Clinical trial results:
A Phase 2, Randomized, Active-Controlled, Observer-Blinded Trial, to Assess the Safety, Tolerability, and Immunogenicity of Gardasil® (HPV) Vaccine and Bivalent Rlp2086 Vaccine When Administered Concomitantly In Healthy Subjects Aged 11 to <18 Years

Summary

EudraCT number	2013-002137-38
Trial protocol	Outside EU/EEA
Global end of trial date	06 July 2013

Results information

Result version number	v1 (current)
This version publication date	29 June 2016
First version publication date	01 August 2015

Trial information

Trial identification

Sponsor protocol code	B1971011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01461993
WHO universal trial number (UTN)	-
Other trial identifiers	Alias ID: 6108A1-2007

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, 001 8007181021, ClinicalTrials.govCallCenter@pfizer.com
Scientific contact	Clinical Trials.gov Call Center, Pfizer Inc, 001 8007181021, ClinicalTrials.govCallCenter@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	15 May 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the immune response (based on geometric mean titer [GMT]) induced by Gardasil given with bivalent recombinant lipoprotein 2086 (rLP2086) vaccine (Group1) is noninferior to the immune response induced by Gardasil alone (Group3) as measured 1month after the 3rd vaccination (Visit5) with Gardasil in both groups.
The immune response to all 4 components of Gardasil will be assessed.
To demonstrate the immune response (based on GMT) induced by bivalent rLP2086 vaccine given with Gardasil (Group1) is noninferior to the immune response induced by bivalent rLP2086 vaccine alone (Group2) as measured by serum bactericidal assay using human complement performed with 2 MnB test strains, 1 expressing LP2086 subfamily A and 1 expressing lipoprotein 2086 (LP2086) subfamily B proteins, when measured 1 month after the third vaccination (Visit5) with bivalent rLP2086 vaccine in both groups.
To evaluate the safety profile of bivalent rLP2086 vaccine as measured by proportion of subject

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: 2499
Worldwide total number of subjects	2499
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)	440
Adolescents (12-17 years)	2059
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:

The total subjects enrolled were 2499 and the study started on 28 September 2011 and completed on 06 July 2013.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1: rLP2086 + Gardasil

Arm description:

Randomized to receive on a 0, 2-, 6- month schedule.

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

Dosage and administration details:

Bivalent rLP2086 was administered at a dose of 0.5 milliliter (mL) into the upper deltoid muscle of the left arm.

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

Dosage and administration details:

Gardasil was administered at a dose of 0.5 mL into the upper deltoid muscle of the right arm.

Arm title	Group 2: rLP2086 + Saline

Arm description:

Randomized to receive on a 0, 2-, 6- month schedule.

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

Dosage and administration details:

Bivalent rLP2086 was administered at a dose of 0.5 mL into the upper deltoid muscle of the left arm.

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 a dose of 0.5 mL into the upper deltoid muscle of the right arm.

Arm title	Group 3: Saline + Gardasil

Arm description:

Randomized to receive on a 0, 2, 6 month schedule.

Arm type	Experimental
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 a dose of 0.5 mL into the upper deltoid muscle of the right arm.

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

Dosage and administration details:

Gardasil was administered at a dose of 0.5 mL into the upper deltoid muscle of the right arm.

Number of subjects in period 1	Group 1: rLP2086 + Gardasil	Group 2: rLP2086 + Saline	Group 3: Saline + Gardasil
Started	999	998	502
Completed	848	841	438
Not completed	151	157	64
Did not meet entrance criteria	2	3	-
Adverse Event	9	11	3
No longer met eligibility criteria	13	18	10
Withdrawal by Subject	60	53	16
Protocol Violation	10	9	7
Unspecified	13	15	6
Lost to follow-up	44	48	22

Baseline characteristics

Reporting groups	
Reporting group title	Group 1: rLP2086 + Gardasil
Reporting group description: Randomized to receive on a 0, 2-, 6- month schedule.	
Reporting group title	Group 2: rLP2086 + Saline
Reporting group description: Randomized to receive on a 0, 2-, 6- month schedule.	
Reporting group title	Group 3: Saline + Gardasil
Reporting group description: Randomized to receive on a 0, 2, 6 month schedule.	

Reporting group values	Group 1: rLP2086 + Gardasil	Group 2: rLP2086 + Saline	Group 3: Saline + Gardasil
Number of subjects	999	998	502
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 13.7 ± 1.94	 13.6 ± 1.93	 13.6 ± 1.86
Gender categorical Units: Subjects			
Female	341	332	170
Male	658	666	332

Reporting group values	Total		
Number of subjects	2499		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 -		
Gender categorical Units: Subjects			
Female	843		
Male	1656		

End points

End points reporting groups

Reporting group title	Group 1: rLP2086 + Gardasil
Reporting group description: Randomized to receive on a 0, 2-, 6- month schedule.	
Reporting group title	Group 2: rLP2086 + Saline
Reporting group description: Randomized to receive on a 0, 2-, 6- month schedule.	
Reporting group title	Group 3: Saline + Gardasil
Reporting group description: Randomized to receive on a 0, 2, 6 month schedule.	

Primary: Geometric Mean Titer (GMT) of Human Papillomavirus (HPV) Antigens

End point title	Geometric Mean Titer (GMT) of Human Papillomavirus (HPV) Antigens[1]
End point description:	
End point type	Primary
End point timeframe: 1 month after Vaccination 3	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was planned to be reported for subjects in rLP2086 + Gardasil and Saline + Gardasil groups only.

End point values	Group 1: rLP2086 + Gardasil	Group 3: Saline + Gardasil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	813	423		
Units: Titer				
geometric mean (confidence interval 95%)				
HPV-6	451.8 (417.5 to 489.01)	550.3 (490.44 to 617.58)		
HPV-11	892.9 (839.52 to 949.57)	1084.3 (997.28 to 1178.96)		
HPV-16	3695.4 (3426.32 to 3985.67)	4763.4 (4285.85 to 5294.21)		
HPV-18	744 (687.67 to 804.96)	1047.4 (939 to 1168.25)		

Statistical analyses

Statistical analysis title	HPV-6

Statistical analysis description:

The non-inferiority criteria margin was 1.5-fold.

Comparison groups	Group 1: rLP2086 + Gardasil v Group 3: Saline + Gardasil
Number of subjects included in analysis	1236
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT Ratio
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	0.94

Statistical analysis title	HPV-11
Comparison groups	Group 3: Saline + Gardasil v Group 1: rLP2086 + Gardasil
Number of subjects included in analysis	1236
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT Ratio
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	0.91

Statistical analysis title	HPV-16
Comparison groups	Group 1: rLP2086 + Gardasil v Group 3: Saline + Gardasil
Number of subjects included in analysis	1236
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT Ratio
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	0.88

Statistical analysis title	HPV-18
Comparison groups	Group 1: rLP2086 + Gardasil v Group 3: Saline + Gardasil

Number of subjects included in analysis	1236
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT Ratio
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	0.81

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

End point title	Serum Bactericidal Assay Using Human Complement (hSBA) GMTs of PMB80 [A22] and PMB2948 [B24][2]

End point description:

End point type	Primary

End point timeframe:

1 month after Vaccination 3

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was planned to be reported for subjects in rLP2086 + Gardasil and rLP2086 + Saline groups only.

End point values	Group 1: rLP2086 + Gardasil	Group 2: rLP2086 + Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	814	812		
Units: Titer				
geometric mean (confidence interval 95%)				
PMB80 [A22] (N= 803, 801)	25.8 (50.22 to 56.66)	57.8 (54.44 to 61.44)		
PMB2948 [B24] (N= 788, 793)	53.3 (24.14 to 27.56)	28 (26.24 to 29.87)		

Statistical analyses

Statistical analysis title	PMB80 [A22]

Statistical analysis description:

The non-inferiority criteria margin was 1.5-fold.

Comparison groups	Group 1: rLP2086 + Gardasil v Group 2: rLP2086 + Saline

Number of subjects included in analysis	1626
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT Ratio
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1

Statistical analysis title	PMB2948 [B24]
Statistical analysis description:	
The non-inferiority criteria margin was 1.5-fold.	
Comparison groups	Group 1: rLP2086 + Gardasil v Group 2: rLP2086 + Saline
Number of subjects included in analysis	1626
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	GMT Ratio
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.01

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

End point title	Percentage of Subjects With at Least One Adverse Event (AE)[3]
End point description:	
End point type	Primary
End point timeframe:	
Vaccination 1 up to 1 month after Vaccination 3	

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this outcome measure.

End point values	Group 1: rLP2086 + Gardasil	Group 2: rLP2086 + Saline	Group 3: Saline + Gardasil	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	992	990	501	
Units: Percentage of subjects				
number (not applicable)	43.9	41.7	49.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving Seroconversion for Human Papillomavirus (HPV)

End point title	Percentage of Subjects Achieving Seroconversion for Human Papillomavirus (HPV)[4]

End point description:

End point type	Secondary

End point timeframe:

1 month after Vaccination 3

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was planned to be reported for subjects in rLP2086 + Gardasil and Saline + Gardasil groups only.

End point values	Group 1: rLP2086 + Gardasil	Group 3: Saline + Gardasil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	809	419		
Units: Percentage of subjects				
number (not applicable)				
HPV-6 (N= 802, 414)	99.4	99.3		
HPV-11 (N= 801, 417)	99.6	99.5		
HPV-16 (N= 800, 413)	99.6	99.5		
HPV-18 (N= 805, 418)	99.5	99		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Baseline Seropositive Participants: Group 1 and 3 Participants

End point title	Percentage of Baseline Seropositive Participants: Group 1 and 3 Participants[5]

End point description:

End point type	Secondary

End point timeframe:

Before vaccination 1

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was planned to be reported for subjects in rLP2086 + Gardasil and Saline + Gardasil groups only.

End point values	Group 1: rLP2086 + Gardasil	Group 3: Saline + Gardasil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	814	423		
Units: Percentage of subjects				
number (not applicable)				
HPV-6	1.4	2.1		
HPV-11	1.5	1.4		
HPV-16	1.6	2.4		
HPV-18	1	1.2		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of Subjects With Serum Bactericidal Assay Using Human Complement (hSBA) Titer Greater Than or Equal to (>=) Lower Limit of Quantitation (LLOQ)[6]

End point description:

End point type	Secondary

End point timeframe:

Before vaccination 1, 1 month after vaccination (Vac) 2, 3

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was planned to be reported for subjects in rLP2086 + Gardasil and rLP2086 + Saline groups only.

End point values	Group 1: rLP2086 + Gardasil	Group 2: rLP2086 + Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	814	812		
Units: Before vaccination 1, 1 month after vacc				
number (not applicable)				
Before Vaccination 1:PMB80[A22] 1:16 (N= 794, 799)	13.7	16.4		
1 month after Vac 2: PMB80[A22] 1:16 (N= 794, 801)	83	85.8		
1 month after Vac 3: PMB80[A22] 1:16 (N= 803, 801)	94	96.3		
Before Vaccination 1:PMB2001[A56] 1:8(N= 757, 740)	9.2	9.3		

1 month after Vac 2: PMB2001[A56] 1:8 (N= 790,795)	97.5	98.5		
1 month after Vac 3: PMB2001[A56] 1:8 (N= 796,802)	98.9	99.4		
Before Vaccination 1:PMB2948[B24] 1:8(N= 801, 793)	5.1	6.9		
1 month after Vac 2: PMB2948[B24] 1:8 (N= 770,770)	70.6	74.2		
1 month after Vac 3: PMB2948[B24] 1:8 (N= 788,793)	90.5	92.6		
Before Vaccination 1:PMB2707[B44] 1:8(N= 806, 805)	1.4	2.5		
1 month after Vac 2: PMB2707[B44] 1:8 (N= 783,776)	54.5	57.1		
1 month after Vac 3: PMB2707[B44] 1:8 (N= 799,795)	82.7	85.7		

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[7]

End point description:

End point type	Secondary

End point timeframe:

Before Vaccination 1, 1 month after Vaccination 2, 3

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was planned to be reported for subjects in rLP2086 + Gardasil and rLP2086 + Saline groups only.

End point values	Group 1: rLP2086 + Gardasil	Group 2: rLP2086 + Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	814	812		
Units: Percentage of subjects				
number (not applicable)				
Before Vaccination 1: PMB80 [A22] 1:4 (N=794,799)	15.2	18.8		
Before Vaccination 1: PMB80 [A22] 1:8 (N=794,799)	14.2	17.4		
Before Vaccination 1: PMB80 [A22] 1:32 (N=794,799)	9.4	10.6		
Before Vaccination 1: PMB80 [A22] 1:64 (N=794,799)	2.8	3.6		
Before Vaccination 1: PMB80[A22] 1:128 (N=794,799)	0.5	0.8		
1 month after Vac 2: PMB80 [A22] 1:4 (N=794,801)	83.8	86.3		

1 month after Vac 2: PMB80 [A22] 1:8 (N=794,801)	83.2	86.1		
1 month after Vac 2: PMB80 [A22] 1:32 (N=794,801)	66.9	69.7		
1 month after Vac 2: PMB80 [A22] 1:64 (N=794,801)	35.9	35.8		
1 month after Vac 2: PMB80 [A22] 1:128 (N=794,801)	11	13		
1 month after Vac 3: PMB80 [A22] 1:4 (N=803,801)	94.3	96.4		
1 month after Vac 3: PMB80 [A22] 1:8 (N=803,801)	94.3	96.4		
1 month after Vac 3: PMB80 [A22] 1:32 (N=803,801)	86.3	87		
1 month after Vac 3: PMB80 [A22] 1:64 (N=803,801)	58	61		
1 month after Vac 3: PMB80 [A22] 1:128 (N=803,801)	28.1	31.6		
Before Vaccination 1: PMB2001[A56] 1:4 (N=757,740)	10.4	10.5		
Before Vaccination 1: PMB2001[A56] 1:16(N=757,740)	9	9.1		
Before Vaccination 1: PMB2001[A56] 1:32(N=757,740)	8.1	7.7		
Before Vaccination 1: PMB2001[A56] 1:64(N=757,740)	4.9	4.6		
Before Vaccination 1:PMB2001[A56] 1:128(N=757,740)	1.7	1.5		
1 month after Vac 2: PMB2001 [A56] 1:4 (N=790,795)	97.8	98.7		
1 month after Vac 2: PMB2001[A56] 1:16 (N=790,795)	97.2	98.4		
1 month after Vac 2: PMB2001[A56] 1:32 (N=790,795)	91.3	93.7		
1 month after Vac 2: PMB2001[A56] 1:64 (N=790,795)	71.6	76.6		
1 month after Vac 2: PMB2001[A56] 1:128(N=790,795)	40.4	41.5		
1 month after Vac 3: PMB2001 [A56] 1:4 (n=796,802)	99.1	99.4		
1 month after Vac 3: PMB2001[A56] 1:16 (N=796,802)	98.9	99.4		
1 month after Vac 3: PMB2001[A56] 1:32 (N=796,802)	96.7	97.3		
1 month after Vac 3: PMB2001[A56] 1:64 (N=796,802)	88.1	89.2		
1 month after Vac 3: PMB2001[A56] 1:128(N=796,802)	63.6	67.2		
Before Vaccination 1: PMB2948[B24] 1:4 (N=801,793)	6.1	8.4		
Before Vaccination 1: PMB2948[B24] 1:16(N=801,793)	4.1	5.4		
Before Vaccination 1: PMB2948[B24] 1:32(N=801,793)	1.7	3		
Before Vaccination 1: PMB2948[B24] 1:64(N=801,793)	0.6	1		
Before Vaccination 1:PMB2948[B24] 1:128(N=801,793)	0.1	0.5		
1 month after Vac 2: PMB2948 [B24] 1:4 (N=770,770)	71.9	77.1		
1 month after Vac 2: PMB2948[B24] 1:16 (N=770,770)	65.2	68.8		

1 month after Vac 2: PMB2948[B24] 1:32 (N=770,770)	33.9	38.7		
1 month after Vac 2: PMB2948[B24] 1:64 (N=770,770)	13.1	12.5		
1 month after Vac 2: PMB2948[B24] 1:128(N=770,770)	5.3	5.6		
1 month after Vac 3: PMB2948 [B24] 1:4 (N=788,793)	91.1	92.8		
1 month after Vac 3: PMB2948[B24] 1:16 (N=788,793)	86.3	89.2		
1 month after Vac 3: PMB2948[B24] 1:32 (N=788,793)	57.2	60.9		
1 month after Vac 3: PMB2948[B24] 1:64 (N=788,793)	23.9	25.2		
1 month after Vac 3: PMB2948[B24] 1:128(N=788,793)	7.6	8.4		
Before Vaccination 1: PMB2707[B44] 1:4 (N=806,805)	1.7	3.2		
Before Vaccination 1: PMB2707[B44] 1:16(N=806,805)	1.2	2.1		
Before Vaccination 1: PMB2707[B44] 1:32(N=806,805)	0.6	1.4		
Before Vaccination 1: PMB2707[B44] 1:64(N=806,805)	0.1	0.7		
Before Vaccination 1:PMB2707[B44] 1:128(N=806,805)	0	0.2		
1 month after Vac 2: PMB2707 [B44] 1:4 (N=783,776)	57.7	60.1		
1 month after Vac 2: PMB2707[B44] 1:16 (N=783,776)	46.4	49.9		
1 month after Vac 2: PMB2707[B44] 1:32 (N=783,776)	25.7	26.9		
1 month after Vac 2: PMB2707[B44] 1:64 (N=783,776)	11.2	11.9		
1 month after Vac 2: PMB2707[B44] 1:128(N=783,776)	5	5.7		
1 month after Vac 3: PMB2707 [B44] 1:4 (N=799,795)	84.4	86.5		
1 month after Vac 3: PMB2707[B44] 1:16 (N=799,795)	78	82.4		
1 month after Vac 3: PMB2707[B44] 1:32 (N=799,795)	57.7	62.3		
1 month after Vac 3: PMB2707[B44] 1:64 (N=799,795)	34.7	39.4		
1 month after Vac 3: PMB2707[B44] 1:128(N=799,795)	15.1	18.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Bactericidal Assay Using Human Complement (hSBA) Geometric Mean Titer (GMT)

End point title	Serum Bactericidal Assay Using Human Complement (hSBA) Geometric Mean Titer (GMT)[8]

End point description:

End point type	Secondary

End point timeframe:

Before Vaccination 1, 1 month after Vaccination 2, 3

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was planned to be reported for subjects in rLP2086 + Gardasil and rLP2086 + Saline groups only.

End point values	Group 1: rLP2086 + Gardasil	Group 2: rLP2086 + Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	814	812		
Units: Titer				
geometric mean (confidence interval 95%)				
Before Vaccination 1: PMB80 [A22] (N=794,799)	9.6 (9.28 to 9.96)	9.9 (9.58 to 10.33)		
1 month after Vac 2: PMB80 [A22] (N=794,801)	31.9 (29.96 to 33.94)	33.7 (31.69 to 35.85)		
Before Vaccination 1: PMB2001 [A56] (N=757,740)	5 (4.78 to 5.32)	5 (4.75 to 5.28)		
1 month after Vac 2: PMB2001 [A56] (N=790,795)	70.6 (66.17 to 75.34)	76.3 (71.93 to 80.99)		
1 month after Vac 3: PMB2001 [A56] (N=796,802)	117.2 (110.14 to 124.76)	128.2 (120.65 to 136.27)		
Before Vaccination 1: PMB2948 [B24] (N=801,793)	4.3 (4.23 to 4.46)	4.5 (4.35 to 4.65)		
1 month after Vac 2: PMB2948 [B24] (N=770,770)	15 (13.88 to 16.15)	16.3 (15.15 to 17.62)		
Before Vaccination 1: PMB2707 [B44] (N=806,805)	4.1 (4.04 to 4.15)	4.2 (4.1 to 4.31)		
1 month after Vac 2: PMB2707 [B44] (N=783,776)	11.1 (10.21 to 12.01)	11.9 (10.94 to 12.96)		
1 month after Vac 3: PMB2707 [B44] (N=799,795)	27.2 (24.99 to 29.68)	31.9 (29.25 to 34.82)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE reported from Vaccination 1 to 1 month after last administration of investigational product (bivalent rLP2086/saline/Gardasil). SAE reported from Vaccination 1 to 6 months after last of investigational product (bivalent rLP2086/saline/Gardasil)

Adverse event reporting additional description:

Events collected on case report form were reported.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Group 1: rLP2086 + Gardasil

Reporting group description:

Randomized to receive on a 0, 2-, 6- month schedule.

Reporting group title	Group 2: rLP2086 + Saline

Reporting group description:

Randomized to receive on a 0, 2-, 6- month schedule.

Reporting group title	Group 3: Saline + Gardasil

Reporting group description:

Randomized to receive on a 0, 2-, 6- month schedule

Serious adverse events	Group 1: rLP2086 + Gardasil	Group 2: rLP2086 + Saline	Group 3: Saline + Gardasil
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 992 (1.21%)	16 / 990 (1.62%)	4 / 501 (0.80%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Nodular fasciitis			
subjects affected / exposed	0 / 992 (0.00%)	1 / 990 (0.10%)	0 / 501 (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
Injury, poisoning and procedural complications			
Burns first degree			
subjects affected / exposed	1 / 992 (0.10%)	0 / 990 (0.00%)	0 / 501 (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
Concussion			

subjects affected / exposed	0 / 992 (0.00%)	1 / 990 (0.10%)	0 / 501 (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
Fibula fracture			
subjects affected / exposed	0 / 992 (0.00%)	1 / 990 (0.10%)	0 / 501 (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
Humerus fracture			
subjects affected / exposed	0 / 992 (0.00%)	1 / 990 (0.10%)	0 / 501 (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
Pelvic fracture			
subjects affected / exposed	0 / 992 (0.00%)	1 / 990 (0.10%)	0 / 501 (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
Road traffic accident			
subjects affected / exposed	1 / 992 (0.10%)	0 / 990 (0.00%)	0 / 501 (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
Skull fracture			
subjects affected / exposed	1 / 992 (0.10%)	0 / 990 (0.00%)	0 / 501 (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
Tibia fracture			
subjects affected / exposed	0 / 992 (0.00%)	1 / 990 (0.10%)	0 / 501 (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
Wrist fracture			
subjects affected / exposed	0 / 992 (0.00%)	1 / 990 (0.10%)	0 / 501 (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
Cardiac disorders			
Supraventricular tachycardia			

subjects affected / exposed	1 / 992 (0.10%)	0 / 990 (0.00%)	0 / 501 (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			
Migraine			
subjects affected / exposed	1 / 992 (0.10%)	0 / 990 (0.00%)	1 / 501 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 992 (0.00%)	1 / 990 (0.10%)	0 / 501 (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
Blood and lymphatic system disorders			
Lymphoid tissue hyperplasia			
subjects affected / exposed	1 / 992 (0.10%)	0 / 990 (0.00%)	0 / 501 (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
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	0 / 992 (0.00%)	1 / 990 (0.10%)	0 / 501 (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
Haemorrhoids			
subjects affected / exposed	0 / 992 (0.00%)	0 / 990 (0.00%)	1 / 501 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary dyskinesia			
subjects affected / exposed	0 / 992 (0.00%)	0 / 990 (0.00%)	1 / 501 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	0 / 992 (0.00%)	1 / 990 (0.10%)	0 / 501 (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			
Depression suicidal			
subjects affected / exposed	2 / 992 (0.20%)	0 / 990 (0.00%)	0 / 501 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	1 / 992 (0.10%)	1 / 990 (0.10%)	0 / 501 (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
Affective disorder			
subjects affected / exposed	0 / 992 (0.00%)	1 / 990 (0.10%)	0 / 501 (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
Anxiety			
subjects affected / exposed	1 / 992 (0.10%)	0 / 990 (0.00%)	0 / 501 (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
Bipolar disorder			
subjects affected / exposed	0 / 992 (0.00%)	1 / 990 (0.10%)	0 / 501 (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
Cyclothymic disorder			
subjects affected / exposed	0 / 992 (0.00%)	0 / 990 (0.00%)	1 / 501 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major depression			
subjects affected / exposed	0 / 992 (0.00%)	1 / 990 (0.10%)	0 / 501 (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
Oppositional defiant disorder			

subjects affected / exposed	1 / 992 (0.10%)	0 / 990 (0.00%)	0 / 501 (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			
Epiphysiolysis			
subjects affected / exposed	0 / 992 (0.00%)	1 / 990 (0.10%)	0 / 501 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	2 / 992 (0.20%)	1 / 990 (0.10%)	0 / 501 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 992 (0.00%)	1 / 990 (0.10%)	0 / 501 (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	Group 1: rLP2086 + Gardasil	Group 2: rLP2086 + Saline	Group 3: Saline + Gardasil
Total subjects affected by non-serious adverse events			
subjects affected / exposed	308 / 992 (31.05%)	289 / 990 (29.19%)	168 / 501 (33.53%)
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	16 / 992 (1.61%)	20 / 990 (2.02%)	10 / 501 (2.00%)
occurrences (all)	18	23	12
Joint injury			
subjects affected / exposed	12 / 992 (1.21%)	5 / 990 (0.51%)	2 / 501 (0.40%)
occurrences (all)	13	5	2
Nervous system disorders			
Headache			
subjects affected / exposed	50 / 992 (5.04%)	38 / 990 (3.84%)	21 / 501 (4.19%)
occurrences (all)	54	43	23
General disorders and administration			

site conditions			
Injection site pain			
subjects affected / exposed	50 / 992 (5.04%)	43 / 990 (4.34%)	21 / 501 (4.19%)
occurrences (all)	73	55	28
Pyrexia			
subjects affected / exposed	15 / 992 (1.51%)	11 / 990 (1.11%)	5 / 501 (1.00%)
occurrences (all)	15	11	5
Fatigue			
subjects affected / exposed	10 / 992 (1.01%)	8 / 990 (0.81%)	3 / 501 (0.60%)
occurrences (all)	10	9	3
Injection site swelling			
subjects affected / exposed	11 / 992 (1.11%)	8 / 990 (0.81%)	2 / 501 (0.40%)
occurrences (all)	13	9	2
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	12 / 992 (1.21%)	10 / 990 (1.01%)	6 / 501 (1.20%)
occurrences (all)	13	10	6
Nausea			
subjects affected / exposed	15 / 992 (1.51%)	6 / 990 (0.61%)	2 / 501 (0.40%)
occurrences (all)	15	6	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	19 / 992 (1.92%)	16 / 990 (1.62%)	14 / 501 (2.79%)
occurrences (all)	20	17	15
Oropharyngeal pain			
subjects affected / exposed	12 / 992 (1.21%)	23 / 990 (2.32%)	6 / 501 (1.20%)
occurrences (all)	14	24	6
Nasal congestion			
subjects affected / exposed	10 / 992 (1.01%)	12 / 990 (1.21%)	7 / 501 (1.40%)
occurrences (all)	10	12	8
Asthma			
subjects affected / exposed	11 / 992 (1.11%)	4 / 990 (0.40%)	4 / 501 (0.80%)
occurrences (all)	12	5	4
Skin and subcutaneous tissue disorders			
Dermatitis contact			

subjects affected / exposed	13 / 992 (1.31%)	10 / 990 (1.01%)	10 / 501 (2.00%)
occurrences (all)	13	10	10
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 992 (0.91%)	11 / 990 (1.11%)	10 / 501 (2.00%)
occurrences (all)	9	11	10
Pain in extremity			
subjects affected / exposed	11 / 992 (1.11%)	8 / 990 (0.81%)	4 / 501 (0.80%)
occurrences (all)	13	9	4
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	49 / 992 (4.94%)	53 / 990 (5.35%)	29 / 501 (5.79%)
occurrences (all)	56	57	29
Pharyngitis			
subjects affected / exposed	20 / 992 (2.02%)	36 / 990 (3.64%)	9 / 501 (1.80%)
occurrences (all)	22	38	9
Nasopharyngitis			
subjects affected / exposed	23 / 992 (2.32%)	23 / 990 (2.32%)	14 / 501 (2.79%)
occurrences (all)	27	29	16
Pharyngitis streptococcal			
subjects affected / exposed	18 / 992 (1.81%)	14 / 990 (1.41%)	15 / 501 (2.99%)
occurrences (all)	19	14	15
Gastroenteritis			
subjects affected / exposed	23 / 992 (2.32%)	11 / 990 (1.11%)	8 / 501 (1.60%)
occurrences (all)	25	11	8
Viral infection			
subjects affected / exposed	14 / 992 (1.41%)	10 / 990 (1.01%)	11 / 501 (2.20%)
occurrences (all)	14	10	11
Sinusitis			
subjects affected / exposed	18 / 992 (1.81%)	11 / 990 (1.11%)	5 / 501 (1.00%)
occurrences (all)	18	12	5
Gastroenteritis viral			
subjects affected / exposed	9 / 992 (0.91%)	8 / 990 (0.81%)	8 / 501 (1.60%)
occurrences (all)	10	8	8
Acute sinusitis			

subjects affected / exposed	5 / 992 (0.50%)	13 / 990 (1.31%)	6 / 501 (1.20%)
occurrences (all)	5	14	6
Otitis media			
subjects affected / exposed	11 / 992 (1.11%)	9 / 990 (0.91%)	2 / 501 (0.40%)
occurrences (all)	12	9	2
Pneumonia			
subjects affected / exposed	7 / 992 (0.71%)	7 / 990 (0.71%)	6 / 501 (1.20%)
occurrences (all)	7	8	6
Viral pharyngitis			
subjects affected / exposed	2 / 992 (0.20%)	6 / 990 (0.61%)	8 / 501 (1.60%)
occurrences (all)	2	6	8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 November 2011	The concomitant treatment section was amended to clarify the guidance for the administration of non study vaccines (other than meningococcal conjugate vaccine [MCV4] and tetanus, diphtheria, and acellular pertussis [Tdap] vaccine) at any time during the study.
18 September 2012	1. Volume of blood draw increased from 10 mL to approximately 20 mL. 2. Added exclusion criterion related to allergen immunotherapy. 3. Added clarification that protocol deviations that exclude subjects from the evaluable immunogenicity population should be determined by the sponsor's global medical monitor.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported