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)	EMEA-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 (>=)11- less than(<)14 years	217	215	432
>=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+Repevax		
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+Repevax		
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+Repevax		
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+Repevax		
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+Repevax		
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 (>=) Prespecified Titer Level

End point title	Percentage of Subjects Achieving Serum Bactericidal Assay Using Human Complement (hSBA) Titer Level Greater Than or Equal to (>=) 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+Repevax		
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: Immunogloblulin G (IgG) Measured by Geometric Mean Titer (GMT)

End point title	Immunogloblulin 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+Repevax		
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+Repevax		
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