



Clinical trial results:

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

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | MRV02C |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00566527 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 29 December 2008 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 December 2008 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

1st primary objective: to demonstrate that a 2-dose regimen of ProQuad administered at a 3-month interval to healthy children of 11 months of age at the time of Dose 1 was as immunogenic as in healthy children of 12 months of age at the time of Dose 1, in terms of antibody response rates to measles, mumps, rubella and varicella at Day 42 following Dose 2.

2nd primary objective (only if the 1st primary objective was reached): similar to the 1st one at 9 months of age.

3rd primary objective: to demonstrate that a 2-dose regimen of ProQuad administered at a 3-month interval to healthy children of 11 months of age and 9 months of age at the time of Dose 1 is well tolerated compared to healthy children of 12 months of age at the time of Dose 1.

Note: "ProQuad® manufactured with rHA" (recombinant Human Albumin) was referred to "ProQuad" to facilitate the reading.

Protection of trial subjects:

Subjects with prior known sensitivity or allergy to any component of the vaccine (including neomycin, sorbitol or gelatin) or true allergy to egg proteins (anaphylactic or anaphylactoid reaction after ingesting eggs) were not vaccinated.

Vaccines were administered by qualified study personnel.

After each vaccination, subjects were kept under observation for at least 20 minutes to ensure their safety.

Background therapy: -

Evidence for comparator:

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

| | |
|---|------------------|
| Actual start date of recruitment | 29 November 2007 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---------------|
| Country: Number of subjects enrolled | Finland: 1290 |
| Country: Number of subjects enrolled | France: 140 |
| Country: Number of subjects enrolled | Germany: 190 |
| Worldwide total number of subjects | 1620 |
| EEA total number of subjects | 1620 |

Notes:

| Subjects enrolled per age group | |
|---|------|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 1620 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

1626 subjects were screened out.

1620 subjects were randomised and constituted the population of the study.

1483 subjects received at least 1 dose of ProQuad.

1465 subjects received the 2 doses of ProQuad.

1459 subjects completed the study.

Period 1

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

Blinding implementation details:

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

Arms

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

Arm description:

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

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

Dosage and administration details:

0.5 mL, subcutaneous route (deltoid region, upper arm), 2 doses with a 3-month interval. Both doses had to be administered in the opposite arm to the blood sampling.

| | |
|------------------|---------------------|
| Arm title | ProQuad - 11 months |
|------------------|---------------------|

Arm description:

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

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

Dosage and administration details:

0.5 mL, subcutaneous route (deltoid region, upper arm), 2 doses with a 3-month interval. Both doses had to be administered in the opposite arm to the blood sampling.

| | |
|------------------|---------------------|
| Arm title | ProQuad - 12 months |
|------------------|---------------------|

Arm description:

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

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

Dosage and administration details:

0.5 mL, subcutaneous route (deltoid region, upper arm), 2 doses with a 3-month interval.
Both doses had to be administered in the opposite arm to the blood sampling.

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

Baseline characteristics

Reporting groups

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

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

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

End points

End points reporting groups

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

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

| | |
|---|--|
| End point title | #1st# Immunogenicity at 11 vs 12 months of age: Antibody (Ab) response rates to measles, mumps, rubella and varicella 42 days after the 2nd dose of ProQuad ^[1] |
| End point description: Percentage of subjects with an anti-measles Ab titre ≥ 255 mIU/mL, an anti-mumps Ab titre ≥ 10.0 ELISA Ab units/mL, an anti-rubella Ab titre ≥ 10.0 IU/mL, and an anti-varicella Ab titre ≥ 5 gpELISA units/mL 42 days after injection of the 2nd dose of ProQuad. All Ab titres were measured by Enzyme-Linked Immunosorbent Assay (ELISA), except Ab to varicella determined by glycoprotein ELISA. Analysis was done on the Post-Dose 2 Antigen-specific Per Protocol set (PPS): i.e., all subjects initially seronegative for those antigens (Measles Ab titre < 255 mIU/mL, Mumps Ab titre < 10.0 ELISA Ab units/mL, Rubella Ab titre < 10.0 IU/mL, and Varicella Ab titre < 1.25 gpELISA units/mL) and with post-dose immunogenicity evaluation for those antigens. Note: (N=***, ***) represents the number of assessed subjects in the "11 months" and "12 months" groups, respectively. | |
| End point type | Primary |
| End point timeframe: 42 days after injection of the 2nd dose of ProQuad. | |
| Notes: | |

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint corresponds to the 1st primary objective of the study, i.e. comparison of the immunogenicity induced by a 2-dose regimen of ProQuad administered to children of 11 months of age at the time of Dose 1 (arm 2) versus children of 12 months of age at the time of Dose 1 (arm 3), in terms of antibody response rates to measles, mumps, rubella and varicella at Day 42 following Dose 2.

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

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

Statistical analyses

| Statistical analysis title | Non-inferiority for Measles |
|----------------------------|-----------------------------|
|----------------------------|-----------------------------|

Statistical analysis description:

The estimates of the differences between Group 2 (11 months) & Group 3 (12 months) response rates were calculated with their 2-sided 95% confidence interval (CI). If all lower bounds of the 95% CI were greater than the non-inferiority margin, it was concluded that Group 2 response rates were non-inferior to Group 3 response rates.

Statistical analysis was based on the Miettinen & Nurminen method using a stratification by country. Analysis was done on the Post-Dose 2 Antigen-specific PPS.

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

Notes:

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

| Statistical analysis title | Non-inferiority for Mumps |
|----------------------------|---------------------------|
|----------------------------|---------------------------|

Statistical analysis description:

The estimates of the differences between Group 2 (11 months) & Group 3 (12 months) response rates were calculated with their 2-sided 95% confidence interval (CI). If all lower bounds of the 95% CI were greater than the non-inferiority margin, it was concluded that Group 2 response rates were non-inferior to Group 3 response rates.

Statistical analysis was based on the Miettinen & Nurminen method using a stratification by country. Analysis was done on the Post-Dose 2 Antigen-specific PPS.

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

Notes:

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

| | |
|--|---|
| Statistical analysis title | Non-inferiority for Rubella |
| Statistical analysis description: | |
| The estimates of the differences between Group 2 (11 months) & Group 3 (12 months) response rates were calculated with their 2-sided 95% confidence interval (CI). If all lower bounds of the 95% CI were greater than the non-inferiority margin, it was concluded that Group 2 response rates were non-inferior to Group 3 response rates. | |
| Statistical analysis was based on the Miettinen & Nurminen method using a stratification by country. Analysis was done on the Post-Dose 2 Antigen-specific PPS. | |
| Comparison groups | ProQuad - 12 months v ProQuad - 11 months |
| Number of subjects included in analysis | 1079 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[4] |
| Parameter estimate | Difference in percentages of subjects |
| Point estimate | -0.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.55 |
| upper limit | 1.03 |

Notes:

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

| | |
|--|---|
| Statistical analysis title | Non-inferiority for Varicella |
| Statistical analysis description: | |
| The estimates of the differences between Group 2 (11 months) & Group 3 (12 months) response rates were calculated with their 2-sided 95% confidence interval (CI). If all lower bounds of the 95% CI were greater than the non-inferiority margin, it was concluded that Group 2 response rates were non-inferior to Group 3 response rates. | |
| Statistical analysis was based on the Miettinen & Nurminen method using a stratification by country. Analysis was done on the Post-Dose 2 Antigen-specific PPS. | |
| Comparison groups | ProQuad - 11 months v ProQuad - 12 months |
| Number of subjects included in analysis | 1079 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[5] |
| Parameter estimate | Difference in percentages of subjects |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.28 |
| upper limit | 1.1 |

Notes:

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

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

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

End point description:

Percentage of subjects with an anti-measles Ab titre ≥ 255 mIU/mL, an anti-mumps Ab titre ≥ 10.0 ELISA Ab units/mL, an anti-rubella Ab titre ≥ 10.0 IU/mL, and an anti-varicella Ab titre ≥ 5 gpELISA units/mL 42 days after injection of the 2nd dose of ProQuad.

All Ab titres were measured by Enzyme-Linked Immunosorbent Assay (ELISA), except Ab to varicella

determined by glycoprotein ELISA.

Analysis was done on the Post-Dose 2 Antigen-specific Per Protocol set (PPS): i.e., all subjects initially seronegative for those antigens (Measles Ab titre <255 mIU/mL, Mumps Ab titre <10.0 ELISA Ab units/mL, Rubella Ab titre <10.0 IU/mL, and Varicella Ab titre <1.25 gpELISA units/mL) and with post-dose immunogenicity evaluation for those antigens.

Note: (N=***, ***) represents the number of assessed subjects in the "9 months" and "12 months" groups, respectively.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

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

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

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

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

Statistical analyses

| | |
|----------------------------|-----------------------------|
| Statistical analysis title | Non-inferiority for Measles |
|----------------------------|-----------------------------|

Statistical analysis description:

The estimates of the differences between Group 1 (9 months) & Group 3 (12 months) response rates were calculated with their 2-sided 95% confidence interval (CI). If all lower bounds of the 95% CI were greater than the non-inferiority margin, it was concluded that Group 1 response rates were non-inferior to Group 3 response rates.

Statistical analysis was based on the Miettinen & Nurminen method using a stratification by country.

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

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

Notes:

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

| Statistical analysis title | Non-inferiority for Mumps |
|---|--|
| Statistical analysis description: | |
| The estimates of the differences between Group 1 (9 months) & Group 3 (12 months) response rates were calculated with their 2-sided 95% confidence interval (CI). If all lower bounds of the 95% CI were greater than the non-inferiority margin, it was concluded that Group 1 response rates were non-inferior to Group 3 response rates. | |
| Statistical analysis was based on the Miettinen & Nurminen method using a stratification by country. Analysis was done on the Post-Dose 2 Antigen-specific PPS. | |
| Comparison groups | ProQuad - 9 months v ProQuad - 12 months |
| Number of subjects included in analysis | 1080 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[8] |
| Parameter estimate | Difference in percentages of subjects |
| Point estimate | -0.35 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.71 |
| upper limit | 1.01 |

Notes:

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

| Statistical analysis title | Non-inferiority for Rubella |
|---|--|
| Statistical analysis description: | |
| The estimates of the differences between Group 1 (9 months) & Group 3 (12 months) response rates were calculated with their 2-sided 95% confidence interval (CI). If all lower bounds of the 95% CI were greater than the non-inferiority margin, it was concluded that Group 1 response rates were non-inferior to Group 3 response rates. | |
| Statistical analysis was based on the Miettinen & Nurminen method using a stratification by country. Analysis was done on the Post-Dose 2 Antigen-specific PPS. | |
| Comparison groups | ProQuad - 9 months v ProQuad - 12 months |
| Number of subjects included in analysis | 1080 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[9] |
| Parameter estimate | Difference in percentages of subjects |
| Point estimate | -0.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.34 |
| upper limit | 1.09 |

Notes:

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

| Statistical analysis title | Non-inferiority for Varicella |
|----------------------------|-------------------------------|
|----------------------------|-------------------------------|

Statistical analysis description:

The estimates of the differences between Group 1 (9 months) & Group 3 (12 months) response rates were calculated with their 2-sided 95% confidence interval (CI). If all lower bounds of the 95% CI were greater than the non-inferiority margin, it was concluded that Group 1 response rates were non-inferior to Group 3 response rates.

Statistical analysis was based on the Miettinen & Nurminen method using a stratification by country.

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

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

Notes:

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

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

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

End point description:

Adverse events (AEs) occurring after injection of the 1st dose of ProQuad were recorded as follows.

1/ From D0 to D4: # solicited injection-site adverse reactions (ISRs) (erythema, pain, and swelling),
2/ From D0 to D28: # unsolicited ISRs (including erythema, pain, and swelling from D5 to D28), # numeric values of temperature, # AEs of interest (a/ injection-site rashes of interest, b/ non-injection site rashes of interest (measles-like rash, rubella-like rash, varicella-like rash and zoster-like rash), c/ mumps-like illness), # other systemic AEs.

AEs at injection sites were always considered as related to vaccine (ISRs). The investigator had to assess whether systemic AEs were vaccine-related systemic AEs or not.

Analysis was done on the Post-Dose 1 Safety set, i.e. all subjects who received at least 1 dose of the study vaccine and who had safety follow-up data following Dose 1.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

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

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal hypothesis was tested. Thus, no statistical results are presented here.

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Adverse events at injection sites were always considered as related to vaccine (Injection-Site Reactions (ISRs)).

Solicited ISRs were defined as injection-site erythema, injection-site pain and injection-site swelling occurring from Day 0 (D0) to D4 after vaccination.

Unsolicited ISRs consisted in all other ISRs, including injection-site erythema, injection-site pain and injection-site swelling starting from D5.

Analysis was done on the Post-Dose 1 Safety set, i.e. all subjects who received at least 1 dose of the study vaccine and who had safety follow-up data following Dose 1.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

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

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal hypothesis was tested. Thus, no statistical results are presented here.

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

Statistical analyses

No statistical analyses for this end point

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

reporting adverse events of interest and temperature $\geq 39.4^{\circ}\text{C}$ from D0 to D28 after the 1st dose of ProQuad

| | |
|-----------------|---|
| End point title | #3rd# Safety at 9 or 11 vs 12 months of age: Proportion of subjects reporting adverse events of interest and temperature $\geq 39.4^{\circ}\text{C}$ from D0 to D28 after the 1st dose of ProQuad ^[13] |
|-----------------|---|

End point description:

Injection-site rashes of interest, non-injection site rashes of interest (measles-like rash, rubella-like rash, varicella-like rash and zoster-like rash), mumps-like illness, and rectal (or equivalent) temperature $\geq 39.4^{\circ}\text{C}$ were reported from D0 to D28 after vaccination.

Percentage of subjects presenting at least once the considered events are presented here.

Analysis was done on the Post-Dose 1 Safety set, i.e. all subjects who received at least 1 dose of the study vaccine and who had safety follow-up data following Dose 1.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

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

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal hypothesis was tested. Thus, no statistical results are presented here.

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Adverse events (AEs) occurring after injection of the 2nd dose of ProQuad were recorded as follows.

1/ From D0 to D4: # solicited injection-site adverse reactions (ISRs) (erythema, pain, and swelling),

2/ From D0 to D28: # unsolicited ISRs (including erythema, pain, and swelling from D5 to D28), # numeric values of temperature, # AEs of interest (a/ injection-site rashes of interest, b/ non-injection site rashes of interest (measles-like rash, rubella-like rash, varicella-like rash and zoster-like rash), c/ mumps-like illness), # other systemic AEs.

AEs at injection sites were always considered as related to vaccine (ISRs). The investigator had to assess whether systemic AEs were vaccine-related systemic AEs or not.

Analysis was done on the Post-Dose 2 Safety set, i.e. all subjects who received at least 1 dose of the

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

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

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

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal hypothesis was tested. Thus, no statistical results are presented here.

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Adverse events at injection sites were always considered as related to vaccine (Injection-Site Reactions (ISRs)).

Solicited ISRs were defined as injection-site erythema, injection-site pain and injection-site swelling occurring from Day 0 (D0) to D4 after vaccination.

Unsolicited ISRs consisted in all other ISRs, including injection-site erythema, injection-site pain and injection-site swelling starting from D5.

Analysis was done on the Post-Dose 2 Safety set, i.e. all subjects who received at least 1 dose of the study vaccine and who had safety follow-up data following Dose 2.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

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

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal hypothesis was tested. Thus, no statistical results are presented here.

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

Statistical analyses

No statistical analyses for this end point

Primary: #3rd# Safety at 9 or 11 vs 12 months of age: Proportion of subjects reporting adverse events of interest and temperature $\geq 39.4^{\circ}\text{C}$ from D0 to D28 after the 2nd dose of ProQuad

| | |
|-----------------|---|
| End point title | #3rd# Safety at 9 or 11 vs 12 months of age: Proportion of subjects reporting adverse events of interest and temperature $\geq 39.4^{\circ}\text{C}$ from D0 to D28 after the 2nd dose of ProQuad ^[16] |
|-----------------|---|

End point description:

Injection-site rashes of interest, non-injection site rashes of interest (measles-like rash, rubella-like rash, varicella-like rash and zoster-like rash), mumps-like illness, and rectal (or equivalent) temperature $\geq 39.4^{\circ}\text{C}$ were reported from D0 to D28 after vaccination.

Percentage of subjects presenting at least once the considered events are presented here.

Analysis was done on the Post-Dose 2 Safety set, i.e. all subjects who received at least 1 dose of the study vaccine and who had safety follow-up data following Dose 2.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

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

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal hypothesis was tested. Thus, no statistical results are presented here.

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

| | | | | |
|---|---------------------------------|--------------------------------|---------------------------------|--|
| Mumps / Mumps-like illness Temperature $\geq 39.4^{\circ}\text{C}$ | 0 (0 to 0) 7.7 (5.6 to 10.4) | 0 (0 to 0) 10 (7.4 to 13.1) | 0 (0 to 0) 7.9 (5.6 to 10.7) | |
|---|---------------------------------|--------------------------------|---------------------------------|--|

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Percentage of subjects with an anti-measles Ab titre ≥ 255 mIU/mL, an anti-mumps Ab titre ≥ 10.0 ELISA Ab units/mL, an anti-rubella Ab titre ≥ 10.0 IU/mL, and an anti-varicella Ab titre ≥ 5 gpELISA units/mL 42 days after injection of the 1st dose of ProQuad.

All Ab titres were measured by Enzyme-Linked Immunosorbent Assay (ELISA), except Ab to varicella determined by glycoprotein ELISA.

Analysis was done on the Post-Dose 1 Antigen-specific Per Protocol set (PPS): i.e., all subjects initially seronegative for those antigens (Measles Ab titre < 255 mIU/mL, Mumps Ab titre < 10.0 ELISA Ab units/mL, Rubella Ab titre < 10.0 IU/mL, and Varicella Ab titre < 1.25 gpELISA units/mL) and with post-dose immunogenicity evaluation for those antigens.

Note: (N=***, ***,***) represents the number of assessed subjects in the "9 months", "11 months" and "12 months" groups, respectively.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

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

End point description:

Ab titres were measured for measles, mumps and rubella by Enzyme-Linked ImmunoSorbent Assay (ELISA) and for varicella by glycoprotein ELISA (gpELISA), 42 days after injection of the 2nd dose of ProQuad.

Analysis was done on the Post-dose 2 Antigen-specific Per Protocol set (PPS): i.e., all subjects initially seronegative for those antigens (Measles Ab titre <255 mIU/mL, Mumps Ab titre <10.0 ELISA Ab units/mL, Rubella Ab titre <10.0 IU/mL, and Varicella Ab titre <1.25 gpELISA units/mL) and with post-dose immunogenicity evaluation for those antigens.

Note: (N=***, ***,***) represents the number of assessed subjects in the "9 months", "11 months" and "12 months" groups, respectively.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Ab titres were measured for measles, mumps and rubella by Enzyme-Linked ImmunoSorbent Assay (ELISA) and for varicella by glycoprotein ELISA (gpELISA), 42 days after injection of the 1st dose of ProQuad.

Analysis was done on the Post-dose 1 Antigen-specific Per Protocol set (PPS): i.e., all subjects initially seronegative for those antigens (Measles Ab titre <255 mIU/mL, Mumps Ab titre <10.0 ELISA Ab units/mL, Rubella Ab titre <10.0 IU/mL, and Varicella Ab titre <1.25 gpELISA units/mL) and with post-dose immunogenicity evaluation for those antigens.

Note: (N=***, ***,***) represents the number of assessed subjects in the "9 months", "11 months"

and "12 months" groups, respectively.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 42 days after injection of the 1st dose of ProQuad. | |

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 42 days after injection of the 1st dose and the 2nd dose of ProQuad. | |

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Adverse events at injection sites were always considered as related to vaccine (Injection-Site Reactions (ISRs)).

Unsolicited ISRs occurring from Day 0 (D0) to D28 after vaccination, including injection-site erythema, injection-site pain and injection-site swelling starting from D5, were reported.

Percentage of subjects presenting at least once the considered events are presented here.

Analysis was done on the Post-Dose 1 Safety set, i.e. all subjects who received at least 1 dose of the study vaccine and who had safety follow-up data following Dose 1.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Adverse events at injection sites were always considered as related to vaccine (Injection-Site Reactions (ISRs)).

Unsolicited ISRs occurring from Day 0 (D0) to D28 after vaccination, including injection-site erythema, injection-site pain and injection-site swelling starting from D5, were reported.

Percentage of subjects presenting at least once the considered events are presented here.

Analysis was done on the Post-Dose 2 Safety set, i.e. all subjects who received at least 1 dose of the study vaccine and who had safety follow-up data following Dose 2.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Unsolicited adverse events (AEs) were collected from D0 to D28 after vaccination with Dose 1 and Dose 2 of ProQuad.

Serious AEs were collected from the 1st vaccination to the last visit of the subjects.

Adverse event reporting additional description:

Analysis of AEs was done on the Post-Dose 1 and Post-Dose 2 Safety sets (i.e., all subjects who received the study vaccine and who had safety follow-up data).

None of the serious AEs were assessed as vaccine-related.

Non-serious systemic AEs (vaccine-related or not) with vaccine-related AEs incidence >1% are presented below.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 10.0 |

Reporting groups

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

Reporting group description:

Subjects received 2 doses of ProQuad vaccine: the 1st dose was administered at 9 months of age, and the 2nd dose 90 days later.

Respectively, 380 (72.0%) subjects reported at least 1 non-serious systemic AE and 195 (36.9%) subjects reported at least 1 vaccine-related non-serious systemic AE within 28 days after dose 1.

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

Reporting group description:

Subjects received 2 doses of ProQuad vaccine: the 1st dose was administered at 11 months of age, and the 2nd dose 90 days later.

Respectively, 345 (71.9%) subjects reported at least 1 non-serious systemic AE and 182 (37.9%) subjects reported at least 1 vaccine-related non-serious systemic AE within 28 days after dose 1.

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

Reporting group description:

Subjects received 2 doses of ProQuad vaccine: the 1st dose was administered at 12 months of age, and the 2nd dose 90 days later.

Respectively, 335 (71.9%) subjects reported at least 1 non-serious systemic AE and 195 (41.8%) subjects reported at least 1 vaccine-related non-serious systemic AE within 28 days after dose 1.

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

Reporting group description:

Subjects received 2 doses of ProQuad vaccine: the 1st dose was administered at 9 months of age, and the 2nd dose 90 days later.

Respectively, 307 (58.6%) subjects reported at least 1 non-serious systemic AE and 139 (26.5%) subjects reported at least 1 vaccine-related non-serious systemic AE within 28 days after dose 2.

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

Reporting group description:

Subjects received 2 doses of ProQuad vaccine: the 1st dose was administered at 11 months of age, and the 2nd dose 90 days later.

Respectively, 272 (57.4%) subjects reported at least 1 non-serious systemic AE and 116 (24.5%) subjects reported at least 1 vaccine-related non-serious systemic AE within 28 days after dose 2.

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

Reporting group description:

Subjects received 2 doses of ProQuad vaccine: the 1st dose was administered at 12 months of age, and the 2nd dose 90 days later.

Respectively, 259 (56.1%) subjects reported at least 1 non-serious systemic AE and 112 (24.2%) subjects reported at least 1 vaccine-related non-serious systemic AE within 28 days after dose 2.

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

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

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

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

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

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

| | | | |
|---|-----------------|-----------------|-----------------|
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 524 (0.00%) | 0 / 474 (0.00%) | 0 / 462 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 524 (0.00%) | 0 / 474 (0.00%) | 0 / 462 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bronchiolitis | | | |
| subjects affected / exposed | 0 / 524 (0.00%) | 0 / 474 (0.00%) | 0 / 462 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 524 (0.19%) | 2 / 474 (0.42%) | 0 / 462 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 524 (0.00%) | 0 / 474 (0.00%) | 0 / 462 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Exanthema subitum | | | |
| subjects affected / exposed | 1 / 524 (0.19%) | 0 / 474 (0.00%) | 0 / 462 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 524 (0.00%) | 0 / 474 (0.00%) | 0 / 462 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis adenovirus | | | |
| subjects affected / exposed | 1 / 524 (0.19%) | 0 / 474 (0.00%) | 0 / 462 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Gastroenteritis Norwalk virus | | | |
| subjects affected / exposed | 0 / 524 (0.00%) | 0 / 474 (0.00%) | 0 / 462 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis rotavirus | | | |
| subjects affected / exposed | 0 / 524 (0.00%) | 1 / 474 (0.21%) | 0 / 462 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 524 (0.00%) | 1 / 474 (0.21%) | 0 / 462 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 524 (0.00%) | 0 / 474 (0.00%) | 0 / 462 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 524 (0.00%) | 0 / 474 (0.00%) | 0 / 462 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Otitis media | | | |
| subjects affected / exposed | 0 / 524 (0.00%) | 0 / 474 (0.00%) | 0 / 462 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Otitis media acute | | | |
| subjects affected / exposed | 0 / 524 (0.00%) | 0 / 474 (0.00%) | 0 / 462 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 524 (0.00%) | 1 / 474 (0.21%) | 0 / 462 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 524 (0.00%) | 1 / 474 (0.21%) | 0 / 462 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 524 (0.00%) | 0 / 474 (0.00%) | 0 / 462 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 524 (0.00%) | 0 / 474 (0.00%) | 0 / 462 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 524 (0.00%) | 0 / 474 (0.00%) | 0 / 462 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Post-Dose 1 - ProQuad - 9 months | Post-Dose 1 - ProQuad - 11 months | Post-Dose 1 - ProQuad - 12 months |
|---|-------------------------------------|--------------------------------------|--------------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 380 / 528 (71.97%) | 345 / 480 (71.88%) | 335 / 466 (71.89%) |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 4 / 528 (0.76%) | 7 / 480 (1.46%) | 13 / 466 (2.79%) |
| occurrences (all) | 4 | 8 | 14 |
| Irritability | | | |
| subjects affected / exposed | 52 / 528 (9.85%) | 56 / 480 (11.67%) | 68 / 466 (14.59%) |
| occurrences (all) | 74 | 77 | 79 |
| Pyrexia | | | |
| subjects affected / exposed | 58 / 528 (10.98%) | 68 / 480 (14.17%) | 60 / 466 (12.88%) |
| occurrences (all) | 70 | 87 | 70 |
| Gastrointestinal disorders | | | |

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported