



Clinical trial results:

A PHASE 2, RANDOMIZED, PLACEBO-CONTROLLED, SINGLE-BLIND TRIAL TO ASSESS THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF REPEVAX AND BIVALENT rLP2086 VACCINE WHEN ADMINISTERED CONCOMITANTLY IN HEALTHY SUBJECTS AGED 11 TO <19 YEARS

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2010-022449-38 |
| Trial protocol | DE FI |
| Global end of trial date | 19 February 2013 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 29 June 2016 |
| First version publication date | 29 July 2015 |

Trial information

Trial identification

| | |
|-----------------------|------------------------|
| Sponsor protocol code | B1971010 (6108A1-2008) |
|-----------------------|------------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01323270 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Pfizer Inc |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, NY 10017 |
| Public contact | Clinical Trials.gov Call Center, Pfizer Inc, +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact | Clinical Trials.gov Call Center, Pfizer Inc, +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-001037-PIP02-11 |
| 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? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 06 December 2013 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|------------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 19 February 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that the immune response induced by Repevax given with the bivalent rLP2086 vaccine (group 1) is non-inferior to the immune response induced by Repevax alone (group 2) when measured 1 month after vaccination 1. The immune responses to all components of Repevax will be assessed.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 18 March 2011 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 6 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Finland: 377 |
| Country: Number of subjects enrolled | Germany: 155 |
| Country: Number of subjects enrolled | Poland: 220 |
| Worldwide total number of subjects | 752 |
| EEA total number of subjects | 752 |

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) | 0 |
| Children (2-11 years) | 147 |
| Adolescents (12-17 years) | 482 |

| | |
|----------------------|-----|
| Adults (18-64 years) | 123 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 753 subjects were enrolled in this study. Of these, 4 subjects were not randomized but were vaccinated rLP2086 vaccine or Repevax or Saline at Vaccination 1. These subjects were included in safety population and not intent-to-treat population.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Subject |

Arms

| | |
|------------------------------|----------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Group 1: rLP2086 + Repevax |

Arm description:

Randomized to receive rLP2086 at 0-, 2-, 6-month and Repevax at 0-month.

| | |
|--|-------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Bivalent rLP2086 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

rLP2086 was administered at 0-, 2-, 6-month.

| | |
|--|-------------------|
| Investigational medicinal product name | Repevax |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Repevax was administered at 0 month.

| | |
|------------------|-------------------------|
| Arm title | Group 2: Saline+Repevax |
|------------------|-------------------------|

Arm description:

Randomized to receive saline at 0-, 2-, 6-month and Repevax at 0-month.

| | |
|--|-------------------|
| Arm type | Control |
| Investigational medicinal product name | Saline |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Saline was administered at 0-, 2-, 6- month.

| | |
|--|---------|
| Investigational medicinal product name | Repevax |
| Investigational medicinal product code | |
| Other name | |

| | |
|--------------------------|-------------------|
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Repevax was administered at 0-month.

| Number of subjects in period 1^[1] | Group 1: rLP2086 + Repevax | Group 2: Saline+Repevax |
|---|----------------------------|-------------------------|
| Started | 373 | 376 |
| Completed | 330 | 347 |
| Not completed | 43 | 29 |
| Consent withdrawn by subject | 19 | 10 |
| Physician decision | - | 2 |
| Not eligible | 1 | 1 |
| Death | 1 | - |
| Randomized but not vaccinated | 1 | - |
| Adverse event | 8 | - |
| Lost to follow-up | 4 | 6 |
| unspecified | - | 3 |
| Protocol deviation | 9 | 7 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 4 Subjects were not randomized but were vaccinated rLP2086 vaccine or repevax or saline at Vaccination 1. These subjects were included in safety population and not intent-to-treat population.

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------------------------|
| Reporting group title | Group 1: rLP2086 + Repevax |
|-----------------------|----------------------------|

Reporting group description:

Randomized to receive rLP2086 at 0-, 2-, 6-month and Repevax at 0-month.

| | |
|-----------------------|-------------------------|
| Reporting group title | Group 2: Saline+Repevax |
|-----------------------|-------------------------|

Reporting group description:

Randomized to receive saline at 0-, 2-, 6-month and Repevax at 0-month.

| Reporting group values | Group 1: rLP2086 + Repevax | Group 2: Saline+Repevax | Total |
|---|-------------------------------|----------------------------|-------|
| Number of subjects | 373 | 376 | 749 |
| Age categorical Units: Subjects | | | |
| greater than or equal (\geq)11- less than($<$)14 years | 217 | 215 | 432 |
| \geq 14-<19 years | 156 | 161 | 317 |
| Gender categorical Units: Subjects | | | |
| Female | 183 | 184 | 367 |
| Male | 190 | 192 | 382 |

End points

End points reporting groups

| | |
|--|----------------------------|
| Reporting group title | Group 1: rLP2086 + Repevax |
| Reporting group description: Randomized to receive rLP2086 at 0-, 2-, 6-month and Repevax at 0-month. | |
| Reporting group title | Group 2: Saline+Repevax |
| Reporting group description: Randomized to receive saline at 0-, 2-, 6-month and Repevax at 0-month. | |
| Subject analysis set title | Group 1: rLP2086 + Repevax |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Safety population | |
| Subject analysis set title | Group 2: Saline+Repevax |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: safety population | |

Primary: Percentage of Subjects Achieving Prespecified Criteria for the Concomitant Antigen

| | |
|---|--|
| End point title | Percentage of Subjects Achieving Prespecified Criteria for the Concomitant Antigen |
| End point description: | |
| End point type | Primary |
| End point timeframe: 1 month after Vaccination 1 | |

| End point values | Group 1: rLP2086 + Repevax | Group 2: Saline+Repeva x | | |
|--|----------------------------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 337 | 348 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Diphtheria | 99.4 | 99.4 | | |
| Tetanus | 100 | 100 | | |
| Pertussis toxoid | 94.7 | 96 | | |
| Pertussis filamentous hemagglutinin | 100 | 100 | | |
| Pertussis pertactin | 100 | 100 | | |
| Pertussis fimbrial agglutinogens types 2+3 | 97.6 | 98.9 | | |
| Poliovirus type 1 | 100 | 100 | | |
| Poliovirus type 2 | 100 | 100 | | |
| Poliovirus type 3 | 100 | 100 | | |

Statistical analyses

| Statistical analysis title | Diphtheria |
|---|--|
| Statistical analysis description: Exact 2-sided confidence interval (based on Chan and Zhang) was reported for the difference in proportions, expressed as a percentage. | |
| Comparison groups | Group 1: rLP2086 + Repevax v Group 2: Saline+Repevax |
| Number of subjects included in analysis | 685 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[1] |
| Parameter estimate | percent difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.6 |
| upper limit | 1.5 |

Notes:

[1] - The non-inferiority criteria margin was 10%.

| Statistical analysis title | Tetanus |
|---|--|
| Statistical analysis description: Exact 2-sided confidence interval (based on Chan and Zhang) was reported for the difference in proportions, expressed as a percentage. | |
| Comparison groups | Group 1: rLP2086 + Repevax v Group 2: Saline+Repevax |
| Number of subjects included in analysis | 685 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[2] |
| Parameter estimate | percent difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 1.1 |

Notes:

[2] - The non-inferiority criteria margin was 10%.

| Statistical analysis title | Pertussis toxoid |
|---|--|
| Statistical analysis description: Exact 2-sided confidence interval (based on Chan and Zhang) was reported for the difference in proportions, expressed as a percentage. | |
| Comparison groups | Group 1: rLP2086 + Repevax v Group 2: Saline+Repevax |
| Number of subjects included in analysis | 685 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[3] |
| Parameter estimate | percent difference |
| Point estimate | -1.3 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.7 |
| upper limit | 1.9 |

Notes:

[3] - The non-inferiority criteria margin was 10%.

| | |
|--|--|
| Statistical analysis title | Pertussis filamentous hemagglutinin |
| Statistical analysis description: | |
| Exact 2-sided confidence interval (based on Chan and Zhang) was reported for the difference in proportions, expressed as a percentage. | |
| Comparison groups | Group 1: rLP2086 + Repevax v Group 2: Saline+Repevax |
| Number of subjects included in analysis | 685 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[4] |
| Parameter estimate | percent difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 1.1 |

Notes:

[4] - The non-inferiority criteria margin was 10%.

