Clinical trial results:
A Phase 2, Randomized, Active-Controlled, Observer-Blinded Trial to Assess the Safety, Tolerability and Immunogenicity of MCV4, Tdap Vaccine and Bivalent rLP2086 Vaccine When Administered Concomitantly in Healthy Subjects Aged > = to 10 Years to Less Than 13 Years

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

Summary

EudraCT number	2013-002145-11
Trial protocol	Outside EU/EEA
Global end of trial date	08 May 2014

Results information

Result version number	v2 (current)
This version publication date	28 July 2016
First version publication date	01 May 2015
Version creation reason	• Correction of full data set reporting periods and duplicate AEs in their data

Trial information

Trial identification

Sponsor protocol code	B1971015 (6108A1-2005)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01461980
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	ClinicalTrials.gov_Inquiries@pfizer.com, Pfizer Inc, +1 8007181021, ClinicalTrials.govCallCenter@pfizer.com
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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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 March 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- Demonstrate that the immune response (based on geometric mean titer [GMT]) induced by Quadrivalent meningococcal polysaccharide conjugate (MCV4) and Tetanus, diphtheria, and acellular pertussis (Tdap) vaccines given with bivalent recombinant lipoprotein 2086 (rLP2086) vaccine (Group 1) was non-inferior to the immune response induced by MCV4 and Tdap vaccines alone (Group 2) measured 1 month after the Vaccination 1 in both groups. The immune response to all components of MCV4 and Tdap vaccines were assessed.
- Demonstrate that the immune response (based on GMT) induced by bivalent rLP2086 vaccine measured by serum bactericidal assay using human complement (hSBA) performed with 2 Neisseria meningitidis serogroup B (MnB) strains (subfamily A and B proteins) given with MCV4 and Tdap vaccines (Group1) was non-inferior to the immune response induced by bivalent rLP2086 vaccine alone (Group3), measured 1 month after Vaccination 3 with bivalent rLP2086 vaccine in both groups.

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	28 September 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	United States: 2648
Worldwide total number of subjects	2648
EEA total number of subjects	0

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)	2340
Adolescents (12-17 years)	308
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 2648 subjects were enrolled in this study. Of these, 19 subjects were randomized but did not receive study vaccination.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	MCV4+Tdap+rLP2086

Arm description:

Randomized to receive MCV4 and Tdap vaccine on 0-- month, MnB rLP2086 vaccine on a 0--, 2--, 6-- month schedule.

Arm type	Active comparator
Investigational medicinal product name	MCV4 vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Randomized to receive MCV4 vaccine intramuscularly into the upper deltoid muscle of the right arm on 0-- month.

Investigational medicinal product name	Tdap vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Randomized to receive Tdap vaccine intramuscularly into the upper deltoid muscle of the right arm on 0-- month.

Investigational medicinal product name	rLP2086 vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Randomized to receive MnB rLP2086 vaccine intramuscularly into the upper deltoid muscle of the left arm on a 0--, 2--, 6-- month schedule.

Arm title	MCV4 + Tdap + Saline

Arm description:

Randomized to receive MCV4 and Tdap vaccine on 0- month, Saline on a 0--, 2--, 6-- month schedule.

Arm type	Active comparator

Investigational medicinal product name	MCV4 vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Randomized to receive MCV4 vaccine intramuscularly into the upper deltoid muscle of the right arm on 0-- month.

Investigational medicinal product name	Tdap vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Randomized to receive Tdap vaccine intramuscularly into the upper deltoid muscle of the right arm on 0-- month.

Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Randomized to receive saline intramuscularly into the upper deltoid muscle of the left arm on a 0--, 2--, 6-- month schedule.

Arm title	Saline+Saline+rLP2086

Arm description:

Randomized to receive Saline on 0-- month, rLP2086 vaccine on a 0--, 2--, 6-- month schedule, MCV4 and Tdap vaccine on 7-- month.

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

Dosage and administration details:

Randomized to receive saline intramuscularly into the upper deltoid muscle of the left arm on 0- month.

Investigational medicinal product name	rLP2086 vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Randomized to receive MnB rLP2086 vaccine intramuscularly into the upper deltoid muscle of the left arm on a 0--, 2--, 6-- month schedule.

Investigational medicinal product name	MCV4 vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Randomized to receive MCV4 vaccine intramuscularly into the upper deltoid muscle of the right arm on 7-- month.

Investigational medicinal product name	Tdap vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Randomized to receive Tdap vaccine intramuscularly into the upper deltoid muscle of the right arm on 7-month.

Number of subjects in period 1	MCV4+Tdap+rLP2086	MCV4 + Tdap + Saline	Saline+Saline+rLP2086
Started	888	878	882
Vaccination 1	884	870	875
Vaccination 2	802	819	799
Vaccination 3	757	777	748
Completed	722	733	717
Not completed	166	145	165
Protocol Violation	12	19	16
Unspecified	9	8	6
Medication error	7	5	6
No longer willing to participate	52	38	54
Lost to follow-up	52	53	51
Adverse Event	12	5	6
No longer meets eligibility criteria	18	9	19
Randomized but not vaccinated	4	8	7

Baseline characteristics

Reporting groups	
Reporting group title	MCV4+Tdap+rLP2086
Reporting group description:	
Randomized to receive MCV4 and Tdap vaccine on 0-- month, MnB rLP2086 vaccine on a 0--, 2--, 6-- month schedule.	
Reporting group title	MCV4 + Tdap + Saline
Reporting group description:	
Randomized to receive MCV4 and Tdap vaccine on 0- month, Saline on a 0--, 2--, 6-- month schedule.	
Reporting group title	Saline+Saline+rLP2086
Reporting group description:	
Randomized to receive Saline on 0-- month, rLP2086 vaccine on a 0--, 2--, 6- - month schedule, MCV4 and Tdap vaccine on 7-- month.	

Reporting group values	MCV4+Tdap+rLP2086	MCV4 + Tdap + Saline	Saline+Saline+rLP2086
Number of subjects	888	878	882
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	10.6	10.6	10.6
standard deviation	± 0.7	± 0.69	± 0.67
Gender categorical			
Units: Subjects			
Female	454	427	417
Male	434	451	465

Reporting group values	Total		
Number of subjects	2648		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	1298		
Male	1350		

End points

End points reporting groups

Reporting group title	MCV4+Tdap+rLP2086
Reporting group description:	
Randomized to receive MCV4 and Tdap vaccine on 0-- month, MnB rLP2086 vaccine on a 0--, 2--, 6-- month schedule.	
Reporting group title	MCV4 + Tdap + Saline
Reporting group description:	
Randomized to receive MCV4 and Tdap vaccine on 0- month, Saline on a 0--, 2--, 6-- month schedule.	
Reporting group title	Saline+Saline+rLP2086
Reporting group description:	
Randomized to receive Saline on 0-- month, rLP2086 vaccine on a 0--, 2--, 6- - month schedule, MCV4 and Tdap vaccine on 7-- month.	

Primary: Geometric Mean Concentrations (GMC) for Diphtheria and Tetanus Antigens

End point title	Geometric Mean Concentrations (GMC) for Diphtheria and Tetanus Antigens[1]
End point description:	
Antibody GMCs of 2 antigens of diphtheria and tetanus toxoid were computed inInternational Units per milliliter (IU/mL) along with corresponding 2-sided 95 percent (%) confidence intervals (CIs). Post vaccination 1 evaluable immunogenicity population: eligible subjects randomized to Group 1 or 2, received scheduled investigational product, had pre and post vaccination blood drawn at pre-- specified time points, had valid, determinate assay results for proposed analysis, received no prohibited vaccines, no other major protocol violations.	
End point type	Primary
End point timeframe:	
1 Month after Vaccination 1	

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:
GMC for Diphtheria and Tetanus antigens was analyzed for subjects in reporting arms MCV4+Tdap+rLP2086 and MCV4+Tdap+Saline only.

End point values	MCV4+Tdap+rLP2086	MCV4 + Tdap + Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	778[2]	780[3]		
Units: IU/mL				
geometric mean (confidence interval 95%)				
Diphtheria	9.3 (8.67 to 9.92)	9.8 (9.23 to 10.51)		
Tetanus	9.4 (8.95 to 9.98)	10.3 (9.75 to 10.85)		

Notes:

[2] - Subjects with valid and determinate assay results for given antigen.

[3] - Subjects with valid and determinate assay results for given antigen.

Statistical analyses

Statistical analysis title	Diphtheria

Statistical analysis description:

CIs for GMC ratio were back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Group 1 - Group 2 for Diphtheria antigens).

Comparison groups	MCV4+Tdap+rLP2086 v MCV4 + Tdap + Saline
Number of subjects included in analysis	1558
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	GMC ratio
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.03

Notes:

[4] - The non--inferiority criteria margin was 1.5--fold and statistical inference was based on the CIs of the GMC ratios. Non-inferiority was achieved when the lower limit of the 2--sided 95% CI for the GMC ratios after vaccination 1 was greater than 0.67.

Statistical analysis title	Tetanus

Statistical analysis description:

CIs for GMC ratio were back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Group 1 - Group 2 for Tetanus antigens).

Comparison groups	MCV4+Tdap+rLP2086 v MCV4 + Tdap + Saline
Number of subjects included in analysis	1558
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	GMC ratio
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	0.99

Notes:

[5] - The non--inferiority criteria margin was 1.5--fold and statistical inference was based on the CIs of the GMC ratios. Non-inferiority was achieved when the lower limit of the 2--sided 95% CI for the GMC ratios after vaccination 1 was greater than 0.67.

Primary: Geometric Mean Concentrations (GMC) for Acellular Pertussis Antigens

End point title	Geometric Mean Concentrations (GMC) for Acellular Pertussis Antigens[6]

End point description:

Antibody GMCs of 4 acellular pertussis antigens (pertussis toxoid, pertussis filamentous hemagglutinin, pertussis pertactin and pertussis fimbrial agglutinogens types 2+3) were computed in Enzyme--linked immunosorbent assay (ELISA) units per milliliter (EU/mL) along with corresponding 2 sided 95% CIs. Post vaccination 1 evaluable immunogenicity population.

End point type	Primary

End point timeframe:

1 Month after Vaccination 1

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:
GMC for Acellular Pertussis antigens was analyzed for subjects in reporting arms MCV4+Tdap+rLP2086 a nd MCV4+Tdap+Saline only.

End point values	MCV4+Tdap+rLP2086	MCV4 + Tdap + Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	778[7]	780[8]		
Units: EU/mL				
geometric mean (confidence interval 95%)				
Pertussis toxoid	13.2 (12.35 to 14.14)	14.2 (13.28 to 15.2)		
Pertussis filamentous hemagglutinin	112 (106.15 to 118.14)	122.9 (116.42 to 129.84)		
Pertussis pertactin	202 (187.77 to 217.25)	228.9 (212.72 to 246.35)		
Pertussis fimbrial agglutinogens types 2 +3	138.1 (121.2 to 157.33)	154.2 (135.3 to 175.79)		

Notes:

[7] - Subjects with valid and determinate assay results for given antigen.

[8] - Subjects with valid and determinate assay results for given antigen.

Statistical analyses

Statistical analysis title	Pertussis toxoid

Statistical analysis description:

CIs for GMC ratio were back transformations of a confidence interval
based on the Student t distribution for the mean difference of the logarithms of the
measures (Group 1 -- Group 2 for Pertussis toxoid).

Comparison groups	MCV4+Tdap+rLP2086 v MCV4 + Tdap + Saline
Number of subjects included in analysis	1558
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
Parameter estimate	GMC ratio
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.02

Notes:

[9] - The non--inferiority criteria margin was 1.5-fold and statistical inference was based on the CIs of the GMC ratios. Non--inferiority was achieved when the lower limit
of the 2- sided 95% CI for the GMC ratios after vaccination 1 was greater than 0.67.

Statistical analysis title	Pertussis filamentous hemagglutinin

Statistical analysis description:

CIs for GMC ratio were back transformations of a confidence interval
based on the Student t distribution for the mean difference of the logarithms of the
measures (Group 1 -- Group 2 for Pertussis filamentous hemagglutinin).

Comparison groups	MCV4 + Tdap + Saline v MCV4+Tdap+rLP2086

Number of subjects included in analysis	1558
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
Parameter estimate	GMC ratio
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	0.98

Notes:

[10] - The non--inferiority criteria margin was 1.5-fold and statistical inference was based on the CIs of the GMC ratios. Non--inferiority was achieved when the lower limit of the 2- sided 95% CI for the GMC ratios after vaccination 1 was greater than 0.67.

Statistical analysis title	Pertussis pertactin

Statistical analysis description:

CIs for GMC ratio were back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Group 1 -- Group 2 for Pertussis pertactin).

Comparison groups	MCV4+Tdap+rLP2086 v MCV4 + Tdap + Saline
Number of subjects included in analysis	1558
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
Parameter estimate	GMC ratio
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	0.98

Notes:

[11] - The non--inferiority criteria margin was 1.5-fold and statistical inference was based on the CIs of the GMC ratios. Non--inferiority was achieved when the lower limit of the 2- sided 95% CI for the GMC ratios after vaccination 1 was greater than 0.67.

Statistical analysis title	Pertussis fimbriae agglutinogens types 2 + 3

Statistical analysis description:

CIs for GMC ratio were back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Group 1 -- Group 2 for Pertussis fimbriae agglutinogens types 2 + 3).

Comparison groups	MCV4+Tdap+rLP2086 v MCV4 + Tdap + Saline
Number of subjects included in analysis	1558
Analysis specification	Pre-specified
Analysis type	non-inferiority[12]
Parameter estimate	GMC ratio
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.08

Notes:

[12] - The non--inferiority criteria margin was 1.5--fold and statistical inference was based on the CIs of the GMC ratios. Non--inferiority was achieved when the lower limit of the 2- sided 95% CI for the GMC ratios after vaccination 1 was greater than 0.67.

Primary: Geometric Mean Titer (GMT) for Meningococcal Conjugate Vaccine (MCV4) Antigens

End point title	Geometric Mean Titer (GMT) for Meningococcal Conjugate Vaccine (MCV4) Antigens [13]

End point description:

Antibody GMTs of 4 MCV4 antigens (serogroup A, serogroup C, serogroup Y and serogroup W - 135) were computed along with corresponding 2-sided 95% CIs. Post vaccination 1 evaluable immunogenicity population. Here, 'N' signifies subjects of post vaccination 1 evaluable immunogenicity population with valid and determinate assay results for given strain for each group, respectively.

End point type	Primary

End point timeframe:

1 Month after Vaccination 1

Notes:

[13] - 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:
GMT for MCV4 was analyzed for subjects in reporting arms MCV4+Tdap+rLP2086 and MCV4+Tdap+Saline only.

End point values	MCV4+Tdap+rLP2086	MCV4 + Tdap + Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	779	781		
Units: titer				
geometric mean (confidence interval 95%)				
Serogroup A (N=763, 772)	4647.3 (4317.66 to 5002.09)	5113 (4748.73 to 5505.17)		
Serogroup C (N=768, 767)	1679.2 (1539.63 to 1831.38)	1650.2 (1519.01 to 1792.65)		
Serogroup Y (N=771, 770)	2212.6 (2056.08 to 2381.08)	2244.9 (2088.7 to 2412.89)		
Serogroup W--135 (N=751, 765)	5925.1 (5469.77 to 6418.33)	6367.9 (5872.68 to 6904.88)		

Statistical analyses

Statistical analysis title	Serogroup A

Statistical analysis description:

CIs for GMT ratio were back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Group 1 - Group 2 for Serogroup A antigens).

Comparison groups	MCV4+Tdap+rLP2086 v MCV4 + Tdap + Saline

Number of subjects included in analysis	1560
Analysis specification	Pre-specified
Analysis type	non-inferiority[14]
Parameter estimate	GMT ratio
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.01

Notes:

[14] - The non--inferiority criteria margin was 1.5--fold and statistical inference was based on the CIs of the GMT ratios. Non-inferiority was achieved when the lower limit of the 2--sided 95% CI for the GMT ratios after vaccination 1 was greater than 0.67

Statistical analysis title	Serogroup C

Statistical analysis description:

CIs for GMT ratio were back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Group 1 - Group 2 for Serogroup C antigens).

Comparison groups	MCV4+Tdap+rLP2086 v MCV4 + Tdap + Saline
Number of subjects included in analysis	1560
Analysis specification	Pre-specified
Analysis type	non-inferiority[15]
Parameter estimate	GMT ratio
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.15

Notes:

[15] - The non--inferiority criteria margin was 1.5--fold and statistical inference was based on the CIs of the GMT ratios. Non-inferiority was achieved when the lower limit of the 2--sided 95% CI for the GMT ratios after vaccination 1 was greater than 0.67

Statistical analysis title	Serogroup Y

Statistical analysis description:

CIs for GMT ratio were back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Group 1 - Group 2 for Serogroup Y antigens).

Comparison groups	MCV4+Tdap+rLP2086 v MCV4 + Tdap + Saline
Number of subjects included in analysis	1560
Analysis specification	Pre-specified
Analysis type	non-inferiority[16]
Parameter estimate	GMT ratio
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.09

Notes:

[16] - The non--inferiority criteria margin was 1.5--fold and statistical inference was based on the CIs of the GMT ratios. Non-inferiority was achieved when the lower limit of the 2--sided 95% CI for the GMT ratios after vaccination 1 was greater than 0.67

Statistical analysis title	Serogroup W--135

Statistical analysis description:

CIs for GMT ratio were back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Group 1 - Group 2 for Serogroup W--135 antigens).

Comparison groups	MCV4+Tdap+rLP2086 v MCV4 + Tdap + Saline
Number of subjects included in analysis	1560
Analysis specification	Pre-specified
Analysis type	non-inferiority[17]
Parameter estimate	GMT ratio
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.04

Notes:

[17] - The non--inferiority criteria margin was 1.5--fold and statistical inference was based on the CIs of the GMT ratios. Non-inferiority was achieved when the lower limit of the 2--sided 95% CI for the GMT ratios after vaccination 1 was greater than 0.67

Primary: Serum Bactericidal Assay Using Human Complement (hSBA) GMTs of PMB80 [A22] and PMB2948 [B24] 1 Month After Vaccination 3

End point title	Serum Bactericidal Assay Using Human Complement (hSBA) GMTs of PMB80 [A22] and PMB2948 [B24] 1 Month After Vaccination 3 [18]

End point description:

Antibody hSBA GMTs of primary strain PMB80 [A22] and PMB2948 [B24] were computed along with corresponding 2-sided 95% CIs. hSBA titers from the 2 primary strains were logarithmically transformed for analysis. Post vaccination 3 evaluable immunogenicity population: eligible subjects randomized to Group 1 or 3, received scheduled investigational product, had pre and post vaccination blood drawn at prespecified time points, had valid, determinate assay results for proposed analysis, received no prohibited vaccines, no other major protocol violations.

End point type	Primary

End point timeframe:

1 Month after Vaccination 3

Notes:

[18] - 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:
hSBA GMTs of PMB80 [A22] and PMB2948 [B24] were analyzed for subjects in reporting arms MCV4+Tdap+rLP2086 and Saline+Saline +rLP2086 only.

End point values	MCV4+Tdap+rLP2086	Saline+Saline+rLP2086		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	683[19]	679[20]		
Units: titer				
geometric mean (confidence interval 95%)				
PMB80 [A22] (N= 679, 674)	45.9 (42.74 to 49.35)	49.7 (46.43 to 53.3)		

PMB2948 [B24] (N= 670, 656)	24.8 (23.11 to 26.58)	27.4 (25.58 to 29.41)		

Notes:

[19] - Evaluable immunogenicity population.

[20] - Evaluable immunogenicity population.

Statistical analyses

Statistical analysis title	PMB80 [A22]

Statistical analysis description:

CIs for GMT ratio were back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Group 1 -- Group 2 for hSBA strain titers).

Comparison groups	MCV4+Tdap+rLP2086 v Saline+Saline+rLP2086
Number of subjects included in analysis	1362
Analysis specification	Pre-specified
Analysis type	non-inferiority[21]
Parameter estimate	GMT ratio
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.02

Notes:

[21] - The non--inferiority criteria margin was 1.5--fold and statistical inference was based on the CIs of the GMT ratios. Non-inferiority was achieved when the lower limit of the 2--sided 95%CI for the GMT ratios after vaccination 1 was greater than 0.67.

Statistical analysis title	PMB2948 [B24]

Statistical analysis description:

CIs for GMT ratio were back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Group 1 -- Group 2 for hSBA strain titers).

Comparison groups	MCV4+Tdap+rLP2086 v Saline+Saline+rLP2086
Number of subjects included in analysis	1362
Analysis specification	Pre-specified
Analysis type	non-inferiority[22]
Parameter estimate	GMT ratio
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1

Notes:

[22] - The non--inferiority criteria margin was 1.5--fold and statistical inference was based on the CIs of the GMT ratios. Non-inferiority was achieved when the lower limit of the 2--sided 95%CI for the GMT ratios after vaccination 1 was greater than 0.67.

Secondary: Percentage of Subjects With Seroresponse for Tetanus, Diphtheria and Acellular Pertussis (Tdap) and Meningococcal Conjugate Vaccine (MCV4) Antigens

End point title	Percentage of Subjects With Seroresponse for Tetanus, Diphtheria and Acellular Pertussis (Tdap) and Meningococcal

	Conjugate Vaccine (MCV4) Antigens[23]

End point description:

Seroconversion rate for Tdap antigens was greater than or equal to (>=) 4-, 2-fold rise in antibody concentration, if prevaccination antibody concentration was less than or equal to (<=),greater than (>) cutoff value,respectively. For MCV4 antigens >=4- fold rise on serum bactericidal assay using rabbit complement (rSBA) titers, postdose rSBA titers >=2×LLOQ if baseline value >=, less than (<) lower limit of quantitation (LLOQ), respectively. Cutoff value=0.1 IU/mL for diphtheria and tetanus, 0.9, 2.9, 3.0, 10.6 EU/mL for pertussis toxoid,filamentous hemagglutinin,pertactin,fimbriae agglutinogens types 2 + 3, respectively. Post vaccination 1 evaluable immunogenicity population. Here, 'N'signifies subjects with seroresponse.

End point type	Secondary

End point timeframe:

1 Month after Vaccination 1

Notes:

[23] - 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:
Seroresponse for Tdap and MCV4 antigens was analyzed for subjects in reporting arms MCV4+Tdap+rLP 2086 and MCV4+Tdap+Saline only.

End point values	MCV4+Tdap+rLP2086	MCV4 + Tdap + Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	779[24]	781[25]		
Units: percentage of subjects				
number (confidence interval 95%)				
Diphtheria (N=774, 780)	98.6 (97.5 to 99.3)	98.3 (97.2 to 99.1)		
Tetanus (N=774, 780)	97.7 (96.3 to 98.6)	97.4 (96.1 to 98.4)		
Pertussis toxoid (N=774, 780)	68.1 (64.7 to 71.4)	72.7 (69.4 to 75.8)		
Pertussis filamentous hemagglutinin (N=774, 780)	85.3 (82.6 to 87.7)	89.2 (86.8 to 91.3)		
Pertussis pertactin (N=774, 780)	96 (94.4 to 97.3)	96.2 (94.6 to 97.4)		
Pertussis fimbriae AG types 2+3 (N=774, 780)	79.5 (76.4 to 82.3)	81.9 (79 to 84.6)		
Serogroup A (N=712, 736)	85.4 (82.6 to 87.9)	88.6 (86.1 to 90.8)		
Serogroup C (N=738, 742)	89.3 (86.8 to 91.4)	88.9 (86.5 to 91.1)		
Serogroup Y (N=754, 753)	90.5 (88.1 to 92.5)	93.6 (91.6 to 95.3)		
Serogroup W-135 (N=729, 752)	97.1 (95.6 to 98.2)	97.2 (95.8 to 98.3)		

Notes:

[24] - Subjects with valid, determinate assay results for given antigen at specified time point, baseline.

[25] - Subjects with valid, determinate assay results for given antigen at specified time point, baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving Predefined Antibody Level for Diphtheria and Tetanus Antigens

End point title	Percentage of Subjects Achieving Predefined Antibody Level for Diphtheria and Tetanus Antigens[26]

End point description:

Subjects with antibody concentration level of greater than or equal to 1.0 IU/mL for diphtheria and tetanus antigens were computed along with corresponding 2-sided 95% CIs. Post vaccination 1 evaluable immunogenicity population.

End point type	Secondary

End point timeframe:

1 Month after Vaccination 1

Notes:

[26] - 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:
Predefined antibody level for Tetanus and Diphtheria toxoid antigens was analyzed for subjects in reporti ng arms MCV4+Tdap+ rLP2086 and MCV4+Tdap+Saline only.

End point values	MCV4+Tdap+rLP2086	MCV4 + Tdap + Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	778[27]	780[28]		
Units: percentage of subjects				
number (confidence interval 95%)				
Tetanus	99.1 (98.2 to 99.6)	99 (98 to 99.6)		
Diphtheria toxoid	98.1 (98.1 to 98.9)	99 (98 to 99.6)		

Notes:

[27] - Subjects with valid and determinate assay results for given antigen.

[28] - Subjects with valid and determinate assay results for given antigen.

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Bactericidal Assay Using Human Complement (hSBA) GMTs of PMB80 [A22] and PMB2948 [B24] Before Vaccination 1 and 1 Month After Vaccination 2

End point title	Serum Bactericidal Assay Using Human Complement (hSBA) GMTs of PMB80 [A22] and PMB2948 [B24] Before Vaccination 1 and 1 Month After Vaccination 2[29]

End point description:

Antibody hSBA of primary strain PMB80 [A22] and PMB2948 [B24] were computed along with corresponding 2--sided 95% CIs. hSBA titers from the 2 primary strains were logarithmically transformed for analysis. Post vaccination 3 evaluable immunogenicity population. Here, 'N' signifies subjects with valid and determinate assay results for given strain for each group, respectively.

End point type	Secondary

End point timeframe:

Before Vaccination 1, 1 Month after Vaccination 2

Notes:

[29] - 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:
hSBA GMT was analyzed for subjects in reporting arms MCV4+Tdap+ rLP2086 and Saline+Saline+rLP20 86 only.

End point values	MCV4+Tdap+rLP2086	Saline+Saline+rLP2086		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	683[30]	679[31]		
Units: titer				
geometric mean (confidence interval 95%)				
Before Vaccination 1: PMB80 [A22] (N= 677, 677)	8.5 (8.28 to 8.64)	8.6 (8.39 to 8.84)		
Before Vaccination 1: PMB2948 [B24] (N= 677, 676)	4.1 (4.04 to 4.19)	4.2 (4.1 to 4.27)		
After Vaccination 2: PMB80 [A22] (N= 669, 665)	23.7 (22.1 to 25.4)	23.8 (22.14 to 25.54)		
After Vaccination 2: PMB2948 [B24] (N = 656, 650)	12 (11.12 to 12.99)	13 (12.03 to 14.13)		

Notes:

[30] - Evaluable immunogenicity population.

[31] - Evaluable immunogenicity population.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Serum Bactericidal Assay Using Human Complement (hSBA) Titer >= Lower Limit of Quantitation (LLOQ)

End point title	Percentage of Subjects With Serum Bactericidal Assay Using Human Complement (hSBA) Titer >= Lower Limit of Quantitation (LLOQ) [32]

End point description:

Percentage of subjects achieving hSBA titer >= LLOQ were computed along with corresponding 2-sided 95% CIs. LLOQ was 1:16 for PMB80 [A22] and 1:8 for PMB2948 [B24]. Post vaccination 3 evaluable immunogenicity population. Here, 'N' signifies subjects with valid and determinate assay results for given strain for each group, respectively.

End point type	Secondary

End point timeframe:

Before Vaccination 1, 1 Month after Vaccination (Vac) 2, 3

Notes:

[32] - 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:
hSBA titer >= LLOQ was analyzed for subjects in reporting arms MCV4+Tdap+ rLP2086 and Saline+Saline+rLP2086 only.

End point values	MCV4+Tdap+rLP2086	Saline+Saline+rLP2086		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	683[33]	679[34]		
Units: percentage of subjects				
number (confidence interval 95%)				
Before Vac 1: PMB80[A22] 1:16 (N=677, 677)	4.4 (3 to 6.3)	5.6 (4 to 7.6)		
1 month after Vac 2: PMB80[A22] 1:16 (N= 669, 665)	68 (64.3 to 71.5)	68 (64.3 to 71.5)		
1 month after Vac 3: PMB80[A22] 1:16 (N=679, 674)	87.5 (84.8 to 89.9)	91.4 (89 to 93.4)		
Before Vaccination 1: PMB2948[B24] 1:8 (N=677,676)	1.6 (0.8 to 2.9)	3.4 (2.2 to 5.1)		

1 month after Vac 2: PMB2948[B24] 1:8 (N=656, 650)	62.3 (58.5 to 66.1)	66 (62.2 to 69.6)		
1 month after Vac 3: PMB2948[B24] 1:8 (N=670, 656)	90 (87.5 to 92.2)	92.7 (90.4 to 94.6)		

Notes:

[33] - Evaluable immunogenicity population.

[34] - Evaluable immunogenicity population.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Serum Bactericidal Assay Using Human Complement (hSBA) Titer >= Prespecified Titer Level

End point title	Percentage of Subjects With Serum Bactericidal Assay Using Human Complement (hSBA) Titer >= Prespecified Titer Level [35]

End point description:

Antibody hSBA of primary strain PMB80 [A22] and PMB2948 [B24] with hSBA titers >=1:4, >=1:8, >=1:16, >=1:32, >=1:64, and >=1:128 were computed along with corresponding 2--sided 95% CIs. Post vaccination 3 evaluable immunogenicity population. Here, 'N' signifies subjects with valid and determinate assay results for given strain for each group, respectively.

End point type	Secondary

End point timeframe:

Before Vaccination 1, 1 Month after Vaccination (Vac) 2, 3

Notes:

[35] - 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:
hSBA titer >= prespecified titer Level was analyzed for subjects in reporting arms MCV4+Tdap+ rLP2086 and Saline+Saline+rLP2086 only.

End point values	MCV4+Tdap+rLP2086	Saline+Saline+rLP2086		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	683[36]	679[37]		
Units: percentage of subjects				
number (confidence interval 95%)				
Before Vaccination 1: PMB80[A22] 1:4 (N=677,677)	6.9 (5.1 to 9.1)	7.5 (5.7 to 9.8)		
1 month after Vac 2: PMB80[A22] 1:4 (N=669, 665)	68.2 (64.5 to 71.7)	68.6 (64.9 to 72.1)		
1 month after Vac 3: PMB80[A22] 1:4 (N=679, 674)	87.8 (85.1 to 90.1)	91.7 (89.3 to 93.7)		
Before Vaccination 1: PMB80[A22] 1:8 (N=677, 677)	68.2 (64.5 to 71.7)	6.4 (4.6 to 8.5)		
1 month after Vac 2: PMB80[A22] 1:8 (N=669, 665)	87.6 (84.9 to 90)	68.1 (64.4 to 71.7)		
1 month after Vac 3: PMB80[A22] 1:8 (N=679, 674)	2.7 (1.6 to 4.2)	91.5 (89.2 to 93.5)		
Before Vaccination 1: PMB80[A22] 1:32 (N=677, 677)	55 (51.1 to 58.8)	3.2 (2 to 4.9)		
1 month after Vac 2: PMB80[A22] 1:32 (N=669, 665)	81.3 (78.2 to 84.2)	54.4 (50.6 to 58.3)		
1 month after Vac 3: PMB80[A22] 1:32 (N=679, 674)	0.7 (0.2 to 1.7)	84.7 (81.8 to 87.4)		
Before Vaccination 1: PMB80[A22] 1:64 (N=677,677)	25.6 (22.3 to 29)	1 (0.4 to 2.1)		

1 month after Vac 2: PMB80[A22] 1:64 (N= 669, 665)	52.7 (48.9 to 56.5)	25 (21.7 to 28.4)		
1 month after Vac 3: PMB80[A22] 1:64 (N=679, 674)	0.1 (0 to 0.8)	55.6 (51.8 to 59.4)		
Before Vaccination 1: PMB80[A22] 1:128 (N=677,677)	6.9 (5.1 to 9.1)	0.4 (0.1 to 1.3)		
1 month after Vac 2: PMB80[A22] 1:128 (N=669, 665)	23.6 (20.4 to 26.9)	7.5 (5.6 to 9.8)		
1 month after Vac 3: PMB80[A22] 1:128 (N=679, 674)	2.1 (1.1 to 3.4)	23.3 (20.2 to 26.7)		
Before Vaccination 1: PMB2948[B24] 1:4 (N=677,676)	64.8 (61 to 68.4)	3.7 (2.4 to 5.4)		
1 month after Vac 2: PMB2948[B24] 1:4 (N=656, 650)	90.7 (88.3 to 92.8)	68.2 (64.4 to 71.7)		
1 month after Vac 3: PMB2948[B24] 1:4 (N=670, 656)	1.5 (0.7 to 2.7)	93.1 (90.9 to 95)		
Before Vaccination 1: PMB2948[B24] 1:16(N=677,676)	57.6 (53.7 to 61.4)	2.1 (1.1 to 3.5)		
1 month after Vac 2: PMB2948[B24] 1:16(N=656,650)	86.7 (83.9 to 89.2)	60.3 (56.4 to 64.1)		
1 month after Vac 3: PMB2948[B24] 1:16(N=670,656)	0.4 (0.1 to 1.3)	88.9 (86.2 to 91.2)		
Before Vaccination 1: PMB2948[B24] 1:32(N=677,676)	26.2 (22.9 to 29.8)	0.6 (0.2 to 1.5)		
1 month after Vac 2: PMB2948[B24] 1:32(N=656,650)	55.1 (51.2 to 58.9)	28.2 (24.7 to 31.8)		
1 month after Vac 3: PMB2948[B24] 1:32(N=670, 656)	0.4 (0.1 to 1.3)	60.7 (56.8 to 64.4)		
Before Vaccination 1:PMB2948[B24] 1:64(N= 677,676)	8.7 (6.6 to 11.1)	0.3 (0 to 1.1)		
1 month after Vac 2: PMB2948[B24] 1:64 (N=656,650)	22.5 (19.4 to 25.9)	10.3 (8.1 to 12.9)		
1 month after Vac 3: PMB2948[B24] 1:64 (N=670,656)	0.1 (0 to 0.8)	24.1 (20.9 to 27.5)		
Before Vaccination 1:PMB2948[B24] 1:128(N=677,676)	2.4 (1.4 to 3.9)	0.1 (0 to 0.8)		
1 month after Vac 2: PMB2948[B24] 1:128(N=656,650)	6.6 (4.8 to 8.7)	3.4 (2.1 to 5.1)		
1 month after Vac 3: PMB2948[B24] 1:128(N=670,656)	5 (3.5 to 6.9)	7.8 (5.8 to 10.1)		

Notes:

[36] - Evaluable immunogenicity population.

[37] - Evaluable immunogenicity population.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Immunogloblulin G (IgG) Measured by GMC

End point title	Immunogloblulin G (IgG) Measured by GMC [38]

End point description:

IgG GMCs of 4 MCV4 antigens (serogroup A, serogroup C, serogroup Y and serogroup W-135) of subjects were computed along with corresponding 2-sided 95% CIs. CIs were back transformations of confidence levels based on Student t distribution for mean logarithm of titers. Post vaccination 1 evaluable immunogenicity population.

End point type	Other pre-specified

End point timeframe:

Before Vaccination 1, 1 Month after Vaccination 1

Notes:

[38] - 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:

IgG GMC was analyzed for subjects in reporting arms MCV4+Tdap+rLP2086 and MCV4+Tdap+Saline onl y.

End point values	MCV4+Tdap+rLP2086	MCV4 + Tdap + Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	779	781		
Units: microgram per milliliter (mcg/mL)				
geometric mean (confidence interval 95%)				
Before Vaccination 1: Serogroup A	0.17 (0.16 to 0.19)	0.15 (0.14 to 0.17)		
1 Month after Vaccination 1: Serogroup A	11.42 (10.3 to 12.65)	11.38 (10.21 to 12.67)		
Before Vaccination 1: Serogroup C	0.11 (0.1 to 0.12)	0.11 (0.1 to 0.12)		
1 Month after Vaccination 1: Serogroup C	5.59 (4.9 to 6.39)	5.47 (4.79 to 6.23)		
Before Vaccination 1: Serogroup Y	0.14 (0.13 to 0.14)	0.13 (0.13 to 0.14)		
1 Month after Vaccination 1: Serogroup Y	2.49 (2.22 to 2.79)	2.14 (1.92 to 2.39)		
Before Vaccination 1: Serogroup W--135	0.13 (0.13 to 0.14)	0.13 (0.13 to 0.14)		
1 Month after Vaccination 1: Serogroup W--135	1.79 (1.59 to 2.01)	1.84 (1.62 to 2.09)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects Achieving at Least 4-Fold Increase in Serum Bactericidal Assay Using Human Complement (hSBA) Titer Level

End point title	Percentage of Subjects Achieving at Least 4-Fold Increase in Serum Bactericidal Assay Using Human Complement (hSBA) Titer Level[39]

End point description:

Post vaccination 3 evaluable immunogenicity population. Here, 'N' signifies subjects with valid and determinate hSBA titers for the given strain at both the specified time point and baseline.

End point type	Other pre-specified

End point timeframe:

1 Month after Vaccination (Vac) 2, 3

Notes:

[39] - 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:

4 fold increase in hSBA titer level was analyzed for subjects in reporting arms MCV4+Tdap+ rLP2086 an d Saline+Saline+rLP2086 only.

End point values	MCV4+Tdap+rLP2086	Saline+Saline+rLP2086		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	683[40]	679[41]		
Units: percentage of subjects				
number (confidence interval 95%)				
1 month after Vac 2 : PMB80 [A22] (N= 663, 663)	64.3 (60.5 to 67.9)	63.7 (59.9 to 67.3)		
1 month after Vac 3 : PMB80 [A22] (N= 673, 672)	84 (81 to 86.6)	88.7 (86 to 91)		
1 month after Vac 2 : PMB2948 [B24] (N= 650, 647)	56.3 (52.4 to 60.2)	58.4 (54.5 to 62.3)		
1 month after Vac 3 : PMB2948 [B24] (N= 664, 653)	85.7 (82.8 to 88.3)	87.7 (85 to 90.2)		

Notes:

[40] - Evaluable immunogenicity population.

[41] - Evaluable immunogenicity population.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Other Pre-specified: Percentage of Subjects With at Least One Adverse Event (AE) and use of Antipyretic Medication

End point title	Other Pre-specified: Percentage of Subjects With at Least One Adverse Event (AE) and use of Antipyretic Medication

End point description:

An AE was any untoward medical occurrence in a subject who received investigational product without regard to possibility of causal relationship. The use of antipyretic medication was recorded in the e--diary for all the subjects of safety population during the vaccination phase. Safety population included all subjects who received at least 1 dose of the investigational product and had safety information available during vaccination phase. Here, 'N' signifies those subjects who were evaluable for this measure during specified time period.

End point type	Other pre-specified

End point timeframe:

Vaccination phase (baseline up to 1 month after Vaccination 3); Follow-up phase (from 1 month up to 6 months after Vaccination 3)

End point values	MCV4+Tdap+rLP2086	MCV4 + Tdap + Saline	Saline+Saline+rLP2086	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	883	870	875	
Units: percentage of subjects				
number (not applicable)				
Adverse Events: Vaccination phase (N=883,870,875)	42.9	42.6	46.2	
Adverse Events: Follow-up phase (N=777,776,771)	1	0.5	1.3	
Use of Antipyretic Medication (N=883,870,875)	53.2	30.4	52	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs: recorded from signing of informed consent form (ICF) to completion of study. SAEs: recorded from signing of ICF to 196 days of follow up period. Subject recorded pre--specified AEs in electronic diary (up to 7 days after vaccination)

Adverse event reporting additional description:

SAEs and AEs were grouped by system organ class and preferred term. AEs included AEs collected in the electronic diary (local and systemic reactions; systematic assessment) and AEs collected on the case report form at each visit (nonsystematic assessment).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	MCV4+Tdap+rLP2086

Reporting group description:

Randomized to receive MCV4 and Tdap vaccine on 0-- month, MnB rLP2086 vaccine on a 0--, 2--, 6-- month schedule.

Reporting group title	Saline+Saline+rLP2086

Reporting group description:

Randomized to receive Saline on 0-- month, rLP2086 vaccine on a 0--, 2--, 6- - month schedule, MCV4 and Tdap vaccine on 7-- month.

Reporting group title	MCV4 + Tdap + Saline

Reporting group description:

Randomized to receive MCV4 and Tdap vaccine on 0-- month, Saline on a 0--, 2--, 6-- month schedule.

Serious adverse events	MCV4+Tdap+rLP2086	Saline+Saline+rLP2086	MCV4 + Tdap + Saline
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 883 (1.70%)	11 / 875 (1.26%)	9 / 870 (1.03%)
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 / 883 (0.00%)	1 / 875 (0.11%)	0 / 870 (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
Epiphyseal fracture			
subjects affected / exposed	0 / 883 (0.00%)	1 / 875 (0.11%)	0 / 870 (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

Excoriation			
subjects affected / exposed	0 / 883 (0.00%)	0 / 875 (0.00%)	1 / 870 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	0 / 883 (0.00%)	0 / 875 (0.00%)	1 / 870 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	1 / 883 (0.11%)	0 / 875 (0.00%)	0 / 870 (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
Wound secretion			
subjects affected / exposed	1 / 883 (0.11%)	0 / 875 (0.00%)	0 / 870 (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
Congenital, familial and genetic disorders			
Adrenogenital syndrome			
subjects affected / exposed	1 / 883 (0.11%)	0 / 875 (0.00%)	0 / 870 (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
Congenital spinal cord anomaly			
subjects affected / exposed	1 / 883 (0.11%)	0 / 875 (0.00%)	0 / 870 (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
Vascular disorders			
Haemorrhage			
subjects affected / exposed	1 / 883 (0.11%)	0 / 875 (0.00%)	0 / 870 (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	0 / 883 (0.00%)	1 / 875 (0.11%)	1 / 870 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dural arteriovenous fistula			
subjects affected / exposed	1 / 883 (0.11%)	0 / 875 (0.00%)	0 / 870 (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
Hemiplegic migraine			
subjects affected / exposed	0 / 883 (0.00%)	1 / 875 (0.11%)	0 / 870 (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
Migraine			
subjects affected / exposed	0 / 883 (0.00%)	0 / 875 (0.00%)	1 / 870 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 883 (0.11%)	0 / 875 (0.00%)	0 / 870 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 883 (0.00%)	1 / 875 (0.11%)	0 / 870 (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
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 883 (0.00%)	1 / 875 (0.11%)	0 / 870 (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
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 883 (0.00%)	1 / 875 (0.11%)	0 / 870 (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

Pneumomediastinum			
subjects affected / exposed	0 / 883 (0.00%)	1 / 875 (0.11%)	0 / 870 (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
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	1 / 883 (0.11%)	0 / 875 (0.00%)	1 / 870 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression suicidal			
subjects affected / exposed	0 / 883 (0.00%)	0 / 875 (0.00%)	1 / 870 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disorientation			
subjects affected / exposed	0 / 883 (0.00%)	1 / 875 (0.11%)	0 / 870 (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
Encopresis			
subjects affected / exposed	1 / 883 (0.11%)	0 / 875 (0.00%)	0 / 870 (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
Post--traumatic stress disorder			
subjects affected / exposed	1 / 883 (0.11%)	0 / 875 (0.00%)	0 / 870 (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
Psychogenic seizure			
subjects affected / exposed	1 / 883 (0.11%)	0 / 875 (0.00%)	0 / 870 (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
Musculoskeletal and connective tissue disorders			
Bone cyst			
subjects affected / exposed	0 / 883 (0.00%)	0 / 875 (0.00%)	1 / 870 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Scoliosis			
subjects affected / exposed	1 / 883 (0.11%)	0 / 875 (0.00%)	0 / 870 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 883 (0.11%)	1 / 875 (0.11%)	0 / 870 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone abscess			
subjects affected / exposed	1 / 883 (0.11%)	0 / 875 (0.00%)	0 / 870 (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	1 / 883 (0.11%)	0 / 875 (0.00%)	0 / 870 (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
Influenza			
subjects affected / exposed	0 / 883 (0.00%)	0 / 875 (0.00%)	1 / 870 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 883 (0.00%)	0 / 875 (0.00%)	1 / 870 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	1 / 883 (0.11%)	0 / 875 (0.00%)	0 / 870 (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
Tooth abscess			
subjects affected / exposed	1 / 883 (0.11%)	0 / 875 (0.00%)	0 / 870 (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
Metabolism and nutrition disorders			

Type 1 diabetes mellitus			
subjects affected / exposed	0 / 883 (0.00%)	1 / 875 (0.11%)	1 / 870 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	1 / 883 (0.11%)	0 / 875 (0.00%)	0 / 870 (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
Hyperglycaemia			
subjects affected / exposed	0 / 883 (0.00%)	1 / 875 (0.11%)	0 / 870 (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

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

Non-serious adverse events	MCV4+Tdap+rLP2086	Saline+Saline+rLP2086	MCV4 + Tdap + Saline
Total subjects affected by non-serious adverse events			
subjects affected / exposed	277 / 883 (31.37%)	292 / 875 (33.37%)	260 / 870 (29.89%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	9 / 883 (1.02%)	3 / 875 (0.34%)	2 / 870 (0.23%)
occurrences (all)	9	3	2
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	12 / 883 (1.36%)	16 / 875 (1.83%)	13 / 870 (1.49%)
occurrences (all)	12	17	13
Ligament sprain			
subjects affected / exposed	12 / 883 (1.36%)	13 / 875 (1.49%)	12 / 870 (1.38%)
occurrences (all)	13	15	12
Nervous system disorders			
Headache			
subjects affected / exposed	24 / 883 (2.72%)	26 / 875 (2.97%)	29 / 870 (3.33%)
occurrences (all)	26	27	33
General disorders and administration site conditions			

Injection site pain			
subjects affected / exposed	19 / 883 (2.15%)	15 / 875 (1.71%)	21 / 870 (2.41%)
occurrences (all)	21	16	24
Pyrexia			
subjects affected / exposed	20 / 883 (2.27%)	17 / 875 (1.94%)	14 / 870 (1.61%)
occurrences (all)	21	18	15
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	18 / 883 (2.04%)	19 / 875 (2.17%)	21 / 870 (2.41%)
occurrences (all)	18	20	24
Nausea			
subjects affected / exposed	10 / 883 (1.13%)	14 / 875 (1.60%)	9 / 870 (1.03%)
occurrences (all)	11	14	9
Abdominal pain			
subjects affected / exposed	2 / 883 (0.23%)	10 / 875 (1.14%)	7 / 870 (0.80%)
occurrences (all)	2	10	7
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	26 / 883 (2.94%)	31 / 875 (3.54%)	20 / 870 (2.30%)
occurrences (all)	27	34	21
Oropharyngeal pain			
subjects affected / exposed	17 / 883 (1.93%)	23 / 875 (2.63%)	13 / 870 (1.49%)
occurrences (all)	20	24	13
Nasal congestion			
subjects affected / exposed	4 / 883 (0.45%)	11 / 875 (1.26%)	5 / 870 (0.57%)
occurrences (all)	5	11	5
Rhinitis allergic			
subjects affected / exposed	6 / 883 (0.68%)	10 / 875 (1.14%)	4 / 870 (0.46%)
occurrences (all)	6	10	4
Asthma			
subjects affected / exposed	6 / 883 (0.68%)	9 / 875 (1.03%)	4 / 870 (0.46%)
occurrences (all)	6	10	4
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	11 / 883 (1.25%)	5 / 875 (0.57%)	1 / 870 (0.11%)
occurrences (all)	13	6	1

Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	9 / 883 (1.02%)	8 / 875 (0.91%)	4 / 870 (0.46%)
occurrences (all)	10	8	4
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	47 / 883 (5.32%)	70 / 875 (8.00%)	61 / 870 (7.01%)
occurrences (all)	50	74	66
Pharyngitis			
subjects affected / exposed	38 / 883 (4.30%)	28 / 875 (3.20%)	27 / 870 (3.10%)
occurrences (all)	41	29	27
Pharyngitis streptococcal			
subjects affected / exposed	23 / 883 (2.60%)	30 / 875 (3.43%)	20 / 870 (2.30%)
occurrences (all)	26	32	22
Nasopharyngitis			
subjects affected / exposed	22 / 883 (2.49%)	16 / 875 (1.83%)	19 / 870 (2.18%)
occurrences (all)	28	17	20
Gastroenteritis viral			
subjects affected / exposed	15 / 883 (1.70%)	25 / 875 (2.86%)	15 / 870 (1.72%)
occurrences (all)	16	27	16
Gastroenteritis			
subjects affected / exposed	14 / 883 (1.59%)	16 / 875 (1.83%)	20 / 870 (2.30%)
occurrences (all)	16	16	21
Sinusitis			
subjects affected / exposed	18 / 883 (2.04%)	17 / 875 (1.94%)	13 / 870 (1.49%)
occurrences (all)	19	17	14
Otitis media			
subjects affected / exposed	17 / 883 (1.93%)	14 / 875 (1.60%)	11 / 870 (1.26%)
occurrences (all)	18	14	12
Bronchitis			
subjects affected / exposed	5 / 883 (0.57%)	15 / 875 (1.71%)	6 / 870 (0.69%)
occurrences (all)	7	15	6
Viral infection			
subjects affected / exposed	4 / 883 (0.45%)	12 / 875 (1.37%)	7 / 870 (0.80%)
occurrences (all)	4	12	7
Conjunctivitis			

subjects affected / exposed	9 / 883 (1.02%)	3 / 875 (0.34%)	6 / 870 (0.69%)
occurrences (all)	9	3	6
Otitis externa			
subjects affected / exposed	3 / 883 (0.34%)	9 / 875 (1.03%)	5 / 870 (0.57%)
occurrences (all)	3	9	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 September 2012	Age range was changed from 10 to 25 years. An exclusion criterion related to allergen immunotherapy, instruction to record concomitant allergen immunotherapy in addition to non-study vaccination, reminder that the time of onset will be recorded for any AEs occurring on the same day of investigational product administration were added. Updated inclusion criteria and Lifestyle Guidelines to reflect new template text regarding contraception and classification of women of childbearing potential. Clarified exclusion criterion related to use of chronic systemic steroids. Additional safety reporting requirements were included.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported