Clinical trial results:
A Phase 3, Single Center, Open-label, Controlled, Randomized Study to Evaluate the Safety and Immunogenicity of Novartis Men ACWY vaccine administered either alone or concomitantly with a Combined Tetanus, Reduced Diphtheria Toxoid, Acellular Pertussis Vaccine (Tdap, Boostrix®) and Quadrivalent Human Papillomavirus [Types 6, 11, 16, 18] Recombinant Vaccine (GARDASIL®) in Healthy Adolescents

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

Summary

EudraCT number	2014-004492-23
Trial protocol	Outside EU/EEA
Global end of trial date	30 September 2008

Results information

Result version number	v2 (current)
This version publication date	04 June 2016
First version publication date	01 March 2015
Version creation reason	• Correction of full data set results need to be updated due to shifting of values

Trial information

Trial identification

Sponsor protocol code	V59P18

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00518180
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Vaccines and Diagnostics S.r.l
Sponsor organisation address	Via Fiorentina, 1, Siena, Italy, 53100
Public contact	Posting Director, Novartis Vaccines and Diagnostics Srl, RegistryContactVaccinesUS@novartis.com
Scientific contact	Posting Director, Novartis Vaccines and Diagnostics Srl, RegistryContactVaccinesUS@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000032-PIP01-07
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	11 February 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 April 2008
Global end of trial reached?	Yes
Global end of trial date	30 September 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that the immune response of MenACWY, when MenACWY is (1) given concomitantly with Tdap and HPV vaccines, is not inferior to MenACWY given alone, and (2) given alone one month after Tdap, is not inferior to MenACWY given alone one month prior to Tdap.
To demonstrate that the immune response to Tdap, when Tdap is given concomitantly with MenACWY and HPV, was not inferior to immune response when Tdap was administered alone.

Protection of trial subjects:

This trial was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP), and the applicable regulatory requirement(s) for the country in which the trial was conducted according to International Conference on Harmonisation (ICH) guidelines, and applicable Standard Operating Procedures (SOPs).

Background therapy:

MenACWY: one 0.5 mL injection of MenACWY was administered Intra Muscular (IM) in the deltoid area of the right arm.
Tdap: one 0.5 mL injection of US-licensed Boostrix vaccine was administered IM in the deltoid area of the left arm.
HPV: one 0.5 mL injection of Gardasil was administered IM in the upper anterolateral area of the thigh.

Evidence for comparator: -

Actual start date of recruitment	19 July 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Costa Rica: 1620
Worldwide total number of subjects	1620
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)	247
Adolescents (12-17 years)	1278
Adults (18-64 years)	95
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at a single center in Costa Rica.

Pre-assignment

Screening details:

All enrolled subjects were randomized at a 1:1:1 ratio to receive MenACWY, Tdap, and HPV vaccines at different schedules.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group I

Arm description:

The MenACWY vaccine was administered concomitantly with the Tdap vaccine and the HPV vaccine at study month 0 followed by two injections of the HPV vaccine at months 2 and 6.

Arm type	Experimental
Investigational medicinal product name	Meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine
Investigational medicinal product code	V59
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

MenACWY: one 0.5 mL injection of MenACWY was administered IM in the deltoid area of the right arm

Arm title	Group II

Arm description:

The MenACWY vaccine was administered at study month 0 followed by one injection of the Tdap vaccine at month 1, followed by three injections of the HPV vaccine at months 2, 4, and 8.

Arm type	Active comparator
Investigational medicinal product name	Meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine
Investigational medicinal product code	V59
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

MenACWY: one 0.5 mL injection of MenACWY was administered IM in the deltoid area of the right arm

Arm title	Group III

Arm description:

Tdap vaccine was administered at month 0 followed by one injection of MenACWY at month 1, followed by three injections of the HPV vaccine at months 2, 4, and 8.

Arm type	Active comparator

Investigational medicinal product name	Meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine
Investigational medicinal product code	V59
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

MenACWY: one 0.5 mL injection of MenACWY was administered IM in the deltoid area of the right arm

Number of subjects in period 1	Group I	Group II	Group III
Started	540	541	539
Completed	475	472	457
Not completed	65	69	82
Consent withdrawn by subject	29	30	42
Adverse event, non-fatal	1	-	-
Administrative reasons	-	2	2
unable to classify	-	2	-
Lost to follow-up	30	28	34
Protocol deviation	5	7	4

Baseline characteristics

Reporting groups	
Reporting group title	Group I
Reporting group description:	
The MenACWY vaccine was administered concomitantly with the Tdap vaccine and the HPV vaccine at study month 0 followed by two injections of the HPV vaccine at months 2 and 6.	
Reporting group title	Group II
Reporting group description:	
The MenACWY vaccine was administered at study month 0 followed by one injection of the Tdap vaccine at month 1, followed by three injections of the HPV vaccine at months 2, 4, and 8.	
Reporting group title	Group III
Reporting group description:	
Tdap vaccine was administered at month 0 followed by one injection of MenACWY at month 1, followed by three injections of the HPV vaccine at months 2, 4, and 8.	

Reporting group values	Group I	Group II	Group III
Number of subjects	540	541	539
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	13.9	13.9	13.8
standard deviation	± 2.1	± 2.2	± 2.2
Gender categorical			
Units: Subjects			
Female	308	309	307
Male	232	232	232

Reporting group values	Total		
Number of subjects	1620		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		

Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	924		
Male	696		

End points

End points reporting groups

Reporting group title	Group I
Reporting group description:	
The MenACWY vaccine was administered concomitantly with the Tdap vaccine and the HPV vaccine at study month 0 followed by two injections of the HPV vaccine at months 2 and 6.	
Reporting group title	Group II
Reporting group description:	
The MenACWY vaccine was administered at study month 0 followed by one injection of the Tdap vaccine at month 1, followed by three injections of the HPV vaccine at months 2, 4, and 8.	
Reporting group title	Group III
Reporting group description:	
Tdap vaccine was administered at month 0 followed by one injection of MenACWY at month 1, followed by three injections of the HPV vaccine at months 2, 4, and 8.	
Subject analysis set title	MenACWY+Tdap+HPV
Subject analysis set type	Per protocol
Subject analysis set description:	
The PP population for immunogenicity analysis included all subjects in the MITT population who provided evaluable serum samples (titer results are available) both before and after vaccination, and had no major protocol deviation. For the HPV analysis only, only subjects negative for anti-HPV at baseline were included in the PP population	
Subject analysis set title	HPV Alone
Subject analysis set type	Per protocol
Subject analysis set description:	
Three injections of the HPV vaccine were administered at study months 2, 4, and 8. This group is a combination of groups II and III	

Primary: 1. Percentage of Subjects With Human Serum Bactericidal Assay (hSBA) Seroresponse

End point title	1. Percentage of Subjects With Human Serum Bactericidal Assay (hSBA) Seroresponse
End point description:	
Immune responses to MenACWY, as measured by the percentage of hSBA seroresponders, when given: (a) alone; (b) concomitantly with a Tetanus diphtheria acellular pertussis(Tdap) vaccine and a Human Papillomavirus Recombinant (HPV) vaccine; and (c) when given one month after a Tdap vaccine. Seroresponse to MenACWY: For a subject with baseline hSBA titer <1:4, seroresponse is defined as a postvaccination hSBA titer ≥ 1:8; for a subject with baseline hSBA titer ≥ 1:4, seroresponse is defined as a postvaccination hSBA titer of at least 4 times the baseline.	
End point type	Primary
End point timeframe:	
1 month post MenACWY vaccination	

End point values	Group I	Group II	Group III	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	494	487	458	
Units: Percentage of Subjects				
number (confidence interval 95%)				
Serogroup A (N=494, 486, 458)	80 (76 to 84)	82 (78 to 85)	87 (83 to 90)	
Serogroup C (N=476, 472, 457)	83 (79 to 86)	84 (81 to 88)	84 (80 to 87)	
Serogroup W (N=487, 474, 458)	77 (73 to 80)	81 (77 to 84)	65 (61 to 70)	

Serogroup Y (N=493, 487, 460)	83 (79 to 86)	82 (79 to 86)	78 (74 to 82)	

Statistical analyses

Statistical analysis title	1.Noninferiority of the immune response to MenACWY

Statistical analysis description:

Immune response to Men A when MenACWY is administered concomitantly with Tdap and HPV, compared with the immune response to MenACWY when administered alone

Comparison groups	Group II v Group I
Number of subjects included in analysis	981
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Method	ANCOVA
Parameter estimate	Vaccine Group Differences
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	3
Variability estimate	Standard deviation

Notes:

[1] - The immunogenicity of MenACWY given concomitantly with HPV and Tdap was considered noninferior to the immunogenicity of MenACWY administered alone if, for each serogroup, the lower limit of the two-sided 95% confidence interaval (CI) for the difference in the percentage of subjects with seroresponse at one month after MenACWY vaccination (PGroup I minus PGroupII) was greater than -10%

Statistical analysis title	2.Noninferiority of the immune response to MenACWY

Statistical analysis description:

Immune response to Men C when MenACWY is administered concomitantly with Tdap and HPV, compared with the immune response to MenACWY when administered alone

Comparison groups	Group I v Group II
Number of subjects included in analysis	981
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Method	ANCOVA
Parameter estimate	Vaccine Group Differences
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	3
Variability estimate	Standard deviation

Notes:

[2] - The immunogenicity of MenACWY given concomitantly with HPV and Tdap was considered noninferior to the immunogenicity of MenACWY administered alone if, for each serogroup, the lower limit of the two-sided 95% confidence interaval (CI) for the difference in the percentage of subjects with seroresponse at one month after MenACWY vaccination (PGroup I minus PGroupII) was greater than

-10%

Statistical analysis title	3.Noninferiority of the immune response to MenACWY

Statistical analysis description:

Immune response to Men W when MenACWY is administered concomitantly with Tdap and HPV, compared with the immune response to MenACWY when administered alone

Comparison groups	Group I v Group II
Number of subjects included in analysis	981
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Method	ANCOVA
Parameter estimate	Vaccine Group Differences
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9
upper limit	1
Variability estimate	Standard deviation

Notes:

[3] - The immunogenicity of MenACWY given concomitantly with HPV and Tdap was considered noninferior to the immunogenicity of MenACWY administered alone if, for each serogroup, the lower limit of the two-sided 95% confidence interaval (CI) for the difference in the percentage of subjects with seroresponse at one month after MenACWY vaccination (PGroup I minus PGroupII) was greater than -10%

Statistical analysis title	4.Noninferiority of the immune response to MenACWY

Statistical analysis description:

Immune response to Men Y when MenACWY is administered concomitantly with Tdap and HPV, compared with the immune response to MenACWY when administered alone

Comparison groups	Group I v Group II
Number of subjects included in analysis	981
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Method	ANCOVA
Parameter estimate	Vaccine Group Differences
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	5
Variability estimate	Standard deviation

Notes:

[4] - The immunogenicity of MenACWY given concomitantly with HPV and Tdap was considered noninferior to the immunogenicity of MenACWY administered alone if, for each serogroup, the lower limit of the two-sided 95% confidence interaval (CI) for the difference in the percentage of subjects with seroresponse at one month after MenACWY vaccination (PGroup I minus PGroupII) was greater than -10%

Statistical analysis title	5.Noninferiority of the immune response to MenACWY

Statistical analysis description:

Immune response to Men A when MenACWY is administered 1 month after Tdap, compared with immune response to MenACWY when administered alone

Comparison groups	Group II v Group III
Number of subjects included in analysis	945
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Method	ANCOVA
Parameter estimate	Vaccine Group Differences
Point estimate	5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	10
Variability estimate	Standard deviation

Notes:

[5] - The immunogenicity of MenACWY given after Tdap was considered noninferior to the immunogenicity of MenACWY administered alone if, for each serogroup, the lower limit of the two-sided 95% CI of the difference in the percentage of subjects with seroresponse at one month after MenACWY vaccination (P Group III minus PGroup II) was greater than -10%

Statistical analysis title	6.Noninferiority of the immune response to MenACWY

Statistical analysis description:

Immune response to Men C when MenACWY is administered 1 month after Tdap, compared with immune response to MenACWY when administered alone

Comparison groups	Group II v Group III
Number of subjects included in analysis	945
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Method	ANCOVA
Parameter estimate	Vaccine Group Differences
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	4
Variability estimate	Standard deviation

Notes:

[6] - The immunogenicity of MenACWY given after Tdap was considered noninferior to the immunogenicity of MenACWY administered alone if, for each serogroup, the lower limit of the two-sided 95% CI of the difference in the percentage of subjects with seroresponse at one month after MenACWY vaccination (P Group III minus PGroup II) was greater than -10%

Statistical analysis title	7.Noninferiority of the immune response to MenACWY

Statistical analysis description:

Immune response to Men W when MenACWY is administered 1 month after Tdap, compared with immune response to MenACWY when administered alone

Comparison groups	Group II v Group III
Number of subjects included in analysis	945
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Method	ANCOVA
Parameter estimate	Vaccine Group Differences
Point estimate	-16

Confidence interval	
level	95 %
sides	2-sided
lower limit	-21
upper limit	-10
Variability estimate	Standard deviation

Notes:

[7] - The immunogenicity of MenACWY given after Tdap was considered noninferior to the immunogenicity of MenACWY administered alone if, for each serogroup, the lower limit of the two-sided 95% CI of the difference in the percentage of subjects with seroresponse at one month after MenACWY vaccination (P Group III minus PGroup II) was greater than -10%

Statistical analysis title	8.Noninferiority of the immune response to MenACWY

Statistical analysis description:

Immune response to Men Y when MenACWY is administered 1 month after Tdap, compared with immune response to MenACWY when administered alone

Comparison groups	Group II v Group III
Number of subjects included in analysis	945
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Method	ANCOVA
Parameter estimate	Vaccine Group Differences
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9
upper limit	1
Variability estimate	Standard deviation

Notes:

[8] - The immunogenicity of MenACWY given after Tdap was considered noninferior to the immunogenicity of MenACWY administered alone if, for each serogroup, the lower limit of the two-sided 95% CI of the difference in the percentage of subjects with seroresponse at one month after MenACWY vaccination (P Group III minus PGroup II) was greater than -10%

Primary: 2. Percentage of Subjects With Antidiphtheria and Antitetanus Toxin ≥1.0 IU/mL

End point title	2. Percentage of Subjects With Antidiphtheria and Antitetanus Toxin ≥1.0 IU/mL[9]

End point description:

To compare the immune response to Tdap given concomitantly with MenACWY and HPV vaccine with the immune response to Tdap when administered alone

End point type	Primary

End point timeframe:

1 month post Tdap vaccination

Notes:

[9] - 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: No statistical analysis is associated to this endpoint.

End point values	Group I	Group III		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	492	487		
Units: Percentages of subjects				
number (confidence interval 95%)				
Diphtheria	100 (99 to 100)	98 (96 to 99)		
Tetanus	100 (99 to 100)	100 (99 to 100)		

Statistical analyses

Statistical analysis title	1.Noninferiority of the immune response to Tdap

Statistical analysis description:

Noninferiority of the immune response to diphtheria antigen, when Tdap is administered concomitantly with MenACWY and HPV, compared with the immune response to Tdap when administered alone

Comparison groups	Group I v Group III
Number of subjects included in analysis	979
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
Method	ANCOVA
Parameter estimate	Vaccine Group Difference
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	4
Variability estimate	Standard deviation

Notes:

[10] - Noninferiority of the immune response to Tdap when administered concomitantly with MenACWY and HPV, compared with the immune response to Tdap when administered alone, was demonstrated for the diphtheria and tetanus antigens if the lower limits of the twosided 95% CIs around the difference in the percentages of subjects with ELISA anti-D toxin and anti-T toxin ≥ 1.0 IU/mL [Group I minus Group III] were greater than -10%

Statistical analysis title	2. Noninferiority of the immune response Tdap

Statistical analysis description:

Noninferiority of the immune response to tetanus antigen, when Tdap is administered concomitantly with MenACWY and HPV, compared with the immune response to Tdap when administered alone

Comparison groups	Group I v Group III
Number of subjects included in analysis	979
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
Method	ANCOVA
Parameter estimate	Vaccine Group Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	1

Variability estimate	Standard deviation

Notes:

[11] - Noninferiority of the immune response to Tdap when administered concomitantly with MenACWY and HPV, compared with the immune response to Tdap when administered alone, was demonstrated for the diphtheria and tetanus antigens if the lower limits of the twosided 95% CIs around the difference in the percentages of subjects with ELISA anti-D toxin and anti-T toxin ≥ 1.0 IU/mL [Group I minus Group III] were greater than -10%

Primary: 3. Geometric Mean Concentrations (GMC) of Antipertussis Toxin [Anti-PT], Antifilamentous Hemagglutinin [Anti-FHA], and Antipertactin [Anti-PRN]

End point title	3. Geometric Mean Concentrations (GMC) of Antipertussis Toxin [Anti-PT], Antifilamentous Hemagglutinin [Anti-FHA], and Antipertactin [Anti-PRN][12]

End point description:

To compare the immune response of Tdap given concomitantly with MenACWY and HPV vaccine with the immune response of Tdap when administered alone

End point type	Primary

End point timeframe:

1 month post Tdap vaccination (Group I and Group III at Visit 2 - Day 31).

Notes:

[12] - 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: No statistical analysis is associated to this endpoint.

End point values	Group I	Group III		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	492	487		
Units: IU/mL				
geometric mean (confidence interval 95%)				
Anti-PT (N=479,477)	51 (47 to 55)	63 (58 to 69)		
Anti-FHA (N=489,485)	342 (310 to 376)	511 (464 to 563)		
Anti-PRN (N=492,487)	819 (727 to 923)	1197 (1061 to 1350)		

Statistical analyses

Statistical analysis title	1.Noninferiority of the immune response to Tdap

Statistical analysis description:

Noninferiority of the immune response to Tdap when administered concomitantly with MenACWY and HPV, compared with the immune response to Tdap when administered alone, for PT antigen

Comparison groups	Group I v Group III
Number of subjects included in analysis	979
Analysis specification	Pre-specified
Analysis type	non-inferiority[13]
Method	ANCOVA
Parameter estimate	Vaccine Group Ratio
Point estimate	0.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	0.9
Variability estimate	Standard deviation

Notes:

[13] - Tdap concomitant with MenACWY was considered noninferior to Tdap alone if, for PT, FHA, and pertactin, the lower limit of the twosided 95% CI for the ratio of the GMCs (GMC Group I / GMC Group III) at one month after vaccination was > 0.67

Statistical analysis title	3.Noninferiority of the immune response to Tdap

Statistical analysis description:

Noninferiority of the immune response to Tdap when administered concomitantly with MenACWY and HPV, compared with the immune response to Tdap when administered alone, for PRN antigen

Comparison groups	Group I v Group III
Number of subjects included in analysis	979
Analysis specification	Pre-specified
Analysis type	non-inferiority[14]
Method	ANCOVA
Parameter estimate	Vaccine Group Ratio
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	0.81
Variability estimate	Standard deviation

Notes:

[14] - Tdap concomitant with MenACWY was considered noninferior to Tdap alone if, for PT, FHA, and pertactin, the lower limit of the twosided 95% CI for the ratio of the GMCs (GMC Group I / GMC Group III) at one month after vaccination was > 0.67

Statistical analysis title	2.Noninferiority of the immune response to Tdap

Statistical analysis description:

Noninferiority of the immune response to Tdap when administered concomitantly with MenACWY and HPV, compared with the immune response to Tdap when administered alone, for FHA antigen

Comparison groups	Group I v Group III
Number of subjects included in analysis	979
Analysis specification	Pre-specified
Analysis type	non-inferiority[15]
Method	ANCOVA
Parameter estimate	Vaccine Group Ratio
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	0.76
Variability estimate	Standard deviation

Notes:

[15] - Tdap concomitant with MenACWY was considered noninferior to Tdap alone if, for PT, FHA, and pertactin, the lower limit of the twosided 95% CI for the ratio of the GMCs (GMC Group I / GMC Group III) at one month after vaccination was > 0.67

Secondary: 4. Effect of Concomitant and Sequential Vaccination on hSBA Geometric Mean Titers (GMTs) for A, C, W, and Y Serogroups

End point title	4. Effect of Concomitant and Sequential Vaccination on hSBA Geometric Mean Titers (GMTs) for A, C, W, and Y Serogroups

End point description:

The immune responses to the MenACWY conjugate vaccine, as measured by the hSBA Geometric Mean Titers (GMTs) when given: (a) alone, (b) concomitantly with the Tdap vaccine and the HPV vaccine, and (c) when given one month after the Tdap vaccine.

End point type	Secondary

End point timeframe:

1 month post MenACWY vaccination

End point values	Group I	Group II	Group III	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	494	487	460	
Units: Titers				
geometric mean (confidence interval 95%)				
Serogroup A (N=494, 486,458)	62 (52 to 74)	67 (56 to 80)	95 (79 to 113)	
Serogroup C (N=476, 472,457)	66 (56 to 77)	70 (60 to 83)	68 (58 to 79)	
Serogroup W (N=487,474, 458)	146 (129 to 165)	159 (140 to 181)	104 (91 to 119)	
Serogroup Y (N=493, 487,460)	72 (62 to 84)	81 (70 to 95)	57 (49 to 67)	

Statistical analyses

No statistical analyses for this end point

Secondary: 5. Percentage of Subjects With Anti-HPV Seroconversion

End point title	5. Percentage of Subjects With Anti-HPV Seroconversion

End point description:

To compare the immune response of HPV vaccine given concomitantly with MenACWY and Tdap to the response when HPV vaccine is given alone. (Immune response against HPV types 6, 11, 16, and 18 was measured at one month after the third HPV vaccination.) Anti-HPV Seroconversion (SC): SC was defined as negative (baseline HPV titer < type-specific cut-off) for anti-HPV and anti-HPV ≥ an HPV type-specific cut-off at one month after the third HPV injection

End point type	Secondary

End point timeframe:

1 month after third HPV vaccination

End point values	MenACWY+Tdap+HPV	HPV Alone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	364	744		
Units: Percentages of subjects				
number (confidence interval 95%)				
HPV 6 (N=361, 737)	99 (98 to 100)	100 (99 to 100)		
HPV 11 (N=362, 744)	100 (99 to 100)	100 (99 to 100)		
HPV 16 (N=360, 744)	100 (99 to 100)	100 (99 to 100)		
HPV 18 (N=364, 743)	100 (98 to 100)	99 (99 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: 6. Anti-HPV Geometric Mean Titers (GMTs)

End point title	6. Anti-HPV Geometric Mean Titers (GMTs)

End point description:

To compare the immune response of HPV vaccine given concomitantly with MenACWY and Tdap to the response when HPV vaccine is given alone. (Immune response against HPV types 6, 11, 16, and 18 was measured at one month after the third HPV vaccine vaccination.)

End point type	Secondary

End point timeframe:

1 month after third HPV vaccination

End point values	MenACWY+Tdap+HPV	HPV Alone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	364	745		
Units: Titers				
geometric mean (confidence interval 95%)				
HPV 6 (N=361, 737)	1059 (926 to 1212)	1461 (1327 to 1608)		
HPV 11 (N=362, 744)	1264 (1134 to 1408)	1701 (1575 to 1837)		
HPV 16 (N=360, 744)	5286 (4705 to 5939)	6590 (6068 to 7158)		
HPV 18 (N=364, 743)	908 (798 to 1032)	1117 (1019 to 1224)		

Statistical analyses

No statistical analyses for this end point

Secondary: 7. Percentage of Subjects With hSBA ≥ 1:8 , hSBA titer ≥ 1:4 for A, C, W, and Y Serogroups

End point title	7. Percentage of Subjects With hSBA ≥ 1:8 , hSBA titer ≥ 1:4 for A, C, W, and Y Serogroups

End point description:

The immune responses to MenACWY, as measured by the number of subjects with hSBA titer ≥ 1:8, hSBA titer ≥ 1:4 when given: (a) alone, (b) concomitantly with Tdap and HPV vaccine; and (c) when given one month after Tdap.

End point type	Secondary

End point timeframe:

1 month post MenACWY vaccination

End point values	Group I	Group II	Group III	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	475	472	457	
Units: Percentage of Subjects				
number (confidence interval 95%)				
Serogroup A¬ hSBA ≥ 1:8 (N=494,486,458)	81 (78 to 85)	82 (79 to 86)	89 (85 to 91)	
Serogroup C- hSBA ≥ 1:8 (N=494,487,457)	92 (89 to 94)	90 (87 to 93)	93 (90 to 95)	
Serogroup W- hSBA ≥ 1:8 (N=487,474,458)	98 (96 to 99)	99 (98 to 100)	95 (93 to 97)	
Serogroup Y- hSBA ≥ 1:8 (N=493,487,460)	93 (90 to 95)	93 (90 to 95)	92 (90 to 95)	
Serogroup A¬ hSBA ≥ 1:4(N=408,404,412)	83 (79 to 86)	83 (79 to 86)	90 (87 to 93)	
Serogroup C- hSBA ≥ 1:4 (N=456,447,430)	92 (90 to 94)	92 (89 to 94)	94 (92 to 96)	
Serogroup W- hSBA ≥ 1:4(N=478,471,443)	98 (97 to 99)	99 (98 to 100)	97 (95 to 98)	
Serogroup Y - hSBA ≥ 1:4 (N=465,456,438)	94 (92 to 96)	94 (91 to 96)	95 (93 to 97)	

Statistical analyses

No statistical analyses for this end point

Secondary: 8. The Effect of Sequential Vaccination on Immunogenicity for Diphtheria and Tetanus

End point title	8. The Effect of Sequential Vaccination on Immunogenicity for Diphtheria and Tetanus[16]

End point description:

To demonstrate that immune response to the Tdap vaccine, as measured by the percentages of subjects with antidiphtheria and antitetanus toxin ≥1.0 IU/mL.

End point type	Secondary

End point timeframe:

1 month post Tdap vaccination

Notes:

[16] - 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: No statistical analysis is associated to this endpoint.

End point values	Group II	Group III		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	458	487		
Units: Percentages of subjects				
number (confidence interval 95%)				
Diphtheria	100 (99 to 100)	98 (96 to 99)		
Tetanus	100 (99 to 100)	100 (99 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: 9. Geometric Mean Concentrations (GMC) for Diphtheria and Tetanus

End point title	9. Geometric Mean Concentrations (GMC) for Diphtheria and Tetanus[17]

End point description:

To compare the immune response of Tdap, as measured by the antidiphtheria and antitetanus GMCs, when administered one month after the MenACWY vaccine with the immune response of the Tdap vaccine when administered alone.

End point type	Secondary

End point timeframe:

1 month post Tdap vaccination (Group II at Visit 3 -Day 61 -and Group III at Visit 2 - Day 31)

Notes:

[17] - 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: No statistical analysis is associated to this endpoint.

End point values	Group II	Group III		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	458	487		
Units: Titers				
geometric mean (confidence interval 95%)				
Diphteria	10 (9.12 to 12)	10 (9.38 to 11)		
Tetanus	12 (11 to 13)	10 (9.46 to 11)		

Statistical analyses

No statistical analyses for this end point

Secondary: 11. Percentages of Subjects With at Least a 4-fold Rise for PT, FHA, and PRN

End point title	11. Percentages of Subjects With at Least a 4-fold Rise for PT, FHA, and PRN[18]

End point description:

To compare the immune response of Tdap, defined by the percentage of subjects with a 4-fold rise in antibody titer over baseline against PT, FHA, PRN, when administered one month after the MenACWY with the immune response of Tdap when administered alone.

End point type	Secondary

End point timeframe:

1 month post Tdap vaccination

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: No statistical analysis is associated to this endpoint.

End point values	Group II	Group III		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	458	487		
Units: Percentage Subjects				
number (confidence interval 95%)				
Anti-PT (N=479, 451,477)	89 (86 to 92)	86 (83 to 89)		
Anti-FHA (N=489, 457,485)	90 (87 to 93)	78 (74 to 82)		
Anti-PRN (N=492, 458,487)	95 (92 to 97)	89 (85 to 91)		

Statistical analyses

No statistical analyses for this end point

Secondary: 12. Number of Subjects With at Least One Reactogenicity Sign After MenACWY and Tdap Vaccination

End point title	12. Number of Subjects With at Least One Reactogenicity Sign After MenACWY and Tdap Vaccination

End point description:

Number of subjects with specified local and systemic reactions were assessed after MenACWY and Tdap vaccinations

End point type	Secondary

End point timeframe:

Days 1 to 7 after MenACWY or Tdap vaccination

End point values	Group I	Group II	Group III	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	540	541	539	
Units: Subjects				
Injection site pain MenACWY	263	246	239	
Injection site pain Tdap	367	310	383	
Injection site erythema MenACWY	68	66	64	

Injection site erythema Tdap	78	38	70	
Injection site induration MenACWY	68	70	63	
Injection site induration Tdap	90	64	110	
Chills postvaccination 1	77	66	70	
Chills postvaccination 2	0	42	45	
Nausea postvaccination 1	88	72	82	
Nausea postvaccination 2	0	42	64	
Malaise postvaccination 1	133	110	115	
Malaise postvaccination 2	0	91	88	
Myalgia postvaccination 1	146	104	142	
Myalgia postvaccination 2	0	81	82	
Arthralgia postvaccination 1	94	62	76	
Arthralgia postvaccination 2	0	52	52	
Headache postvaccination 1	217	194	200	
Headache postvaccination 2	0	125	138	
Rash postvaccination 1	21	17	20	
Rash postvaccination 2	0	15	13	
Fever ≥ 38°Celsius postvaccination 1	27	19	17	
Fever ≥ 38°Celsius postvaccination 2	0	25	30	
Analgesic/Antipyretic Med. Used postvac 1	110	83	96	
Analgesic/Antipyretic Med. Used postvac 2	0	58	49	

Statistical analyses

No statistical analyses for this end point

Secondary: 13. Number of Subjects With at Least One Reactogenicity Sign After Each HPV Vaccination

End point title	13. Number of Subjects With at Least One Reactogenicity Sign After Each HPV Vaccination
End point description:	
Number of subjects with specified local and systemic reactions was solicited for 7 days after the HPV vaccination.	
End point type	Secondary
End point timeframe:	
Days 1 to 7	

End point values	Group I	Group II	Group III	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	540	494	486	
Units: Subjects				
Injection site pain postvaccination 1	265	180	204	
Injection site erythema postvaccination 1	74	36	42	
Injection site induration postvaccination 1	54	27	26	

Injection site pain postvac 2 (N=498, 483, 468)	208	208	189	
Injection site erythema postvaccination 2	62	48	57	
Injection site induration postvaccination 2	46	37	50	
Injection site pain postvaccination 3	229	227	208	
Injection site erythema postvaccination 3	60	56	55	
Injection site induration postvaccination 3	60	47	48	
Chills postvaccination 1	77	27	30	
Nausea postvaccination 1	88	39	32	
Malaise postvaccination 1	133	49	55	
Myalgia postvaccination 1	146	32	56	
Arthralgia postvaccination 1	94	33	28	
Headache postvaccination 1	217	93	97	
Rash postvaccination 1	21	7	6	
Fever (≥ 38°C) postvaccination 1	27	17	20	
Stayed home postvaccination 1	110	26	34	
Chills postvaccination 2	23	22	26	
Nausea postvaccination 2	38	30	29	
Malaise postvaccination 2	53	45	34	
Myalgia postvaccination 2	42	38	51	
Arthralgia postvaccination 2	30	28	21	
Headache postvaccination 2	88	78	71	
Rash postvaccination 2	4	11	9	
Fever (≥ 38°C) postvaccination 2	21	22	16	
Chills postvaccination 3	22	24	25	
Nausea postvaccination 3	32	35	34	
Malaise postvaccination 3	49	50	41	
Myalgia postvaccination 3	53	49	37	
Arthralgia postvaccination 3	37	26	30	
Headache postvaccination 3	79	85	79	
Rash postvaccination 3	9	7	10	
Fever (≥ 38°C) postvaccination 3	23	22	25	

Statistical analyses

No statistical analyses for this end point

Secondary: 10. Geometric Mean Titers (GMTs) of Pertussis Antigens

End point title	10. Geometric Mean Titers (GMTs) of Pertussis Antigens[19]

End point description:

To compare the immune response to Tdap administered one month after MenACWY vaccine with the immune response of the Tdap administered alone.

End point type	Secondary

End point timeframe:

1 month post Tdap vaccination (Group II at Visit 3 - Day 61 - and Group III at Visit 2 - Day 31).

Notes:

[19] - 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: No statistical analysis is associated to this endpoint.

End point values	Group II	Group III		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	458	487		
Units: Titers				
geometric mean (confidence interval 95%)				
Anti-PT (N=451,477)	79 (72 to 87)	63 (58 to 69)		
Anti-FHA (N=457,485)	1106 (989 to 1238)	498 (446 to 556)		
Anti-PRN (N=458,487)	1563 (1390 to 1758)	1180 (1052 to 1323)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Throughout the study period	
Adverse event reporting additional description:	
Data provided in Other Adverse Events (>5%) were collected throughout the study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Group I
Reporting group description:	
The MenACWY vaccine was administered concomitantly with the Tdap vaccine and the HPV vaccine at study month 0 followed by two injections of the HPV vaccine at months 2 and 6.	
Reporting group title	Group II
Reporting group description:	
The MenACWY vaccine was administered at study month 0 followed by one injection of the Tdap vaccine at month 1, followed by three injections of the HPV vaccine at months 2, 4, and 8.	
Reporting group title	Group III
Reporting group description:	
Tdap vaccine was administered at month 0 followed by one injection of MenACWY at month 1, followed by three injections of the HPV vaccine at months 2, 4, and 8.	

Serious adverse events	Group I	Group II	Group III
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 540 (0.19%)	7 / 541 (1.29%)	3 / 539 (0.56%)
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)			
Pituitary tumour benign			
subjects affected / exposed	1 / 540 (0.19%)	0 / 541 (0.00%)	0 / 539 (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
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	0 / 540 (0.00%)	0 / 541 (0.00%)	1 / 539 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Behcet's Syndrome			
subjects affected / exposed	0 / 540 (0.00%)	1 / 541 (0.18%)	0 / 539 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 540 (0.00%)	1 / 541 (0.18%)	1 / 539 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Bezoar			
subjects affected / exposed	0 / 540 (0.00%)	1 / 541 (0.18%)	0 / 539 (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
Reproductive system and breast disorders			
Haemorrhagic Ovarian Cyst			
subjects affected / exposed	0 / 540 (0.00%)	1 / 541 (0.18%)	0 / 539 (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
Testicular Torsion			
subjects affected / exposed	0 / 540 (0.00%)	1 / 541 (0.18%)	0 / 539 (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
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 540 (0.00%)	0 / 541 (0.00%)	1 / 539 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Cushing's Syndrome			
subjects affected / exposed	1 / 540 (0.19%)	0 / 541 (0.00%)	0 / 539 (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	0 / 540 (0.00%)	2 / 541 (0.37%)	0 / 539 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Group I	Group II	Group III
Total subjects affected by non-serious adverse events			
subjects affected / exposed	481 / 540 (89.07%)	449 / 541 (82.99%)	467 / 539 (86.64%)
Nervous system disorders			
headache			
subjects affected / exposed	260 / 540 (48.15%)	284 / 541 (52.50%)	278 / 539 (51.58%)
occurrences (all)	519	749	804
General disorders and administration site conditions			
injection site pain (MenACWY)			
subjects affected / exposed	264 / 540 (48.89%)	246 / 541 (45.47%)	239 / 539 (44.34%)
occurrences (all)	307	289	266
injection site erythema (MenACWY)			
subjects affected / exposed	69 / 540 (12.78%)	66 / 541 (12.20%)	65 / 539 (12.06%)
occurrences (all)	80	68	71
injection site induration(MenACWY)			
subjects affected / exposed	68 / 540 (12.59%)	70 / 541 (12.94%)	65 / 539 (12.06%)
occurrences (all)	76	72	68
injection site erythema (Tdap)			
subjects affected / exposed	78 / 540 (14.44%)	38 / 541 (7.02%)	72 / 539 (13.36%)
occurrences (all)	93	40	82
injection site induration (Tdap)			
subjects affected / exposed	90 / 540 (16.67%)	64 / 541 (11.83%)	110 / 539 (20.41%)
occurrences (all)	101	67	125
injection site pain (HPV)			
subjects affected / exposed	387 / 540 (71.67%)	320 / 541 (59.15%)	313 / 539 (58.07%)
occurrences (all)	778	666	648
injection site induration (HPV)			
subjects affected / exposed	119 / 540 (22.04%)	81 / 541 (14.97%)	84 / 539 (15.58%)
occurrences (all)	178	115	134

injection site erythema (HPV)			
subjects affected / exposed	134 / 540 (24.81%)	105 / 541 (19.41%)	101 / 539 (18.74%)
occurrences (all)	212	147	166
injection site pain (Tdap)			
subjects affected / exposed	367 / 540 (67.96%)	310 / 541 (57.30%)	383 / 539 (71.06%)
occurrences (all)	410	351	428
malaise			
subjects affected / exposed	171 / 540 (31.67%)	209 / 541 (38.63%)	194 / 539 (35.99%)
occurrences (all)	284	402	428
Pyrexia			
subjects affected / exposed	62 / 540 (11.48%)	87 / 541 (16.08%)	83 / 539 (15.40%)
occurrences (all)	77	129	123
chills			
subjects affected / exposed	100 / 540 (18.52%)	117 / 541 (21.63%)	130 / 539 (24.12%)
occurrences (all)	131	201	238
Gastrointestinal disorders			
nausea			
subjects affected / exposed	124 / 540 (22.96%)	133 / 541 (24.58%)	142 / 539 (26.35%)
occurrences (all)	191	255	289
Skin and subcutaneous tissue disorders			
rash			
subjects affected / exposed	31 / 540 (5.74%)	47 / 541 (8.69%)	42 / 539 (7.79%)
occurrences (all)	36	64	66
Musculoskeletal and connective tissue disorders			
myalgia			
subjects affected / exposed	178 / 540 (32.96%)	187 / 541 (34.57%)	200 / 539 (37.11%)
occurrences (all)	276	339	440
arthralgia			
subjects affected / exposed	119 / 540 (22.04%)	131 / 541 (24.21%)	131 / 539 (24.30%)
occurrences (all)	188	225	248

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2007	Amendment 1, dated 15 Oct 2007,changed the number of subjects to be enrolled from 1500 to 1620.
11 March 2008	Amendment 2, dated 11 Mar 2008 (prior to interim database lock), included a change in the study objectives (i.e., to demonstrate that the immune response to MenACWY administered alone one month after Tdap is not inferior to the immune response of MenACWY administered alone one month prior to Tdap was elevated from a secondary to become the third co-primary objective) and the adding of a new laboratory for Tdap testing.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported