Clinical trial results:
An Open-label, Multi-centre Study of the Safety of a 2-dose Regimen of a Combined Measles, Mumps, Rubella and Varicella Live Vaccine (ProQuad®) Manufactured with Recombinant Human Albumin (rHA) when administered to Children in their Second Year of Life

Summary

EudraCT number	2007-002438-12
Trial protocol	DE GR NL DK SE ES IT
Global end of trial date	24 November 2008

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	11 June 2015

Trial information

Trial identification

Sponsor protocol code	MRV01C

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00560755
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	24 November 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 November 2008
Global end of trial reached?	Yes
Global end of trial date	24 November 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To describe the safety profile of a second dose of ProQuad® manufactured with rHA when administered to children in their second year of life.
ProQuad® manufactured with rHA was called "ProQuad rHA" to facilitate the reading.

Protection of trial subjects:

Subjects received 2 doses of ProQuad rHA vaccine with an interval of at least 1 month in accordance with the European Summary of Product Characteristics (Euro SmPC).
Subjects with allergy to any of the vaccine components or history of a life-threatening reaction to a vaccine containing the same substances as the study vaccine 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: -

Actual start date of recruitment	24 October 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	Netherlands: 331
Country: Number of subjects enrolled	Spain: 885
Country: Number of subjects enrolled	Sweden: 309
Country: Number of subjects enrolled	Denmark: 142
Country: Number of subjects enrolled	Germany: 1212
Country: Number of subjects enrolled	Greece: 133
Country: Number of subjects enrolled	Italy: 376
Worldwide total number of subjects	3388
EEA total number of subjects	3388

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)	3388
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 in 84 active centres in 7 European countries.

Pre-assignment

Screening details:

3414 subjects were screened out.
3388 subjects were included and vaccinated.
3346 subjects received the 2 doses of ProQuad rHA.
3328 subjects completed the study.

Period 1

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

Blinding implementation details:

Not applicable as this study was open-label.

Arms

Arm title	All subjects

Arm description:

Subjects in the study received 2 doses of ProQuad rHA (measles, mumps, rubella and varicella (live attenuated)) vaccine with an interval of at least 1 month in accordance with the European Summary of Product Characteristics (Euro SmPC): the 1st dose at 12 to 22 months of age, and the 2nd dose 28 to 42 days later. Both doses were administered subcutaneously in the deltoid region, and the second dose had to be administered in the contralateral arm.

Arm type	Experimental
Investigational medicinal product name	ProQuad® manufactured with rHA
Investigational medicinal product code	MMRV
Other name	
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 an interval of at least 1 month. The second dose had to be administered in the contralateral arm (i.e. if the1st dose was injected in the right upper arm, it was recommended to inject the 2nd dose in the left upper arm; and vice versa).

Number of subjects in period 1	All subjects
Started	3388
Completed	3328
Not completed	60
Consent withdrawn by subject	26
Physician decision	2
Adverse event, non-fatal	8
Lost to follow-up	9
Protocol deviation	15

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (overall period)

Reporting group description:

Subjects received 2 doses of ProQuad rHA (measles, mumps, rubella and varicella (live attenuated)) vaccine with an interval of at least 1 month in accordance with the European Summary of Product Characteristics (Euro SmPC): the 1st dose at 12 to 22 months of age, and the 2nd dose 28 to 42 days later. Both doses were administered subcutaneously in the deltoid region, and the second dose had to be administered in the contralateral arm.

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	3388	3388	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	3388	3388	
Age continuous Units: months			
arithmetic mean	14.6		
standard deviation	± 2.3	-	
Gender categorical Units: Subjects			
Female	1650	1650	
Male	1738	1738	

End points

End points reporting groups

Reporting group title	All subjects

Reporting group description:

Subjects in the study received 2 doses of ProQuad rHA (measles, mumps, rubella and varicella (live attenuated)) vaccine with an interval of at least 1 month in accordance with the European Summary of Product Characteristics (Euro SmPC): the 1st dose at 12 to 22 months of age, and the 2nd dose 28 to 42 days later. Both doses were administered subcutaneously in the deltoid region, and the second dose had to be administered in the contralateral arm.

Primary: Global safety from D0 to D28 following the 2nd dose of ProQuad rHA

End point title	Global safety from D0 to D28 following the 2nd dose of ProQuad rHA[1]

End point description:

Adverse events (AEs) occurring after injection of the 2nd dose of ProQuad rHA were recorded as follows.
1/ From D0 to D4: # solicited injection-site adverse reactions (ISRs) (erythema, swelling, and pain),
2/ From D0 to D28: # unsolicited ISRs (including erythema, swelling, and pain 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.

End point type	Primary

End point timeframe:

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

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Objectives were only descriptive. Thus, no formal statistical hypothesis was tested in this study.

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	3342[2]			
Units: Percentage of subjects				
number (confidence interval 95%)				
At least 1 AE	57.66 (55.96 to 59.34)			
At least 1 vaccine-related AE	41.77 (40.09 to 43.47)			
At least 1 ISR	34.23 (32.62 to 35.87)			
At least 1 systemic AE	40.42 (38.76 to 42.11)			
At least 1 vaccine-related systemic AE	13.44 (12.3 to 14.64)			

Notes:

[2] - Post-Dose 2 Safety set

Statistical analyses

No statistical analyses for this end point

Primary: Proportion of subjects reporting solicited injection-site reactions (ISR) from D0 to D4 following the 2nd dose of ProQuad rHA

End point title	Proportion of subjects reporting solicited injection-site reactions (ISR) from D0 to D4 following the 2nd dose of ProQuad rHA[3]

End point description:

The immediate injection-site adverse reactions (within 20 minutes following vaccination) were recorded directly by the investigator into the CRF and in the subject's source documents.
Solicited injection-site reactions (ISRs) (injection-site erythema, injection-site swelling and injection-site pain) occurring from 20 minutes (Day 0 (D0)) to D4 after vaccination were then reported on the Diary Card by the parent(s) or legal representative.
Adverse events at injection sites were always considered as related to vaccine (Injection-Site Reactions (ISRs)).
Analysis was done on the Post-Dose 2 Safety set.

End point type	Primary

End point timeframe:

Day 0 (D0) to D4 after injection of the 2nd dose or ProQuad rHA.

Notes:

[3] - 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: Objectives were only descriptive. Thus, no formal statistical hypothesis was tested in this study.

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	3342[4]			
Units: Percentage of subjects				
number (confidence interval 95%)				
At least 1 solicited ISR	33.72 (32.12 to 35.35)			
Injection-site erythema	30.46 (28.9 to 32.05)			
Injection-site swelling	13.23 (12.09 to 14.42)			
Injection-site pain	11.49 (10.43 to 12.62)			

Notes:

[4] - Post-Dose 2 Safety set

Statistical analyses

No statistical analyses for this end point

Primary: Proportion of subjects reporting unsolicited injection-site reactions (ISR) from D0 to D28 following the 2nd dose of ProQuad rHA

End point title	Proportion of subjects reporting unsolicited injection-site reactions (ISR) from D0 to D28 following the 2nd dose of ProQuad rHA[5]

End point description:

The immediate injection-site adverse reactions (within 20 minutes following vaccination) were recorded directly by the investigator into the CRF and in the subject's source documents.
Unsolicited injection-site reactions (ISRs) occurring from 20 minutes (Day 0 (D0)) to D28 after vaccination as well as injection-site erythema, injection-site swelling and injection-site pain starting from D5 were then reported on the Diary Card by the parent(s) or legal representative.
Adverse events at injection sites were always considered as related to vaccine (Injection-Site Reactions (ISRs)).
Analysis was done on the Post-Dose 2 Safety set.

End point type	Primary

End point timeframe:

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

Notes:

[5] - 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: Objectives were only descriptive. Thus, no formal statistical hypothesis was tested in this study.

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	3342[6]			
Units: Percentage of subjects				
number (not applicable)				
At least 1 unsolicited ISR	1.65			
Injection-site bruising	0.06			
Injection-site eczema	0.09			
Injection-site erythema	0.24			
Injection-site haematoma	0.81			
Injection-site haemorrhage	0.03			
Injection-site induration	0.09			
Injection-site pruritus	0.03			
Injection-site rash	0.24			
Injection-site swelling	0.15			
Injection-site vesicles	0.03			

Notes:

[6] - Post-Dose 2 Safety set

Statistical analyses

No statistical analyses for this end point

Primary: Proportion of subjects reporting adverse events of interest from D0 to D28 following the 2nd dose of ProQuad rHA

End point title	Proportion of subjects reporting adverse events of interest from D0 to D28 following the 2nd dose of ProQuad rHA[7]

End point description:

The immediate injection-site adverse reactions and systemic adverse events (AEs) were recorded directly by the investigator into the CRF and in the subject's source documents following 20 minutes after vaccination.
Systemic AEs of interest (injection-site and non-injection site rashes of interest (measles-like rash, rubella-like rash, varicella-like rash and zoster-like rash) as well as mumps-like illness) were then reported on the Diary Card by the parent(s) or legal representative from 20 minutes (D0) to D28 to 42 after vaccination.
Analysis was done on the Post-Dose 2 Safety set.

End point type	Primary

End point timeframe:

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

Notes:

[7] - 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: Objectives were only descriptive. Thus, no formal statistical hypothesis was tested in this study.

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	3342[8]			
Units: Percentage of subjects				
number (confidence interval 95%)				
At least 1 injection-site rash of interest	0.03 (0 to 0.17)			
At least 1 non-injection-site rash of interest	2.78 (2.25 to 3.4)			
Measles / Measles-like rash	1.62 (1.22 to 2.1)			
Rubella / Rubella-like rash	0.57 (0.34 to 0.89)			
Varicella / Varicella-like rash	0.63 (0.39 to 0.96)			
Zoster / Zoster-like rash	0.03 (0 to 0.17)			
Mumps / Mumps-like illness	0.03 (0 to 0.17)			

Notes:

[8] - Post-Dose 2 Safety set

Statistical analyses

No statistical analyses for this end point

Primary: Proportion of subjects reporting rectal (or equivalent) temperature ≥38.0°C from D0 to D28 following the 2nd dose of ProQuad rHA

End point title	Proportion of subjects reporting rectal (or equivalent) temperature ≥38.0°C from D0 to D28 following the 2nd dose of ProQuad rHA[9]

End point description:

The parent(s) or legal representative were instructed to measure the temperature from the day of vaccination to Day 28 following vaccination using a digital thermometer supplied by Sanofi Pasteur MSD, each time the subject was febrile (or felt feverish) and until resolution of fever (or feverish feeling). In case of several measurements of the temperature during the day, the daily highest temperature had to be recorded in the Diary Card.
For the analysis of the numeric values of temperature, any axillary value was converted to rectal equivalent by adding +0.9°C (according to thermometer instructions).
Analysis was done on the Post-Dose 2 Safety set.

End point type	Primary

End point timeframe:

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

Notes:

[9] - 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: Objectives were only descriptive. Thus, no formal statistical hypothesis was tested in this study.

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	3342[10]			
Units: Percentage of subjects				
number (not applicable)				
At least 1 temperature ≥38.0°C	26.12			
At least 1 temperature ≥39.4°C	12.06			

Notes:
[10] - Post-Dose 2 Safety set

Statistical analyses

No statistical analyses for this end point

Secondary: Global safety from D0 to D28 following the 1st dose of ProQuad rHA

End point title	Global safety from D0 to D28 following the 1st dose of ProQuad rHA

End point description:

Adverse events (AEs) occurring after injection of the 1st dose of ProQuad rHA were recorded as follows.
1/ From D0 to D4: # solicited injection-site adverse reactions (ISRs) (erythema, swelling, and pain),
2/ From D0 to D28: # unsolicited ISRs (including erythema, swelling, and pain 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.

End point type	Secondary

End point timeframe:

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

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	3376[11]			
Units: Percentage of subjects				
number (confidence interval 95%)				
At least 1 AE	71.62 (70.07 to 73.14)			
At least 1 vaccine-related AE	50.62 (48.92 to 52.32)			
At least 1 ISR	26.27 (24.8 to 27.79)			
At least 1 systemic AE	64.1 (62.45 to 65.72)			
At least 1 vaccine-related systemic AE	34.86 (33.26 to 36.5)			

Notes:
[11] - Post-Dose 1 Safety set

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects reporting solicited injection-site reactions (ISR) from D0 to D4 following the 1st dose of ProQuad rHA

End point title	Proportion of subjects reporting solicited injection-site reactions

	(ISR) from D0 to D4 following the 1st dose of ProQuad rHA

End point description:

The immediate injection-site adverse reactions (within 20 minutes following vaccination) were recorded directly by the investigator into the CRF and in the subject's source documents.
Solicited injection-site reactions (ISRs) (injection-site erythema, injection-site swelling and injection-site pain) occurring from 20 minutes (Day 0 (D0)) to D4 after vaccination were then reported on the Diary Card by the parent(s) or legal representative.
Adverse events at injection sites were always considered as related to vaccine (Injection-Site Reactions (ISRs)).
Analysis was done on the Post-Dose 1 Safety set.

End point type	Secondary

End point timeframe:

Day 0 (D0) to D4 after injection of the 1st dose or ProQuad rHA.

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	3376[12]			
Units: Percentage of subjects				
number (confidence interval 95%)				
At least 1 solicited ISR	21.42 (20.04 to 22.84)			
Injection-site erythema	14.31 (13.14 to 15.53)			
Injection-site swelling	5.57 (4.82 to 6.4)			
Injection-site pain	10.31 (9.3 to 11.38)			

Notes:

[12] - Post-Dose 1 Safety set

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects reporting unsolicited injection-site reactions (ISR) from D0 to D28 following the 1st dose of ProQuad rHA

End point title	Proportion of subjects reporting unsolicited injection-site reactions (ISR) from D0 to D28 following the 1st dose of ProQuad rHA

End point description:

The immediate injection-site adverse reactions (within 20 minutes following vaccination) were recorded directly by the investigator into the CRF and in the subject's source documents.
Unsolicited injection-site reactions (ISRs) occurring from 20 minutes (Day 0 (D0)) to D28 to 42 after vaccination, as well as injection-site erythema, injection-site swelling and injection-site pain starting from D5 were then reported on the Diary Card by the parent(s) or legal representative.
Adverse events at injection sites were always considered as related to vaccine (Injection-Site Reactions (ISRs)).
Analysis was done on the Post-Dose 1 Safety set.

End point type	Secondary

End point timeframe:

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

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	3376[13]			
Units: Percentage of subjects				
number (not applicable)				
At least 1 unsolicited ISR	7.43			
Injection-site bruising	0.12			
Injection-site dermatitis	0.03			
Injection-site erythema	5.21			
Injection-site haematoma	0.71			
Injection-site haemorrhage	0.09			
Injection-site induration	0.09			
Injection-site macule	0.06			
Injection-site mass	0.09			
Injection-site pain	0.09			
Injection-site papule	0.18			
Injection-site pustule	0.03			
Injection-site rash	0.83			
Injection-site swelling	1.18			
Injection-site urticaria	0.06			
Injection-site vesicles	0.09			

Notes:

[13] - Post-Dose 1 Safety set

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects reporting adverse events of interest from D0 to D28 following the 1st dose of ProQuad rHA

End point title	Proportion of subjects reporting adverse events of interest from D0 to D28 following the 1st dose of ProQuad rHA

End point description:

The immediate injection-site adverse reactions and systemic adverse events (AEs) were recorded directly by the investigator into the CRF and in the subject's source documents following 20 minutes after vaccination.
Systemic AEs of interest (injection-site and non-injection site rashes of interest (measles-like rash, rubella-like rash, varicella-like rash and zoster-like rash) as well as mumps-like illness) were then reported on the Diary Card by the parent(s) or legal representative from 20 minutes (D0) to D28 to 42 after vaccination.
Analysis was done on the Post-Dose 1 Safety set.

End point type	Secondary

End point timeframe:

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

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	3376[14]			
Units: Percentage of subjects				
number (confidence interval 95%)				
At least 1 injection-site rash of interest	0.47 (0.27 to 0.77)			
At least 1 non-injection-site rash of interest	11.4 (10.35 to 12.52)			
Measles / Measles-like rash	6.9 (6.07 to 7.81)			
Rubella / Rubella-like rash	2.9 (2.36 to 3.53)			
Varicella / Varicella-like rash	2.1 (1.65 to 2.65)			
Zoster / Zoster-like rash	0.03 (0 to 0.16)			
Mumps / Mumps-like illness	0.21 (0.08 to 0.43)			

Notes:

[14] - Post-Dose 1 Safety set

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects reporting rectal (or equivalent) temperature ≥38.0°C from D0 to D28 following the 1st dose of ProQuad rHA

End point title	Proportion of subjects reporting rectal (or equivalent) temperature ≥38.0°C from D0 to D28 following the 1st dose of ProQuad rHA

End point description:

The parent(s) or legal representative were instructed to measure the temperature from the day of vaccination to Day 28 following vaccination using a digital thermometer supplied by Sanofi Pasteur MSD, each time the subject was febrile (or felt feverish) and until resolution of fever (or feverish feeling). In case of several measurements of the temperature during the day, the daily highest temperature had to be recorded in the Diary Card.
For the analysis of the numeric values of temperature, any axillary value was converted to rectal equivalent by adding +0.9°C (according to thermometer instructions).
Analysis was done on the Post-Dose 1 Safety set.

End point type	Secondary

End point timeframe:

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

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	3376[15]			
Units: Percentage of subjects				
number (not applicable)				
At least 1 temperature ≥38.0°C	56.1			
At least 1 temperature ≥39.4°C	25.24			

Notes:
[15] - Post-Dose 1 Safety set

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 the 1st (Post-Dose 1) and the 2nd (Post-Dose 2) dose of ProQuad rHA.
Serious AEs were collected from the 1st vaccination to the last visit of the subjects.

Adverse event reporting additional description:

Analysis of adverse events was done on the Safety sets (i.e., all subjects who received the study vaccine and who have safety follow-up data).
Post-Dose 1 Safety set, N= 3376.
Post-Dose 2 Safety set, N= 3342.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	All subjects

Reporting group description:

Subjects in the study received 2 doses of ProQuad rHA vaccine: the 1st dose at 12 to 22 months of age, and the 2nd dose 28 to 42 days later. Both doses were administered subcutaneously in the deltoid region (2nd dose in the contralateral arm).
Analysis of adverse events (AEs) was done on the Post-Dose 1 and Post-Dose 2 Safety sets (SSs) (i.e., all subjects who received the study vaccine and who have safety follow-up data).
Subjects exposed (i.e. vaccinated), N= 3388; Post-Dose 1 SS, N= 3376; Post-Dose 2 SS, N= 3342.
The number of subjects reporting at least 1 unsolicited non-serious ISR or AE with incidence ≥1% are presented hereafter. In the Post-Dose 1 SS, 2418 reported at least 1 AE; in the Post-Dose 2 SS, 1927 reported at least 1 AE (by convention, this number was reported below for "number of subjects affected by non-serious AEs" as only 1 number could be reported, and the primary objective of this study was to describe the safety profile of a 2nd dose of ProQuad rHA).

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	62 / 3388 (1.83%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Post-Dose 1, Respiratory fume inhalation disorder	Additional description: 1 subject experienced respiratory fume inhalation disorder of moderate intensity 12 days after injection of the 1st dose of ProQuad rHA. This serious AE lasted 2 days and was assessed as not related to vaccine.		
subjects affected / exposed[1]	1 / 3376 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post-Dose 1, Thermal burn	Additional description: 1 subject experienced thermal burn of moderate intensity 21 days after injection of the 1st dose of ProQuad rHA. This serious AE lasted 16 days and was assessed as not related to vaccine.		

subjects affected / exposed[2]	1 / 3376 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post-Dose 1, Tongue injury	Additional description: 1 subject experienced tongue injury of mild intensity 34 days after injection of the 1st dose of ProQuad rHA. This serious AE lasted 1 day and was assessed as not related to vaccine.		
subjects affected / exposed[3]	1 / 3376 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post-Dose 2, Burns second degree	Additional description: 1 subject experienced burns second degree of moderate intensity 1 day after injection of the 2nd dose of ProQuad rHA. This serious AE lasted 4 days and was assessed as not related to vaccine.		
subjects affected / exposed[4]	1 / 3342 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post-Dose 2, Concussion	Additional description: 1 subject experienced concussion of mild intensity 10 days after injection of the 2nd dose of ProQuad rHA. This serious AE lasted 3 days and was assessed as not related to vaccine.		
subjects affected / exposed[5]	1 / 3342 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post-Dose 2, Head injury	Additional description: 2 subjects experienced head injury of mild to moderate intensity 9 to 10 days after injection of the 2nd dose of ProQuad rHA. These serious AEs lasted 2 to 4 days and were assessed as not related to vaccine.		
subjects affected / exposed[6]	2 / 3342 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Post-Dose 2, Traumatic brain injury	Additional description: 1 subject experienced traumatic brain injury of mild intensity 8 days after injection of the 2nd dose of ProQuad rHA. This serious AE lasted 3 days and was assessed as not related to vaccine.		
subjects affected / exposed[7]	1 / 3342 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Post-Dose 2, Cyanosis	Additional description: 1 subject experienced cyanosis of moderate intensity 9 days after injection of the 2nd dose of ProQuad rHA. This serious AE lasted 1 day and was assessed as possibly related to vaccine.		
subjects affected / exposed[8]	1 / 3342 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Post-Dose 1, Febrile convulsion	Additional description: 10 subjects experienced febrile convulsion or febrile seizure of mild to severe intensity 3 to 34 days after injection of the 1st dose of ProQuad rHA. 8 of these serious AEs were assessed as possibly related to		

	vaccine.		
subjects affected / exposed[9]	10 / 3376 (0.30%)		
occurrences causally related to treatment / all	8 / 10		
deaths causally related to treatment / all	0 / 0		
Post-Dose 1, Loss of consciousness	Additional description: 1 subject experienced loss of consciousness of moderate intensity 10 days after injection of the 1st dose of ProQuad rHA. This serious AE lasted 1 day and was assessed as possibly related to vaccine.		
subjects affected / exposed[10]	1 / 3376 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Post-Dose 2, Facial paresis	Additional description: 1 subject experienced facial paresis of moderate intensity 12 days after injection of the 2nd dose of ProQuad rHA. This serious AE lasted 6 days and was assessed as not related to vaccine.		
subjects affected / exposed[11]	1 / 3342 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post-Dose 2, Febrile convulsion	Additional description: 6 subjects experienced febrile convulsion or febrile seizure of mild to severe intensity 6 to 23 days after injection of the 2nd dose of ProQuad rHA. 4 of these serious AEs were assessed as possibly related to vaccine.		
subjects affected / exposed[12]	6 / 3342 (0.18%)		
occurrences causally related to treatment / all	4 / 6		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Post-Dose 1, Pyrexia	Additional description: 2 subjects experienced pyrexia after injection of the 1st dose of ProQuad rHA: # 1 moderate, 35 days post-vaccination, lasting 5 days, not vaccine-related, # 1 severe, 1 day post-vaccination, lasting 13 days, possibly related to vaccine.		
subjects affected / exposed[13]	2 / 3376 (0.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Post-Dose 2, Pyrexia	Additional description: 1 subject experienced pyrexia of severe intensity 12 days after injection of the 2nd dose of ProQuad rHA. This serious AE lasted 17 days and was assessed as possibly related to vaccine.		
subjects affected / exposed[14]	1 / 3346 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Post-Dose 1, Vomiting	Additional description: 1 subject experienced vomiting of severe intensity 8 days after injection of the 1st dose of ProQuad rHA. This serious AEs lasted 4 days and was assessed as not related to vaccine.		

subjects affected / exposed[15]	1 / 3376 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Post-Dose 1, Asthma	Additional description: 1 subject experienced asthma of severe intensity 11 days after injection of the 1st dose of ProQuad rHA. This serious AE lasted 5 days, was assessed as possibly related to vaccine, and led to premature withdrawal.		
subjects affected / exposed[16]	1 / 3376 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Post-Dose 2, Asthma	Additional description: 1 subject experienced asthma of severe intensity 9 days after injection of the 2nd dose of ProQuad rHA. This serious AE lasted 4 days and was assessed as not related to vaccine.		
subjects affected / exposed[17]	1 / 3342 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Post-Dose 1, Dermatitis allergic	Additional description: 1 subject experienced dermatitis allergic of moderate intensity 29 days after injection of the 1st dose of ProQuad rHA. This serious AE lasted 3 days and was assessed as not related to vaccine.		
subjects affected / exposed[18]	1 / 3376 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post-Dose 1, Rash	Additional description: 1 subject experienced rash of severe intensity 1 day after injection of the 1st dose of ProQuad rHA. This serious AE lasted 20 days and was assessed as possibly related to vaccine.		
subjects affected / exposed[19]	1 / 3376 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Post-Dose 2, Sleep terror	Additional description: 1 subject experienced sleep terror of severe intensity 16 days after injection of the 2nd dose of ProQuad rHA. This serious AE lasted 7 days and was assessed as not related to vaccine.		
subjects affected / exposed[20]	1 / 3342 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Post-Dose 1, Acute tonsillitis	Additional description: 1 subject experienced acute tonsillitis of moderate intensity 6 days after injection of the 1st dose of ProQuad rHA. This serious AE lasted 9 days and was assessed as possibly related to vaccine.		

subjects affected / exposed[21]	1 / 3376 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Post-Dose 1, Appendicitis	Additional description: 1 subject experienced appendicitis of severe intensity 36 days after injection of the 1st dose of ProQuad rHA. This serious AE lasted 19 days and was assessed as not related to vaccine.		
subjects affected / exposed[22]	1 / 3376 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post-Dose 1, Bronchitis	Additional description: 2 subjects experienced bronchitis of severe intensity 4 to 6 days after injection of the 1st dose of ProQuad rHA. These serious AEs lasted 9 to 15 days and were assessed as not related to vaccine.		
subjects affected / exposed[23]	2 / 3376 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Post-Dose 1, Gastroenteritis	Additional description: 6 subjects experienced gastroenteritis of moderate to severe intensity 4 to 29 days after injection of the 1st dose of ProQuad rHA. These serious AEs lasted 2 to 13 days and 1 of severe intensity was assessed as possibly related to vaccine.		
subjects affected / exposed[24]	6 / 3376 (0.18%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Post-Dose 1, Gastroenteritis Norwalk virus	Additional description: 1 subject experienced gastroenteritis Norwalk virus of severe intensity 17 days after injection of the 1st dose of ProQuad rHA. This serious AE lasted 7 days and was assessed as not related to vaccine.		
subjects affected / exposed[25]	1 / 3376 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post-Dose 1, Gastroenteritis rotavirus	Additional description: 2 subjects experienced rotavirus gastroenteritis of severe intensity 23 to 27 days after injection of the 1st dose of ProQuad rHA. These serious AEs lasted 9 to 13 days and were assessed as not related to vaccine.		
subjects affected / exposed[26]	2 / 3376 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Post-Dose 1, Oral herpes	Additional description: 1 subject experienced oral herpes of moderate intensity 12 days after injection of the 1st dose of ProQuad rHA. This serious AE lasted 7 days and was assessed as not related to vaccine.		
subjects affected / exposed[27]	1 / 3376 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post-Dose 1, Pneumonia	Additional description: 2 subjects experienced pneumonia of mild to moderate intensity 3 to 16 days after injection of the 1st dose of ProQuad rHA. These serious AEs lasted 7 to 17 days and 1 of them was assessed as possibly related to vaccine.		

subjects affected / exposed[28]	2 / 3376 (0.06%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Post-Dose 1, Pseudocroup	Additional description: 1 subject experienced pseudocroup of severe intensity 13 days after injection of the 1st dose of ProQuad rHA. This serious AE lasted 2 days and was assessed as not related to vaccine.		
subjects affected / exposed[29]	1 / 3376 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post-Dose 1, Respiratory tract infection	Additional description: 1 subject experienced respiratory tract infection of severe intensity 6 days after injection of the 1st dose of ProQuad rHA. This serious AE lasted 8 days and was assessed as not related to vaccine.		
subjects affected / exposed[30]	1 / 3376 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post-Dose 1, Tonsillitis	Additional description: 2 subjects experienced tonsillitis of moderate to severe intensity 5 to 29 days after injection of the 1st dose of ProQuad rHA. These serious AEs lasted 3 to 8 days and were assessed as not related to vaccine.		
subjects affected / exposed[31]	2 / 3376 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Post-Dose 1, Upper respiratory tract infection	Additional description: 2 subjects experienced upper respiratory tract infection of moderate to severe intensity 1 to 16 days after injection of the 1st dose of ProQuad rHA. These serious AEs lasted 4 to 13 days and were assessed as not related to vaccine.		
subjects affected / exposed[32]	2 / 3376 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Post-Dose 1, Viral infection	Additional description: 1 subject experienced viral infection of moderate intensity 24 days after injection of the 1st dose of ProQuad® rHA. This serious AE lasted 13 days and was assessed as possibly related to vaccine.		
subjects affected / exposed[33]	1 / 3376 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Post-Dose 2, Bronchitis	Additional description: 2 subjects experienced bronchitis of moderate intensity 1 to 5 days after injection of the 2nd dose of ProQuad rHA. These serious AEs lasted 3 to 5 days and 1 of them was assessed as possibly related to vaccine.		
subjects affected / exposed[34]	2 / 3342 (0.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Post-Dose 2, Gastroenteritis	Additional description: 2 subjects experienced gastroenteritis of moderate to severe intensity 0 to 6 days after injection of the 2nd dose of ProQuad rHA. These serious AEs lasted 4 to 11 days and were assessed as not related to vaccine.		

subjects affected / exposed[35]	2 / 3342 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Post-Dose 2, Gastroenteritis rotavirus	Additional description: 2 subjects experienced gastroenteritis rotavirus of severe intensity 17 to 18 days after injection of the 2nd dose of ProQuad rHA. These serious AEs lasted 7 to 8 days and were assessed as not related to vaccine.		
subjects affected / exposed[36]	2 / 3342 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Post-Dose 2, Upper respiratory tract infection	Additional description: 1 subject experienced upper respiratory tract infection of moderate intensity 10 days after injection of the 2nd dose of ProQuad rHA. This serious AE lasted 4 days and was assessed as not related to vaccine.		
subjects affected / exposed[37]	1 / 3342 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Post-Dose 1, Dehydration	Additional description: 1 subject experienced dehydration of severe intensity 6 days after injection of the 1st dose of ProQuad rHA. This serious AE lasted 8 days and was assessed as not related to vaccine.		
subjects affected / exposed[38]	1 / 3376 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post-Dose 2, Dehydration	Additional description: 1 subject experienced dehydration of severe intensity 1 day after injection of the 2nd dose of ProQuad rHA. This serious AE lasted 2 days and was assessed as not related to vaccine.		
subjects affected / exposed[39]	1 / 3342 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post-Dose 2, Diabetes mellitus insulin-dependent	Additional description: 1 subject experienced diabetes mellitus insulin-dependent of severe intensity 2 days after injection of the 2nd dose of ProQuad rHA. This serious AE lasted 26 days and was assessed as not related to vaccine.		
subjects affected / exposed[40]	1 / 3342 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: In this study, 3388 subjects were exposed (received at least 1 dose of the vaccine). Analysis of AEs was done on the Post-Dose 1 Safety set (i.e., all subjects who received the 1st dose of study vaccine and who have safety data, N= 3376).
[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Idem justification note [1]

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Idem justification note [1]

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: In this study, 3388 subjects were exposed (received at least 1 dose of the vaccine). Analysis of AEs was done on the Post-Dose 2 Safety set (i.e., all subjects who received the 2nd dose of study vaccine and who have safety data, N= 3342).

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Idem justification note [4]

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
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[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
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Justification: Idem justification note [4]

[15] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
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[17] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Idem justification note [4]

[18] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
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Justification: Idem justification note [4]

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Justification: Idem justification note [4]

[40] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Idem justification note [4]

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

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1927 / 3388 (56.88%)		
General disorders and administration site conditions			
Post-Dose 1, Pyrexia			
subjects affected / exposed[41]	1124 / 3376 (33.29%)		
occurrences (all)	1276		
Post-Dose 2, Pyrexia			
subjects affected / exposed[42]	527 / 3342 (15.77%)		
occurrences (all)	593		
Eye disorders			
Post-Dose 1, Conjunctivitis			
subjects affected / exposed[43]	63 / 3376 (1.87%)		
occurrences (all)	66		
Post-Dose 2, Conjunctivitis			
subjects affected / exposed[44]	50 / 3342 (1.50%)		
occurrences (all)	50		
Gastrointestinal disorders			
Post-Dose 1, Diarrhoea			
subjects affected / exposed[45]	191 / 3376 (5.66%)		
occurrences (all)	207		
Post-Dose 1, Vomiting			
subjects affected / exposed[46]	107 / 3376 (3.17%)		
occurrences (all)	111		
Post-Dose 2, Diarrhoea			
subjects affected / exposed[47]	111 / 3342 (3.32%)		
occurrences (all)	120		
Post-Dose 2, Vomiting			
subjects affected / exposed[48]	54 / 3342 (1.62%)		
occurrences (all)	57		
Respiratory, thoracic and mediastinal disorders			
Post-Dose 1, Cough			
subjects affected / exposed[49]	199 / 3376 (5.89%)		
occurrences (all)	211		
Post-Dose 2, Cough			

subjects affected / exposed[50]	166 / 3342 (4.97%)		
occurrences (all)	178		
Skin and subcutaneous tissue disorders			
Post-Dose 1, Dermatitis diaper			
subjects affected / exposed[51]	71 / 3376 (2.10%)		
occurrences (all)	74		
Post-Dose 1, Eczema			
subjects affected / exposed[52]	41 / 3376 (1.21%)		
occurrences (all)	42		
Post-Dose 1, Heat rash			
subjects affected / exposed[53]	37 / 3376 (1.10%)		
occurrences (all)	37		
Post-Dose 1, Rash			
subjects affected / exposed[54]	227 / 3376 (6.72%)		
occurrences (all)	236		
Post-Dose 1, Rash morbilliform			
subjects affected / exposed[55]	232 / 3376 (6.87%)		
occurrences (all)	236		
Post-Dose 1, Rash rubelliform			
subjects affected / exposed[56]	96 / 3376 (2.84%)		
occurrences (all)	97		
Post-Dose 1, Rash vesicular			
subjects affected / exposed[57]	66 / 3376 (1.95%)		
occurrences (all)	67		
Post-Dose 2, Dermatitis diaper			
subjects affected / exposed[58]	43 / 3342 (1.29%)		
occurrences (all)	44		
Post-Dose 2, Rash			
subjects affected / exposed[59]	101 / 3342 (3.02%)		
occurrences (all)	103		
Post-Dose 2, Rash morbilliform			
subjects affected / exposed[60]	54 / 3342 (1.62%)		
occurrences (all)	55		
Infections and infestations			
Post-Dose 1, Bronchitis			

subjects affected / exposed[61]	49 / 3376 (1.45%)			
occurrences (all)	52			
Post-Dose 1, Ear infection				
subjects affected / exposed[62]	73 / 3376 (2.16%)			
occurrences (all)	75			
Post-Dose 1, Gastroenteritis				
subjects affected / exposed[63]	67 / 3376 (1.98%)			
occurrences (all)	70			
Post-Dose 1, Nasopharyngitis				
subjects affected / exposed[64]	183 / 3376 (5.42%)			
occurrences (all)	196			
Post-Dose 1, Otitis media				
subjects affected / exposed[65]	53 / 3376 (1.57%)			
occurrences (all)	55			
Post-Dose 1, Pharyngitis				
subjects affected / exposed[66]	36 / 3376 (1.07%)			
occurrences (all)	38			
Post-Dose 1, Respiratory tract infection				
subjects affected / exposed[67]	36 / 3376 (1.07%)			
occurrences (all)	37			
Post-Dose 1, Rhinitis				
subjects affected / exposed[68]	181 / 3376 (5.36%)			
occurrences (all)	198			
Post-Dose 1, Tonsillitis				
subjects affected / exposed[69]	63 / 3376 (1.87%)			
occurrences (all)	64			
Post-Dose 1, Upper respiratory tract infection				
subjects affected / exposed[70]	75 / 3376 (2.22%)			
occurrences (all)	78			
Post-Dose 2, Bronchitis				
subjects affected / exposed[71]	58 / 3342 (1.74%)			
occurrences (all)	60			
Post-Dose 2, Ear infection				

subjects affected / exposed[72]	42 / 3342 (1.26%)		
occurrences (all)	42		
Post-Dose 2, Gastroenteritis			
subjects affected / exposed[73]	57 / 3342 (1.71%)		
occurrences (all)	57		
Post-Dose 2, Nasopharyngitis			
subjects affected / exposed[74]	174 / 3342 (5.21%)		
occurrences (all)	184		
Post-Dose 2, Otitis media			
subjects affected / exposed[75]	35 / 3342 (1.05%)		
occurrences (all)	35		
Post-Dose 2, Rhinitis			
subjects affected / exposed[76]	142 / 3342 (4.25%)		
occurrences (all)	148		
Post-Dose 2, Upper respiratory tract infection			
subjects affected / exposed[77]	46 / 3342 (1.38%)		
occurrences (all)	50		

Notes:

[41] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Idem justification note [1]

[42] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[58] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Idem justification note [4]

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Justification: Idem justification note [4]

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 June 2008	# Administrative changes. # Extension of the recruitment period from July 2008 to October 2008 to reach the recruitment target of 3,000 evaluable subjects, and extension of the Clinical Study Report delivery date from May 2009 to September 2009. # Update of the list of investigational sites.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported