



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 the 1st 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 standard deviation | 14.6 ± 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 of 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

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 of 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 $\geq 38.0^{\circ}\text{C}$ from D0 to D28 following the 2nd dose of ProQuad rHA

| | |
|-----------------|---|
| End point title | Proportion of subjects reporting rectal (or equivalent) temperature $\geq 38.0^{\circ}\text{C}$ 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 $+0.9^{\circ}\text{C}$ (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 $\geq 38.0^{\circ}\text{C}$ | 26.12 | | | |
| At least 1 temperature $\geq 39.4^{\circ}\text{C}$ | 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 of 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 |
|-----------------|---|

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 of 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 of 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 $\geq 38.0^{\circ}\text{C}$ from D0 to D28 following the 1st dose of ProQuad rHA

| | |
|-----------------|--|
| End point title | Proportion of subjects reporting rectal (or equivalent) temperature $\geq 38.0^{\circ}\text{C}$ 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 $+0.9^{\circ}\text{C}$ (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 of 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 $\geq 38.0^{\circ}\text{C}$ | 56.1 | | | |
| At least 1 temperature $\geq 39.4^{\circ}\text{C}$ | 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 $\geq 1\%$ 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.

Justification: Idem justification note [4]

[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.

Justification: Idem justification note [4]

[8] - 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]

[9] - 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]

[10] - 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]

[11] - 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]

[12] - 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]

[13] - 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]

[14] - 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]

[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.

Justification: Idem justification note [1]

[16] - 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]

[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.

Justification: Idem justification note [1]

[19] - 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]

[20] - 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]

[21] - 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]

[22] - 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]

| | | | |
|---|-------------------------|--|--|
| 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.

Justification: Idem justification note [4]

[43] - 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]

[44] - 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]

[45] - 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]

[46] - 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]

[47] - 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]

[48] - 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]

[49] - 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]

Justification: Idem justification note [4]

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[70] - 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]

[71] - 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]

[72] - 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]

[73] - 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]

[74] - 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]

[75] - 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]

[76] - 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]

[77] - 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]

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