| | |
|--|--|
| Statistical analysis title | Pertussis pertactin |
| Statistical analysis description: | |
| Exact 2-sided confidence interval (based on Chan and Zhang) was reported for the difference in proportions, expressed as a percentage. | |
| Comparison groups | Group 1: rLP2086 + Repevax v Group 2: Saline+Repevax |
| Number of subjects included in analysis | 685 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[5] |
| Parameter estimate | percent difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 1.1 |

Notes:

[5] - The non-inferiority criteria margin was 10%.

| | |
|--|--|
| Statistical analysis title | Pertussis fimbrial agglutinogens types 2+3 |
| Statistical analysis description: | |
| Exact 2-sided confidence interval (based on Chan and Zhang) was reported for the difference in proportions, expressed as a percentage. | |
| Comparison groups | Group 1: rLP2086 + Repevax v Group 2: Saline+Repevax |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 685 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[6] |
| Parameter estimate | percent difference |
| Point estimate | -1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.6 |
| upper limit | 0.8 |

Notes:

[6] - The non-inferiority criteria margin was 10%.

| | |
|--|--|
| Statistical analysis title | Poliovirus type 1 |
| Statistical analysis description: | |
| Exact 2-sided confidence interval (based on Chan and Zhang) was reported for the difference in proportions, expressed as a percentage. | |
| Comparison groups | Group 1: rLP2086 + Repevax v Group 2: Saline+Repevax |
| Number of subjects included in analysis | 685 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[7] |
| Parameter estimate | percent difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 1.1 |

Notes:

[7] - The non-inferiority criteria margin was 10%.

| | |
|--|--|
| Statistical analysis title | Poliovirus type 2 |
| Statistical analysis description: | |
| Exact 2-sided confidence interval (based on Chan and Zhang) was reported for the difference in proportions, expressed as a percentage. | |
| Comparison groups | Group 1: rLP2086 + Repevax v Group 2: Saline+Repevax |
| Number of subjects included in analysis | 685 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[8] |
| Parameter estimate | percent difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 1.1 |

Notes:

[8] - The non-inferiority criteria margin was 10%.

| | |
|-----------------------------------|-------------------|
| Statistical analysis title | Poliovirus type 3 |
|-----------------------------------|-------------------|

Statistical analysis description:

Exact 2-sided confidence interval (based on Chan and Zhang) was reported for the difference in proportions, expressed as a percentage.

| | |
|---|--|
| Comparison groups | Group 1: rLP2086 + Repevax v Group 2: Saline+Repevax |
| Number of subjects included in analysis | 685 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[9] |
| Parameter estimate | percent difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 1.1 |

Notes:

[9] - The non-inferiority criteria margin was 10%.

Primary: Percentage of Subjects With at Least One Adverse Event (AE)

| | |
|---|--|
| End point title | Percentage of Subjects With at Least One Adverse Event |
| End point description: | |
| Summary was performed for subjects as per vaccine administration. | |
| End point type | Primary |
| End point timeframe: | |
| Vaccination 1 up to 1 month after Vaccination 3 | |

Notes:

[10] - 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: Only descriptive data was planned to be reported for this endpoint.

| End point values | Group 1: rLP2086 + Repevax | Group 2: Saline+Repeva x | | |
|-------------------------------|----------------------------------|--------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 374 | 378 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 37.4 | 40.2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Concentration (GMC) for Diphtheria and Tetanus Antigens

| | |
|-----------------------------|--|
| End point title | Geometric Mean Concentration (GMC) for Diphtheria and Tetanus Antigens |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 1 month after Vaccination 1 | |

| End point values | Group 1: rLP2086 + Repevax | Group 2: Saline+Repeva x | | |
|---|----------------------------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 337 | 348 | | |
| Units: International units per milliliter | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Diphtheria | 1.4 (1.28 to 1.55) | 1.5 (1.34 to 1.63) | | |
| Tetanus | 12.3 (11.5 to 13.11) | 12.4 (11.52 to 13.25) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: GMC for Acellular Pertussis Antigens

| | |
|--|--------------------------------------|
| End point title | GMC for Acellular Pertussis Antigens |
| End point description: | |
| Enzyme-linked immunosorbent assay (ELISA) units per milliliter (EU/mL) | |
| End point type | Secondary |
| End point timeframe: | |
| 1 month after Vaccination 1 | |

| End point values | Group 1: rLP2086 + Repevax | Group 2: Saline+Repeva x | | |
|--|----------------------------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 337 | 348 | | |
| Units: EU/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Pertussis toxoid | 27.1 (24.45 to 30.07) | 26.5 (23.95 to 29.38) | | |
| Pertussis filamentous hemagglutinin | 119.4 (111.15 to 128.17) | 122.9 (115.14 to 131.13) | | |
| Pertussis pertactin | 317 (285.64 to 351.8) | 336.1 (305.82 to 369.3) | | |
| Pertussis fimbrial agglutinogens types 2+3 | 339.1 (296.35 to 387.94) | 364.5 (320.62 to 414.42) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titer (GMT) for Poliomyelitis Antigens

| | |
|-----------------|---|
| End point title | Geometric Mean Titer (GMT) for Poliomyelitis Antigens |
|-----------------|---|

End point description:

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

End point timeframe:

1 month after Vaccination 1

| End point values | Group 1: rLP2086 + Repevax | Group 2: Saline+Repeva x | | |
|---|-----------------------------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 337 | 348 | | |
| Units: titer | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Poliovirus type 1 | 662.1 (567.36 to 772.67) | 672.6 (581.87 to 777.55) | | |
| Poliovirus type 2 | 840.5 (725.11 to 974.29) | 995.8 (860.54 to 1152.41) | | |
| Poliovirus type 3 | 2237.4 (1945.81 to 2572.65) | 2450.1 (2152.6 to 2788.7) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving Serum Bactericidal Assay Using Human Complement (hSBA) Titer Level Greater Than or Equal to (\geq) Prespecified Titer Level

| | |
|-----------------|--|
| End point title | Percentage of Subjects Achieving Serum Bactericidal Assay Using Human Complement (hSBA) Titer Level Greater Than or Equal to (\geq) Prespecified Titer Level |
|-----------------|--|

End point description:

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

End point timeframe:

1 month after Vaccination 3

| End point values | Group 1: rLP2086 + Repevax | Group 2: Saline+Repeva x | | |
|--------------------------------|----------------------------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 307 | 330 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| PMB80 [A22] 1:16 (N=158, 166) | 95.6 | 19.9 | | |
| PMB2001 [A56] 1:8 (N=148, 152) | 100 | 26.3 | | |
| PMB2948 [B24] 1:8 (N=157, 170) | 96.8 | 12.9 | | |
| PMB2707 [B44] 1:8 (N=146, 159) | 81.5 | 8.2 | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Immunoglobulin G (IgG) Measured by Geometric Mean Titer (GMT)

| | |
|--|---|
| End point title | Immunoglobulin G (IgG) Measured by Geometric Mean Titer (GMT) |
| End point description: hSBA Neisseria meningitidis serogroup B (MnB) immunogenicity assay results were disclosed instead of the IgG assay originally planned. | |
| End point type | Other pre-specified |
| End point timeframe: Before vaccination 1, 1 month after Vaccination 2, 3 | |

| End point values | Group 1: rLP2086 + Repevax | Group 2: Saline+Repeva x | | |
|-------------------------------------|----------------------------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[11] | 0 ^[12] | | |
| Units: titer | | | | |
| geometric mean (standard deviation) | () | () | | |

Notes:

[11] - hSBA MnB immunogenicity assay results were disclosed instead of the IgG assay originally planned.

[12] - hSBA MnB immunogenicity assay results were disclosed instead of the IgG assay originally planned.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Geometric Mean Fold-Rise (GMFR) for IgG

| | |
|---|---|
| End point title | Geometric Mean Fold-Rise (GMFR) for IgG |
| End point description: hSBA MnB immunogenicity assay results were disclosed instead of the IgG assay originally planned. | |
| End point type | Other pre-specified |

End point timeframe:

Before Vaccination 1, 1 month after Vaccination 2, 3

| End point values | Group 1: rLP2086 + Repevax | Group 2: Saline+Repeva x | | |
|-----------------------------|----------------------------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[13] | 0 ^[14] | | |
| Units: fold rise | | | | |

Notes:

[13] - hSBA MnB immunogenicity assay results were disclosed instead of the IgG assay originally planned.

[14] - hSBA MnB immunogenicity assay results were disclosed instead of the IgG assay originally planned.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE: Vaccination 1 to 1 month after last administration of investigational product (bivalent rLP2086/saline/Repevax). Serious adverse event (SAE) reported from Vaccination 1 to 6 months after last of investigational product (bivalent rLP2086/saline/Repevax)

Adverse event reporting additional description:

Events collected on case report form were reported. Summary was performed for subjects as per vaccine administration.

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------------|
| Reporting group title | Group 1: rLP2086 + Repevax |
|-----------------------|----------------------------|

Reporting group description:

Randomized to receive rLP2086 at 0,-2,-6-month and Repevax at 0-month.

| | |
|-----------------------|-------------------------|
| Reporting group title | Group 2: Saline+Repevax |
|-----------------------|-------------------------|

Reporting group description:

Randomized to receive saline at 0,-2,-6-month and Repevax at 0-month.

| Serious adverse events | Group 1: rLP2086 + Repevax | Group 2: Saline+Repevax | |
|---|----------------------------|-------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 12 / 374 (3.21%) | 9 / 378 (2.38%) | |
| number of deaths (all causes) | 1 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 374 (0.00%) | 1 / 378 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury | | | |
| subjects affected / exposed | 0 / 374 (0.00%) | 1 / 378 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint dislocation | | | |
| subjects affected / exposed | 0 / 374 (0.00%) | 1 / 378 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 374 (0.27%) | 0 / 378 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Syndactyly | | | |
| subjects affected / exposed | 0 / 374 (0.00%) | 1 / 378 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 374 (0.27%) | 0 / 378 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydrocephalus | | | |
| subjects affected / exposed | 1 / 374 (0.27%) | 0 / 378 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 374 (0.00%) | 1 / 378 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Idiopathic thrombocytopenic purpura | | | |
| subjects affected / exposed | 1 / 374 (0.27%) | 0 / 378 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo positional | | | |
| subjects affected / exposed | 1 / 374 (0.27%) | 0 / 378 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Ovarian cyst ruptured | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 374 (0.00%) | 1 / 378 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 374 (0.00%) | 1 / 378 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 1 / 374 (0.27%) | 1 / 378 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug abuse | | | |
| subjects affected / exposed | 0 / 374 (0.00%) | 1 / 378 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 374 (0.27%) | 2 / 378 (0.53%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal abscess | | | |
| subjects affected / exposed | 1 / 374 (0.27%) | 0 / 378 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis perforated | | | |
| subjects affected / exposed | 1 / 374 (0.27%) | 0 / 378 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis infective | | | |
| subjects affected / exposed | 1 / 374 (0.27%) | 0 / 378 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Cellulitis | | | |
| subjects affected / exposed | 1 / 374 (0.27%) | 0 / 378 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 374 (0.27%) | 0 / 378 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonsillar abscess | | | |
| subjects affected / exposed | 0 / 374 (0.00%) | 1 / 378 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 374 (0.27%) | 0 / 378 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 374 (0.27%) | 0 / 378 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 374 (0.00%) | 1 / 378 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Group 1: rLP2086 + Repevax | Group 2: Saline+Repevax | |
|---|----------------------------|-------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 98 / 374 (26.20%) | 118 / 378 (31.22%) | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 4 / 374 (1.07%) | 3 / 378 (0.79%) | |
| occurrences (all) | 5 | 3 | |

| | | | |
|--|-----------------|-----------------|--|
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 9 / 374 (2.41%) | 9 / 378 (2.38%) | |
| occurrences (all) | 10 | 11 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 5 / 374 (1.34%) | 4 / 378 (1.06%) | |
| occurrences (all) | 5 | 4 | |
| Injection site pain | | | |
| subjects affected / exposed | 4 / 374 (1.07%) | 0 / 378 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Injection site swelling | | | |
| subjects affected / exposed | 4 / 374 (1.07%) | 0 / 378 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Eye disorders | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 4 / 374 (1.07%) | 3 / 378 (0.79%) | |
| occurrences (all) | 5 | 3 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 374 (1.07%) | 3 / 378 (0.79%) | |
| occurrences (all) | 4 | 3 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 374 (0.27%) | 4 / 378 (1.06%) | |
| occurrences (all) | 1 | 7 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 2 / 374 (0.53%) | 6 / 378 (1.59%) | |
| occurrences (all) | 2 | 6 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 6 / 374 (1.60%) | 7 / 378 (1.85%) | |
| occurrences (all) | 6 | 7 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |

| | | |
|-----------------------------------|------------------|------------------|
| subjects affected / exposed | 30 / 374 (8.02%) | 31 / 378 (8.20%) |
| occurrences (all) | 37 | 36 |
| Pharyngitis | | |
| subjects affected / exposed | 17 / 374 (4.55%) | 19 / 378 (5.03%) |
| occurrences (all) | 18 | 23 |
| Upper respiratory tract infection | | |
| subjects affected / exposed | 16 / 374 (4.28%) | 19 / 378 (5.03%) |
| occurrences (all) | 20 | 19 |
| Bronchitis | | |
| subjects affected / exposed | 9 / 374 (2.41%) | 18 / 378 (4.76%) |
| occurrences (all) | 9 | 20 |
| Gastroenteritis | | |
| subjects affected / exposed | 8 / 374 (2.14%) | 11 / 378 (2.91%) |
| occurrences (all) | 8 | 12 |
| Sinusitis | | |
| subjects affected / exposed | 8 / 374 (2.14%) | 6 / 378 (1.59%) |
| occurrences (all) | 9 | 6 |
| Otitis media | | |
| subjects affected / exposed | 3 / 374 (0.80%) | 7 / 378 (1.85%) |
| occurrences (all) | 3 | 7 |
| Acute tonsillitis | | |
| subjects affected / exposed | 1 / 374 (0.27%) | 7 / 378 (1.85%) |
| occurrences (all) | 1 | 8 |
| Tonsillitis | | |
| subjects affected / exposed | 1 / 374 (0.27%) | 7 / 378 (1.85%) |
| occurrences (all) | 2 | 8 |
| Rhinitis | | |
| subjects affected / exposed | 2 / 374 (0.53%) | 4 / 378 (1.06%) |
| occurrences (all) | 2 | 4 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 15 July 2011 | 1) Subject participation in the study was increased from 14 to 17 months. 2) Duration of the study was increased from 17 to 20 months. |
| 18 April 2012 | 1) Any non-serious AE that was determined by the sponsor to be serious was reported as an SAE. To assist in the determination of case seriousness further information was being requested from the investigator to provide clarity and understanding of the event in the context of the trial. 2) Active reporting period and necessity to report all SAEs post-active reporting period was specified as follows-A subject's AE (serious and non serious) was reported and recorded from the signing of the Informed consent form (ICF) to visit 6 (postvaccination 3 blood draw) and at month 12 (Final Telephone Contact), the parent/legal guardian or subject was to be contacted by telephone to inquire about SAEs including hospitalizations, and newly diagnosed major illnesses or conditions since visit 6. 3) Exposure during pregnancy was updated as- A female becomes, or is found to be, pregnant either while receiving or being exposed (eg, due to treatment or environmental exposure) or after discontinuing or having been directly exposed to the investigational product. 4)In the case of a live birth, the structural integrity of the neonate was assessed by gross visual inspection (unless pre-procedure test findings were conclusive for a congenital anomaly and the findings are reported).In case of termination, the reason(s) for the termination was to be specified. 5) Clarification added regarding persistent or significant disability/ incapacity (SAE) as substantial disruption of the ability to conduct normal life functions. 6) Definition of AE updated to include drug abuse and drug dependency factor along with signs and symptoms resulting from exposure via breastfeeding and medication error. 7) Definition for Medication errors was updated to provide clarity. |
| 13 December 2012 | 1) Safety endpoint was updated to in consistent to Phase 3 program with definite window (time-frame) of assessment of proportion of subjects reporting local reactions, systemic reactions , SAE and AE. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|--------------|--|------------------|
| 01 July 2011 | Study injections for this study were temporarily paused on during investigation of a suspected, unexpected, serious adverse reaction (SUSAR) identified after hospitalization of the subject. The subject experienced severe chills, headache and vertigo approximately 70 minutes after receiving the second dose of rLP2086 vaccine in study B1971012. | 01 November 2011 |

Notes:

Limitations and caveats

None reported