre ≥5 gpELISA units/mL # Non-inferiority margin, -10%.

Primary: #3rd# Safety at 9 or 11 vs 12 months of age: Global safety from D0 to D28 after the 1st dose of ProQuad

End point title	#3rd# Safety at 9 or 11 vs 12 months of age: Global safety from D0 to D28 after the 1st dose of ProQuad[11]

End point description:

Adverse events (AEs) occurring after injection of the 1st dose of ProQuad 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), # numeric values of temperature, # 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 zoster-like rash), c/ mumps-like illness), # other systemic AEs.
AEs at injection sites were always considered as related to vaccine (ISRs). The investigator had to assess whether systemic AEs were vaccine-related systemic AEs or not.
Analysis was done on the Post-Dose 1 Safety set, i.e. all subjects who received at least 1 dose of the study vaccine and who had safety follow-up data following Dose 1.

End point type	Primary

End point timeframe:

From Day 0 (D0) to D28 after injection of the 1st dose of ProQuad.

Notes:

[11] - 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 formal hypothesis was tested. Thus, no statistical results are presented here.

End point values	ProQuad - 9 months	ProQuad - 11 months	ProQuad - 12 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	528	480	466	
Units: Percentage of subjects				
number (confidence interval 95%)				
At least 1 ISR or systemic AE	81.3 (77.7 to 84.5)	81.9 (78.1 to 85.2)	81.1 (77.3 to 84.6)	
At least 1 ISR or vaccine-related systemic AE	58.7 (54.4 to 62.9)	60.8 (56.3 to 65.2)	63.9 (59.4 to 68.3)	
At least 1 ISR	40.9 (36.7 to 45.2)	40.2 (35.8 to 44.7)	40.8 (36.3 to 45.4)	
At least 1 systemic AE	72 (67.9 to 75.8)	71.9 (67.6 to 75.9)	71.9 (67.6 to 75.9)	
At least 1 vaccine-related systemic AE	36.9 (32.8 to 41.2)	37.9 (33.6 to 42.4)	41.8 (37.3 to 46.5)	

Statistical analyses

No statistical analyses for this end point

Primary: #3rd# Safety at 9 or 11 vs 12 months of age: Proportion of subjects reporting injection-site reactions (ISRs) after the 1st dose of ProQuad

End point title	#3rd# Safety at 9 or 11 vs 12 months of age: Proportion of subjects reporting injection-site reactions (ISRs) after the 1st dose of ProQuad[12]

End point description:

Adverse events at injection sites were always considered as related to vaccine (Injection-Site Reactions (ISRs)).
Solicited ISRs were defined as injection-site erythema, injection-site pain and injection-site swelling occurring from Day 0 (D0) to D4 after vaccination.
Unsolicited ISRs consisted in all other ISRs, including injection-site erythema, injection-site pain and injection-site swelling starting from D5.
Analysis was done on the Post-Dose 1 Safety set, i.e. all subjects who received at least 1 dose of the study vaccine and who had safety follow-up data following Dose 1.

End point type	Primary

End point timeframe:

From Day 0 (D0) to D28 after injection of the 1st dose of ProQuad.

Notes:

[12] - 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 formal hypothesis was tested. Thus, no statistical results are presented here.

End point values	ProQuad - 9 months	ProQuad - 11 months	ProQuad - 12 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	528	480	466	
Units: Percentage of subjects				
number (confidence interval 95%)				
At least 1 solicited ISR	21.8 (18.3 to 25.5)	23.3 (19.6 to 27.4)	27.7 (23.7 to 32)	
Injection-site erythema	14.4 (11.5 to 17.7)	15.4 (12.3 to 19)	17.2 (13.9 to 20.9)	
Injection-site pain	11.4 (8.8 to 14.4)	10.4 (7.8 to 13.5)	13.7 (10.7 to 17.2)	
Injection-site swelling	2.3 (1.2 to 3.9)	4.6 (2.9 to 6.9)	2.4 (1.2 to 4.2)	
At least 1 unsolicited ISR	24.8 (21.2 to 28.7)	23.3 (19.6 to 27.4)	19.1 (15.6 to 23)	

Statistical analyses

No statistical analyses for this end point

Primary: #3rd# Safety at 9 or 11 vs 12 months of age: Proportion of subjects

reporting adverse events of interest and temperature ≥39.4°C from D0 to D28 after the 1st dose of ProQuad

End point title	#3rd# Safety at 9 or 11 vs 12 months of age: Proportion of subjects reporting adverse events of interest and temperature ≥39.4°C from D0 to D28 after the 1st dose of ProQuad[13]

End point description:

Injection-site rashes of interest, non-injection site rashes of interest (measles-like rash, rubella-like rash, varicella-like rash and zoster-like rash), mumps-like illness, and rectal (or equivalent) temperature ≥39.4°C were reported from D0 to D28 after vaccination.
Percentage of subjects presenting at least once the considered events are presented here.
Analysis was done on the Post-Dose 1 Safety set, i.e. all subjects who received at least 1 dose of the study vaccine and who had safety follow-up data following Dose 1.

End point type	Primary

End point timeframe:

From Day 0 (D0) to D28 after injection of the 1st dose of ProQuad.

Notes:

[13] - 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 formal hypothesis was tested. Thus, no statistical results are presented here.

End point values	ProQuad - 9 months	ProQuad - 11 months	ProQuad - 12 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	528	480	466	
Units: Percentage of subjects				
number (confidence interval 95%)				
At least 1 injection-site rash of interest	0.2 (0 to 1.1)	1.5 (0.6 to 3)	0.2 (0 to 1.2)	
At least 1 non-injection-site rash of interest	10.6 (8.1 to 13.6)	11.7 (8.9 to 14.9)	14.4 (11.3 to 17.9)	
Measles / Measles-like rash	4 (2.5 to 6)	5.8 (3.9 to 8.3)	6.9 (4.7 to 9.6)	
Rubella / Rubella-like rash	1.3 (0.5 to 2.7)	1.9 (0.9 to 3.5)	1.5 (0.6 to 3.1)	
Varicella / Varicella-like rash	5.3 (3.6 to 7.6)	4 (2.4 to 6.1)	6.4 (4.4 to 9.1)	
Zoster / Zoster-like rash	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	
Mumps / Mumps-like illness	0 (0 to 0)	0 (0 to 0)	0.4 (0.1 to 1.5)	
Temperature ≥39.4°C	8.8 (6.5 to 11.5)	10.3 (7.7 to 13.4)	14.8 (11.7 to 18.4)	

Statistical analyses

No statistical analyses for this end point

Primary: #3rd# Safety at 9 or 11 vs 12 months of age: Global safety from D0 to D28 after the 2nd dose of ProQuad

End point title	#3rd# Safety at 9 or 11 vs 12 months of age: Global safety from D0 to D28 after the 2nd dose of ProQuad[14]

End point description:

Adverse events (AEs) occurring after injection of the 2nd dose of ProQuad 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), # numeric values of temperature, # 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 zoster-like rash), c/ mumps-like illness), # other systemic AEs.
AEs at injection sites were always considered as related to vaccine (ISRs). The investigator had to assess whether systemic AEs were vaccine-related systemic AEs or not.
Analysis was done on the Post-Dose 2 Safety set, i.e. all subjects who received at least 1 dose of the

study vaccine and who had safety follow-up data following Dose 2.

End point type	Primary

End point timeframe:

From Day 0 (D0) to D28 after injection of the 2nd dose of ProQuad.

Notes:

[14] - 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 formal hypothesis was tested. Thus, no statistical results are presented here.

End point values	ProQuad - 9 months	ProQuad - 11 months	ProQuad - 12 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	524	474	462	
Units: Percentage of subjects				
number (confidence interval 95%)				
At least 1 ISR or systemic AE	72.5 (68.5 to 76.3)	75.7 (71.6 to 79.5)	72.7 (68.4 to 76.7)	
At least 1 ISR or vaccine-related systemic AE	55 (50.6 to 59.3)	57.8 (53.2 to 62.3)	54.8 (50.1 to 59.4)	
At least 1 ISR	43.9 (39.6 to 48.3)	45.4 (40.8 to 50)	44.2 (39.6 to 48.8)	
At least 1 systemic AE	58.6 (54.2 to 62.8)	57.4 (52.8 to 61.9)	56.1 (51.4 to 60.6)	
At least 1 vaccine-related systemic AE	26.5 (22.8 to 30.5)	24.5 (20.7 to 28.6)	24.2 (20.4 to 28.4)	

Statistical analyses

No statistical analyses for this end point

Primary: #3rd# Safety at 9 or 11 vs 12 months of age: Proportion of subjects reporting injection-site reactions (ISRs) after the 2nd dose of ProQuad

End point title	#3rd# Safety at 9 or 11 vs 12 months of age: Proportion of subjects reporting injection-site reactions (ISRs) after the 2nd dose of ProQuad[15]

End point description:

Adverse events at injection sites were always considered as related to vaccine (Injection-Site Reactions (ISRs)).
Solicited ISRs were defined as injection-site erythema, injection-site pain and injection-site swelling occurring from Day 0 (D0) to D4 after vaccination.
Unsolicited ISRs consisted in all other ISRs, including injection-site erythema, injection-site pain and injection-site swelling starting from D5.
Analysis was done on the Post-Dose 2 Safety set, i.e. all subjects who received at least 1 dose of the study vaccine and who had safety follow-up data following Dose 2.

End point type	Primary

End point timeframe:

From Day 0 (D0) to D28 after injection of the 2nd dose of ProQuad.

Notes:

[15] - 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 formal hypothesis was tested. Thus, no statistical results are presented here.

End point values	ProQuad - 9 months	ProQuad - 11 months	ProQuad - 12 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	524	474	462	
Units: Percentage of subjects				
number (confidence interval 95%)				
At least 1 solicited ISR	43.1 (38.8 to 47.5)	44.7 (40.2 to 49.3)	44.2 (39.6 to 48.8)	
Injection-site erythema	40.8 (36.6 to 45.2)	40.7 (36.3 to 45.3)	39 (34.5 to 43.6)	
Injection-site pain	12.4 (9.7 to 15.5)	14.8 (11.7 to 18.3)	15.6 (12.4 to 19.2)	
Injection-site swelling	16.4 (13.3 to 19.9)	12.2 (9.4 to 15.5)	14.5 (11.4 to 18)	
At least 1 unsolicited ISR	1.9 (0.9 to 3.5)	4.4 (2.8 to 6.7)	3.9 (2.3 to 6.1)	

Statistical analyses

No statistical analyses for this end point

Primary: #3rd# Safety at 9 or 11 vs 12 months of age: Proportion of subjects reporting adverse events of interest and temperature ≥39.4°C from D0 to D28 after the 2nd dose of ProQuad

End point title	#3rd# Safety at 9 or 11 vs 12 months of age: Proportion of subjects reporting adverse events of interest and temperature ≥39.4°C from D0 to D28 after the 2nd dose of ProQuad[16]

End point description:

Injection-site rashes of interest, non-injection site rashes of interest (measles-like rash, rubella-like rash, varicella-like rash and zoster-like rash), mumps-like illness, and rectal (or equivalent) temperature ≥39.4°C were reported from D0 to D28 after vaccination.
Percentage of subjects presenting at least once the considered events are presented here.
Analysis was done on the Post-Dose 2 Safety set, i.e. all subjects who received at least 1 dose of the study vaccine and who had safety follow-up data following Dose 2.

End point type	Primary

End point timeframe:

From Day 0 (D0) to D28 after injection of the 2nd dose of ProQuad.

Notes:

[16] - 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 formal hypothesis was tested. Thus, no statistical results are presented here.

End point values	ProQuad - 9 months	ProQuad - 11 months	ProQuad - 12 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	524	474	462	
Units: Percentage of subjects				
number (confidence interval 95%)				
At least 1 injection-site rash of interest	0 (0 to 0)	0 (0 to 0)	0.2 (0 to 1.2)	
At least 1 non-injection-site rash of interest	5.7 (3.9 to 8.1)	8.4 (6.1 to 11.3)	6.3 (4.2 to 8.9)	
Measles / Measles-like rash	2.1 (1.1 to 3.7)	2.7 (1.5 to 4.6)	2.8 (1.5 to 4.8)	
Rubella / Rubella-like rash	1.5 (0.7 to 3)	1.9 (0.9 to 3.6)	0.9 (0.2 to 2.2)	
Varicella / Varicella-like rash	2.1 (1.1 to 3.7)	3.8 (2.3 to 5.9)	2.6 (1.3 to 4.5)	
Zoster / Zoster-like rash	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	

Mumps / Mumps-like illness	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	
Temperature ≥39.4°C	7.7 (5.6 to 10.4)	10 (7.4 to 13.1)	7.9 (5.6 to 10.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: # Immunogenicity: Antibody (Ab) response rates to measles, mumps, rubella and varicella 42 days after the 1st dose of ProQuad

End point title	# Immunogenicity: Antibody (Ab) response rates to measles, mumps, rubella and varicella 42 days after the 1st dose of ProQuad

End point description:

Percentage of subjects with an anti-measles Ab titre ≥255 mIU/mL, an anti-mumps Ab titre ≥10.0 ELISA Ab units/mL, an anti-rubella Ab titre ≥10.0 IU/mL, and an anti-varicella Ab titre ≥5 gpELISA units/mL 42 days after injection of the 1st dose of ProQuad.
All Ab titres were measured by Enzyme-Linked Immunosorbent Assay (ELISA), except Ab to varicella determined by glycoprotein ELISA.
Analysis was done on the Post-Dose 1 Antigen-specific Per Protocol set (PPS): i.e., all subjects initially seronegative for those antigens (Measles Ab titre <255 mIU/mL, Mumps Ab titre <10.0 ELISA Ab units/mL, Rubella Ab titre <10.0 IU/mL, and Varicella Ab titre <1.25 gpELISA units/mL) and with post-dose immunogenicity evaluation for those antigens.
Note: (N=***, ***,***) represents the number of assessed subjects in the "9 months", "11 months" and "12 months" groups, respectively.

End point type	Secondary

End point timeframe:

42 days after injection of the 1st dose of ProQuad.

End point values	ProQuad - 9 months	ProQuad - 11 months	ProQuad - 12 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	541	540	539	
Units: Percentage of subjects				
number (confidence interval 95%)				
Anti-Measles ≥255 mIU/mL (N= 508, 455, 438)	72.6 (68.5 to 76.5)	87.9 (84.6 to 90.8)	90.2 (87 to 92.8)	
Anti-Mumps ≥10 ELISA Ab units/mL (N= 499, 453, 417	96.6 (94.6 to 98)	98.7 (97.1 to 99.5)	98.3 (96.6 to 99.3)	
Anti-Rubella ≥10 IU/mL (N= 518, 460, 447)	97.7 (96 to 98.8)	98.9 (97.5 to 99.6)	98 (96.2 to 99.1)	
Anti-Varicella ≥5 gpELISA (N= 220, 312, 353)	95 (91.2 to 97.5)	97.8 (95.4 to 99.1)	97.5 (95.2 to 98.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: # Immunogenicity: Geometric Mean Titres (GMTs) of anti- measles, anti-

mumps, anti-rubella and anti-varicella antibodies (Abs) 42 days after the 2nd dose of ProQuad

End point title	# Immunogenicity: Geometric Mean Titres (GMTs) of anti-measles, anti-mumps, anti-rubella and anti-varicella antibodies (Abs) 42 days after the 2nd dose of ProQuad

End point description:

Ab titres were measured for measles, mumps and rubella by Enzyme-Linked ImmunoSorbent Assay (ELISA) and for varicella by glycoprotein ELISA (gpELISA), 42 days after injection of the 2nd dose of ProQuad.
Analysis was done on the Post-dose 2 Antigen-specific Per Protocol set (PPS): i.e., all subjects initially seronegative for those antigens (Measles Ab titre <255 mIU/mL, Mumps Ab titre <10.0 ELISA Ab units/mL, Rubella Ab titre <10.0 IU/mL, and Varicella Ab titre <1.25 gpELISA units/mL) and with post-dose immunogenicity evaluation for those antigens.
Note: (N=***, ***,***) represents the number of assessed subjects in the "9 months", "11 months" and "12 months" groups, respectively.

End point type	Secondary

End point timeframe:

42 days after injection of the 2nd dose of ProQuad.

End point values	ProQuad - 9 months	ProQuad - 11 months	ProQuad - 12 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	541	540	539	
Units: Titres				
geometric mean (confidence interval 95%)				
Anti-Measles GMT (N= 490, 440, 434)	1817 (1645 to 2006)	2320 (2129 to 2529)	2703 (2492 to 2933)	
Anti-Mumps GMT (N= 481, 436, 414)	157 (147 to 168)	163 (151 to 175)	172 (159 to 185)	
Anti-Rubella GMT (N= 500, 445, 443)	106 (99 to 113)	116 (109 to 124)	118 (111 to 126)	
Anti-Varicella GMT (N= 208, 299, 347)	431 (372 to 500)	460 (410 to 517)	515 (466 to 569)	

Statistical analyses

No statistical analyses for this end point

Secondary: # Immunogenicity: Geometric Mean Titres (GMTs) of anti- measles, anti-mumps, anti-rubella and anti-varicella antibodies (Abs) 42 days after the 1st dose of ProQuad

End point title	# Immunogenicity: Geometric Mean Titres (GMTs) of anti-measles, anti-mumps, anti-rubella and anti-varicella antibodies (Abs) 42 days after the 1st dose of ProQuad

End point description:

Ab titres were measured for measles, mumps and rubella by Enzyme-Linked ImmunoSorbent Assay (ELISA) and for varicella by glycoprotein ELISA (gpELISA), 42 days after injection of the 1st dose of ProQuad.
Analysis was done on the Post-dose 1 Antigen-specific Per Protocol set (PPS): i.e., all subjects initially seronegative for those antigens (Measles Ab titre <255 mIU/mL, Mumps Ab titre <10.0 ELISA Ab units/mL, Rubella Ab titre <10.0 IU/mL, and Varicella Ab titre <1.25 gpELISA units/mL) and with post-dose immunogenicity evaluation for those antigens.
Note: (N=***, ***,***) represents the number of assessed subjects in the "9 months", "11 months"

and “12 months” groups, respectively.

End point type	Secondary

End point timeframe:

42 days after injection of the 1st dose of ProQuad.

End point values	ProQuad - 9 months	ProQuad - 11 months	ProQuad - 12 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	541	540	539	
Units: Titres				
geometric mean (confidence interval 95%)				
Anti-Measles GMT (N= 508, 455, 438)	942 (808 to 1098)	1977 (1736 to 2252)	2500 (2199 to 2841)	
Anti-Mumps GMT (N= 499, 453, 417)	73 (68 to 79)	91 (84 to 99)	86 (79 to 93)	
Anti-Rubella GMT (N= 518, 460, 447)	64 (60 to 70)	77 (71 to 83)	81 (75 to 88)	
Anti-Varicella GMT (N= 220, 312, 353)	15 (13 to 16)	15 (14 to 16)	15 (14 to 16)	

Statistical analyses

No statistical analyses for this end point

Secondary: # Immunogenicity: Rates of subjects with anti-varicella antibody (Ab) titres ≥1.25 gpELISA units/mL 42 days after each dose of ProQuad

End point title	# Immunogenicity: Rates of subjects with anti-varicella antibody (Ab) titres ≥1.25 gpELISA units/mL 42 days after each dose of ProQuad

End point description:

Percentage of subjects with an anti-varicella Ab titre ≥1.25 gpELISA units/mL (measured by glycoprotein ELISA) 42 days after injection of the 1st dose and the 2nd dose of ProQuad.
Analysis was done on the Full Analysis set (FAS): i.e., all randomised subjects who received at least 1 dose of the study vaccine and with any post-vaccination immunogenicity evaluation.
Note: (N=***, ***,***) represents the number of assessed subjects in the “9 months”, “11 months” and “12 months” groups, respectively.

End point type	Secondary

End point timeframe:

42 days after injection of the 1st dose and the 2nd dose of ProQuad.

End point values	ProQuad - 9 months	ProQuad - 11 months	ProQuad - 12 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	541	540	539	
Units: Percentage of subjects				
number (confidence interval 95%)				
Post-Dose 1 (N= 523, 474, 458)	99.8 (98.9 to 100)	100 (99.2 to 100)	99.8 (98.8 to 100)	
Post-Dose 2 (N= 521, 469, 459)	100 (99.3 to 100)	100 (99.2 to 100)	100 (99.2 to 100)	

Statistical analyses

No statistical analyses for this end point

Secondary: # Safety: Proportion of subjects reporting unsolicited injection-site reactions (ISRs) from D0 to D28 after the 1st dose of ProQuad

End point title	# Safety: Proportion of subjects reporting unsolicited injection-site reactions (ISRs) from D0 to D28 after the 1st dose of ProQuad

End point description:

Adverse events at injection sites were always considered as related to vaccine (Injection-Site Reactions (ISRs)).
Unsolicited ISRs occurring from Day 0 (D0) to D28 after vaccination, including injection-site erythema, injection-site pain and injection-site swelling starting from D5, were reported.
Percentage of subjects presenting at least once the considered events are presented here.
Analysis was done on the Post-Dose 1 Safety set, i.e. all subjects who received at least 1 dose of the study vaccine and who had safety follow-up data following Dose 1.

End point type	Secondary

End point timeframe:

From Day 0 (D0) to D28 after injection of the 1st dose of ProQuad.

End point values	ProQuad - 9 months	ProQuad - 11 months	ProQuad - 12 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	528	480	466	
Units: Percentage of subjects				
number (not applicable)				
At least 1 unsolicited ISR	24.8	23.3	19.1	
Injection-site bruising	1.3	1.3	1.1	
Injection-site eczema	0.2	0.2	0	
Injection-site erythema	16.7	16.5	13.1	
Injection-site haematoma	1.3	0.4	1.5	
Injection-site haemorrhage	1.7	1.3	1.7	
Injection-site induration	1.1	0.4	0.6	
Injection-site irritation	0	0.4	0	
Injection-site mass	0	0.2	0	
Injection-site nodule	0.2	0.2	0	
Injection-site pain	0.2	0.4	0.2	
Injection-site papule	0.8	0.2	0	
Injection-site pruritus	0.2	0	0	
Injection-site rash	2.7	4	2.6	
Injection-site swelling	3.6	4.2	2.8	
Injection-site urticaria	0	0.2	0.2	
Injection-site vesicles	0.8	0	0.6	
Injection-site warmth	0	0	0.2	

Statistical analyses

No statistical analyses for this end point

Secondary: # Safety: Proportion of subjects reporting unsolicited injection-site reactions (ISRs) from D0 to D28 after the 2nd dose of ProQuad

End point title	# Safety: Proportion of subjects reporting unsolicited injection-site reactions (ISRs) from D0 to D28 after the 2nd dose of ProQuad

End point description:

Adverse events at injection sites were always considered as related to vaccine (Injection-Site Reactions (ISRs)).
Unsolicited ISRs occurring from Day 0 (D0) to D28 after vaccination, including injection-site erythema, injection-site pain and injection-site swelling starting from D5, were reported.
Percentage of subjects presenting at least once the considered events are presented here.
Analysis was done on the Post-Dose 2 Safety set, i.e. all subjects who received at least 1 dose of the study vaccine and who had safety follow-up data following Dose 2.

End point type	Secondary

End point timeframe:

From Day 0 (D0) to D28 after injection of the 2nd dose of ProQuad.

End point values	ProQuad - 9 months	ProQuad - 11 months	ProQuad - 12 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	524	474	462	
Units: Percentage of subjects				
number (not applicable)				
At least 1 unsolicited ISR	1.9	4.4	3.9	
Injection-site bruising	0.4	1.1	0.6	
Injection-site eczema	0	0	0.2	
Injection-site erythema	0.6	0.4	0	
Injection-site haematoma	0.4	0.2	0.2	
Injection-site haemorrhage	0.2	1.1	0.6	
Injection-site induration	0.2	0.2	0.4	
Injection-site irritation	0	0	0.2	
Injection-site movement impairment	0	0	0.2	
Injection-site papule	0	0	0.4	
Injection-site rash	0.4	0.8	0.6	
Injection-site swelling	0	0	0.2	
Injection-site urticaria	0	0.4	0	
Injection-site vesicles	0	0.2	0	
Injection-site warmth	0	0	0.2	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Unsolicited adverse events (AEs) were collected from D0 to D28 after vaccination with Dose 1 and Dose 2 of ProQuad.
Serious AEs were collected from the 1st vaccination to the last visit of the subjects.

Adverse event reporting additional description:

Analysis of AEs was done on the Post-Dose 1 and Post-Dose 2 Safety sets (i.e., all subjects who received the study vaccine and who had safety follow-up data).
None of the serious AEs were assessed as vaccine-related.
Non-serious systemic AEs (vaccine-related or not) with vaccine-related AEs incidence >1% are presented below.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Post-Dose 1 - ProQuad - 9 months

Reporting group description:

Subjects received 2 doses of ProQuad vaccine: the 1st dose was administered at 9 months of age, and the 2nd dose 90 days later.
Respectively, 380 (72.0%) subjects reported at least 1 non-serious systemic AE and 195 (36.9%) subjects reported at least 1 vaccine-related non-serious systemic AE within 28 days after dose 1.

Reporting group title	Post-Dose 1 - ProQuad - 11 months

Reporting group description:

Subjects received 2 doses of ProQuad vaccine: the 1st dose was administered at 11 months of age, and the 2nd dose 90 days later.
Respectively, 345 (71.9%) subjects reported at least 1 non-serious systemic AE and 182 (37.9%) subjects reported at least 1 vaccine-related non-serious systemic AE within 28 days after dose 1.

Reporting group title	Post-Dose 1 - ProQuad - 12 months

Reporting group description:

Subjects received 2 doses of ProQuad vaccine: the 1st dose was administered at 12 months of age, and the 2nd dose 90 days later.
Respectively, 335 (71.9%) subjects reported at least 1 non-serious systemic AE and 195 (41.8%) subjects reported at least 1 vaccine-related non-serious systemic AE within 28 days after dose 1.

Reporting group title	Post-Dose 2 - ProQuad - 9 months

Reporting group description:

Subjects received 2 doses of ProQuad vaccine: the 1st dose was administered at 9 months of age, and the 2nd dose 90 days later.
Respectively, 307 (58.6%) subjects reported at least 1 non-serious systemic AE and 139 (26.5%) subjects reported at least 1 vaccine-related non-serious systemic AE within 28 days after dose 2.

Reporting group title	Post-Dose 2 - ProQuad - 11 months

Reporting group description:

Subjects received 2 doses of ProQuad vaccine: the 1st dose was administered at 11 months of age, and the 2nd dose 90 days later.
Respectively, 272 (57.4%) subjects reported at least 1 non-serious systemic AE and 116 (24.5%) subjects reported at least 1 vaccine-related non-serious systemic AE within 28 days after dose 2.

Reporting group title	Post-Dose 2 - ProQuad - 12 months

Reporting group description:

Subjects received 2 doses of ProQuad vaccine: the 1st dose was administered at 12 months of age, and the 2nd dose 90 days later.
Respectively, 259 (56.1%) subjects reported at least 1 non-serious systemic AE and 112 (24.2%) subjects reported at least 1 vaccine-related non-serious systemic AE within 28 days after dose 2.

Serious adverse events	Post-Dose 1 - ProQuad - 9 months	Post-Dose 1 - ProQuad - 11 months	Post-Dose 1 - ProQuad - 12 months
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 528 (3.41%)	8 / 480 (1.67%)	8 / 466 (1.72%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 528 (0.00%)	1 / 480 (0.21%)	3 / 466 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	0 / 528 (0.00%)	1 / 480 (0.21%)	0 / 466 (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
Head injury			
subjects affected / exposed	1 / 528 (0.19%)	0 / 480 (0.00%)	0 / 466 (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
Humerus fracture			
subjects affected / exposed	0 / 528 (0.00%)	0 / 480 (0.00%)	0 / 466 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 528 (0.19%)	0 / 480 (0.00%)	0 / 466 (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
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 528 (0.19%)	0 / 480 (0.00%)	0 / 466 (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
Febrile convulsion			

subjects affected / exposed	1 / 528 (0.19%)	0 / 480 (0.00%)	0 / 466 (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
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 528 (0.19%)	0 / 480 (0.00%)	0 / 466 (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
Bronchospasm			
subjects affected / exposed	1 / 528 (0.19%)	0 / 480 (0.00%)	0 / 466 (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
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 528 (0.00%)	1 / 480 (0.21%)	0 / 466 (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
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	1 / 528 (0.19%)	0 / 480 (0.00%)	1 / 466 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 528 (0.19%)	2 / 480 (0.42%)	2 / 466 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 528 (0.00%)	0 / 480 (0.00%)	1 / 466 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exanthema subitum			
subjects affected / exposed	0 / 528 (0.00%)	0 / 480 (0.00%)	0 / 466 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastroenteritis			
subjects affected / exposed	3 / 528 (0.57%)	3 / 480 (0.63%)	0 / 466 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis adenovirus			
subjects affected / exposed	0 / 528 (0.00%)	0 / 480 (0.00%)	0 / 466 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis Norwalk virus			
subjects affected / exposed	2 / 528 (0.38%)	0 / 480 (0.00%)	0 / 466 (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
Gastroenteritis rotavirus			
subjects affected / exposed	6 / 528 (1.14%)	0 / 480 (0.00%)	1 / 466 (0.21%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 528 (0.00%)	0 / 480 (0.00%)	0 / 466 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	0 / 528 (0.00%)	1 / 480 (0.21%)	0 / 466 (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
Nasopharyngitis			
subjects affected / exposed	1 / 528 (0.19%)	0 / 480 (0.00%)	0 / 466 (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
Otitis media			
subjects affected / exposed	1 / 528 (0.19%)	0 / 480 (0.00%)	1 / 466 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media acute			

subjects affected / exposed	0 / 528 (0.00%)	1 / 480 (0.21%)	0 / 466 (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
Pneumonia			
subjects affected / exposed	0 / 528 (0.00%)	1 / 480 (0.21%)	1 / 466 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 528 (0.00%)	0 / 480 (0.00%)	0 / 466 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 528 (0.19%)	0 / 480 (0.00%)	0 / 466 (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
Sepsis			
subjects affected / exposed	0 / 528 (0.00%)	1 / 480 (0.21%)	0 / 466 (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
Viral infection			
subjects affected / exposed	1 / 528 (0.19%)	0 / 480 (0.00%)	0 / 466 (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

Serious adverse events	Post-Dose 2 - ProQuad - 9 months	Post-Dose 2 - ProQuad - 11 months	Post-Dose 2 - ProQuad - 12 months
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 524 (0.57%)	6 / 474 (1.27%)	1 / 462 (0.22%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Concussion			

subjects affected / exposed	0 / 524 (0.00%)	0 / 474 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	0 / 524 (0.00%)	0 / 474 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 524 (0.00%)	0 / 474 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 524 (0.00%)	0 / 474 (0.00%)	1 / 462 (0.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 524 (0.00%)	0 / 474 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 524 (0.00%)	0 / 474 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile convulsion			
subjects affected / exposed	0 / 524 (0.00%)	0 / 474 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 524 (0.00%)	0 / 474 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bronchospasm			
subjects affected / exposed	0 / 524 (0.00%)	0 / 474 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 524 (0.00%)	0 / 474 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	0 / 524 (0.00%)	0 / 474 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 524 (0.19%)	2 / 474 (0.42%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 524 (0.00%)	0 / 474 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exanthema subitum			
subjects affected / exposed	1 / 524 (0.19%)	0 / 474 (0.00%)	0 / 462 (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			
subjects affected / exposed	0 / 524 (0.00%)	0 / 474 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis adenovirus			
subjects affected / exposed	1 / 524 (0.19%)	0 / 474 (0.00%)	0 / 462 (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 Norwalk virus			
subjects affected / exposed	0 / 524 (0.00%)	0 / 474 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 524 (0.00%)	1 / 474 (0.21%)	0 / 462 (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
Influenza			
subjects affected / exposed	0 / 524 (0.00%)	1 / 474 (0.21%)	0 / 462 (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
Laryngitis			
subjects affected / exposed	0 / 524 (0.00%)	0 / 474 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			
subjects affected / exposed	0 / 524 (0.00%)	0 / 474 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	0 / 524 (0.00%)	0 / 474 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media acute			
subjects affected / exposed	0 / 524 (0.00%)	0 / 474 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 524 (0.00%)	1 / 474 (0.21%)	0 / 462 (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
Pyelonephritis			

subjects affected / exposed	0 / 524 (0.00%)	1 / 474 (0.21%)	0 / 462 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 524 (0.00%)	0 / 474 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 524 (0.00%)	0 / 474 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 524 (0.00%)	0 / 474 (0.00%)	0 / 462 (0.00%)
occurrences causally related to treatment / all	0 / 0	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	Post-Dose 1 - ProQuad - 9 months	Post-Dose 1 - ProQuad - 11 months	Post-Dose 1 - ProQuad - 12 months
Total subjects affected by non-serious adverse events			
subjects affected / exposed	380 / 528 (71.97%)	345 / 480 (71.88%)	335 / 466 (71.89%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 528 (0.76%)	7 / 480 (1.46%)	13 / 466 (2.79%)
occurrences (all)	4	8	14
Irritability			
subjects affected / exposed	52 / 528 (9.85%)	56 / 480 (11.67%)	68 / 466 (14.59%)
occurrences (all)	74	77	79
Pyrexia			
subjects affected / exposed	58 / 528 (10.98%)	68 / 480 (14.17%)	60 / 466 (12.88%)
occurrences (all)	70	87	70
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	46 / 528 (8.71%)	46 / 480 (9.58%)	45 / 466 (9.66%)
occurrences (all)	49	53	50
Vomiting			
subjects affected / exposed	25 / 528 (4.73%)	17 / 480 (3.54%)	18 / 466 (3.86%)
occurrences (all)	28	19	19
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	42 / 528 (7.95%)	36 / 480 (7.50%)	27 / 466 (5.79%)
occurrences (all)	43	39	29
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	6 / 528 (1.14%)	17 / 480 (3.54%)	15 / 466 (3.22%)
occurrences (all)	7	19	16
Rash			
subjects affected / exposed	30 / 528 (5.68%)	26 / 480 (5.42%)	26 / 466 (5.58%)
occurrences (all)	35	30	29
Rash morbilliform			
subjects affected / exposed	21 / 528 (3.98%)	28 / 480 (5.83%)	32 / 466 (6.87%)
occurrences (all)	22	28	32
Rash rubelliform			
subjects affected / exposed	7 / 528 (1.33%)	9 / 480 (1.88%)	7 / 466 (1.50%)
occurrences (all)	7	9	8
Rash vesicular			
subjects affected / exposed	28 / 528 (5.30%)	19 / 480 (3.96%)	30 / 466 (6.44%)
occurrences (all)	28	22	30
Psychiatric disorders			
Crying			
subjects affected / exposed	24 / 528 (4.55%)	12 / 480 (2.50%)	10 / 466 (2.15%)
occurrences (all)	26	20	12
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	38 / 528 (7.20%)	22 / 480 (4.58%)	18 / 466 (3.86%)
occurrences (all)	40	24	19
Otitis media			

subjects affected / exposed	28 / 528 (5.30%)	27 / 480 (5.63%)	18 / 466 (3.86%)
occurrences (all)	33	28	20
Rhinitis			
subjects affected / exposed	64 / 528 (12.12%)	67 / 480 (13.96%)	43 / 466 (9.23%)
occurrences (all)	75	70	49
Upper respiratory tract infection			
subjects affected / exposed	40 / 528 (7.58%)	34 / 480 (7.08%)	29 / 466 (6.22%)
occurrences (all)	45	35	34
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	15 / 528 (2.84%)	2 / 480 (0.42%)	12 / 466 (2.58%)
occurrences (all)	15	2	13

Non-serious adverse events	Post-Dose 2 - ProQuad - 9 months	Post-Dose 2 - ProQuad - 11 months	Post-Dose 2 - ProQuad - 12 months
Total subjects affected by non-serious adverse events			
subjects affected / exposed	307 / 524 (58.59%)	272 / 474 (57.38%)	259 / 462 (56.06%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 524 (0.95%)	3 / 474 (0.63%)	3 / 462 (0.65%)
occurrences (all)	6	3	3
Irritability			
subjects affected / exposed	39 / 524 (7.44%)	24 / 474 (5.06%)	29 / 462 (6.28%)
occurrences (all)	53	26	34
Pyrexia			
subjects affected / exposed	39 / 524 (7.44%)	38 / 474 (8.02%)	27 / 462 (5.84%)
occurrences (all)	47	46	29
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	22 / 524 (4.20%)	24 / 474 (5.06%)	20 / 462 (4.33%)
occurrences (all)	22	24	22
Vomiting			
subjects affected / exposed	15 / 524 (2.86%)	11 / 474 (2.32%)	8 / 462 (1.73%)
occurrences (all)	16	12	9
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	23 / 524 (4.39%)	12 / 474 (2.53%)	15 / 462 (3.25%)
occurrences (all)	25	13	15
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	15 / 524 (2.86%)	7 / 474 (1.48%)	7 / 462 (1.52%)
occurrences (all)	17	7	8
Rash			
subjects affected / exposed	29 / 524 (5.53%)	16 / 474 (3.38%)	18 / 462 (3.90%)
occurrences (all)	29	16	19
Rash morbilliform			
subjects affected / exposed	11 / 524 (2.10%)	13 / 474 (2.74%)	13 / 462 (2.81%)
occurrences (all)	11	13	13
Rash rubelliform			
subjects affected / exposed	8 / 524 (1.53%)	9 / 474 (1.90%)	4 / 462 (0.87%)
occurrences (all)	9	9	4
Rash vesicular			
subjects affected / exposed	11 / 524 (2.10%)	18 / 474 (3.80%)	12 / 462 (2.60%)
occurrences (all)	11	18	13
Psychiatric disorders			
Crying			
subjects affected / exposed	15 / 524 (2.86%)	7 / 474 (1.48%)	11 / 462 (2.38%)
occurrences (all)	17	9	15
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	18 / 524 (3.44%)	25 / 474 (5.27%)	21 / 462 (4.55%)
occurrences (all)	19	27	23
Otitis media			
subjects affected / exposed	20 / 524 (3.82%)	21 / 474 (4.43%)	25 / 462 (5.41%)
occurrences (all)	20	22	28
Rhinitis			
subjects affected / exposed	49 / 524 (9.35%)	35 / 474 (7.38%)	47 / 462 (10.17%)
occurrences (all)	52	39	50
Upper respiratory tract infection			
subjects affected / exposed	36 / 524 (6.87%)	45 / 474 (9.49%)	59 / 462 (12.77%)
occurrences (all)	40	52	64
Metabolism and nutrition disorders			

Anorexia subjects affected / exposed occurrences (all)	3 / 524 (0.57%) 4	0 / 474 (0.00%) 0	1 / 462 (0.22%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 August 2007	Protocol amendment applicable only to France, made to answer the demand of the French Competent Authorities (AFSSAPS). Addition of a special warning in order for the investigators to perform a supervision after vaccination and to have an appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of the vaccine.
15 February 2008	# Implementation of Protocol amendment 1 in Finland and Germany. # Update of logistics and study timelines. # Correction of some typos.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported