

**Clinical trial results:****A Phase IV, Placebo-Controlled, Randomized Study to Evaluate the Immunogenicity and Safety of 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 when Administered with MenACWY Conjugate Vaccine**

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

Summary

EudraCT number	2011-000476-34
Trial protocol	IT
Global end of trial date	20 December 2012

Results information

Result version number	v2 (current)
This version publication date	15 June 2016
First version publication date	12 April 2015
Version creation reason	• Correction of full data set re-QC if the study needed because of EudraCT system glitch and updates are required.

Trial information**Trial identification**

Sponsor protocol code	V59_40
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01424644
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	CR&D Southern Europe, Novartis Vaccines and Diagnostic, +39 0577 249226, noemi.giglioli@novartis.com
Scientific contact	CR&D Southern Europe, Novartis Vaccines and Diagnostic, +39 0577 249226, noemi.giglioli@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No	Yes

1901/2006 apply to this trial?

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 October 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 December 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Immunogenicity Objectives:

Co-primary 1. To demonstrate that the immune response of Tdap given concomitantly with MenACWY-CRM and HPV vaccine is non inferior to the response of Tdap vaccine when given with placebo and HPV when measured at 1 month after 1 dose of Tdap. 2. To demonstrate that the immune response of HPV vaccine given concomitantly with MenACWY and Tdap is non-inferior to the response when HPV is given with placebo and Tdap when measured at 1 month after the third dose of HPV vaccination. Safety objectives: - To describe the safety profile of Tdap + HPV + MenACWY versus Tdap + HPV + placebo

Protection of trial subjects:

This clinical study was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations, including the European Directive 2001/20/EC, the US Code of Federal Regulations Title 21, Novartis codes on the protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 September 2011
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	United States: 554
Country: Number of subjects enrolled	Italy: 247
Worldwide total number of subjects	801
EEA total number of subjects	247

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)	498
Adolescents (12-17 years)	284
Adults (18-64 years)	19
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled from 20 centers located in Italy and USA.

Pre-assignment

Screening details:

All subjects enrolled were included in the trial.

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, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	MenACWY-CRM+Tdap+HPV

Arm description:

Subjects received one dose of Tdap, MenACWY-CRM, and HPV concomitantly on day 1. A second and third dose of HPV was administered at 2 and 6 months, respectively, after the first dose.

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

Dosage and administration details:

After reconstitution, one dose (0.5 ml) of MenACWY injectable solution was administered by IM.

Investigational medicinal product name	Tdap vaccine
Investigational medicinal product code	
Other name	(GSK Boostrix vaccine)
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.5 ml) of Tdap was administered by IM.

Investigational medicinal product name	HPV vaccine
Investigational medicinal product code	
Other name	(Merck & Co. Gardasil vaccine)
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.5 ml) of HPV was administered by IM on day 1, month 2 and 6 months after the first dose.

Arm title	Placebo+Tdap+HPV
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Arm description:

Subjects received one dose of Tdap, placebo, and HPV concomitantly on day 1. A second and third dose of HPV was administered at 2 and 6 months, respectively, after the first dose.

Arm type	Placebo Comparator
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Investigational medicinal product name	Tdap vaccine
Investigational medicinal product code	
Other name	(GSK Boostrix vaccine)
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.5 ml) of Tdap was administered by IM.

Investigational medicinal product name	HPV vaccine
Investigational medicinal product code	
Other name	(Merck & Co. Gardasil vaccine)
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.5 ml) of HPV was administered by IM on day 1, month 2 and 6 months after the first dose.

Investigational medicinal product name	Placebo (NaCl 0.9%)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One 0.5 ml dose of saline placebo was administered by IM injection.

Number of subjects in period 1	MenACWY-CRM+Tdap+HPV	Placebo+Tdap+HPV
Started	402	399
Completed	369	372
Not completed	33	27
Consent withdrawn by subject	9	12
Adverse Event	2	-
Administrative Reason	1	-
Lost to follow-up	16	12
Unable to Classify	1	-
Protocol deviation	4	3

Baseline characteristics

Reporting groups

Reporting group title	MenACWY-CRM+Tdap+HPV
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Reporting group description:

Subjects received one dose of Tdap, MenACWY-CRM, and HPV concomitantly on day 1. A second and third dose of HPV was administered at 2 and 6 months, respectively, after the first dose.

Reporting group title	Placebo+Tdap+HPV
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Reporting group description:

Subjects received one dose of Tdap, placebo, and HPV concomitantly on day 1. A second and third dose of HPV was administered at 2 and 6 months, respectively, after the first dose.

Reporting group values	MenACWY-CRM+Tdap+HPV	Placebo+Tdap+HPV	Total
Number of subjects	402	399	801
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	11.9	11.8	
standard deviation	± 1.7	± 1.5	-
Gender categorical			
Units: Subjects			
Female	169	155	324
Male	233	244	477

End points

End points reporting groups

Reporting group title	MenACWY-CRM+Tdap+HPV
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Reporting group description:

Subjects received one dose of Tdap, MenACWY-CRM, and HPV concomitantly on day 1. A second and third dose of HPV was administered at 2 and 6 months, respectively, after the first dose.

Reporting group title	Placebo+Tdap+HPV
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Reporting group description:

Subjects received one dose of Tdap, placebo, and HPV concomitantly on day 1. A second and third dose of HPV was administered at 2 and 6 months, respectively, after the first dose.

Subject analysis set title	All Enrolled Population
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

The enrolled population contained all subjects enrolled and randomized in the study, ie, all subjects who had data in panel DEMOG. These were subjects who signed informed consent, were enrolled into the study and were randomized. This population was used for the analysis of demographics and all subject listings.

Subject analysis set title	Exposed Population
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Subject analysis set type	Safety analysis
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Subject analysis set description:

All subjects in the enrolled population who received a study vaccination.

Subject analysis set title	MITT Population -Tdap
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

The MITT population included all subjects in the enrolled population who received all the relevant doses of vaccine, and provided at least 1 evaluable serum sample after baseline. For purposes of analysis of this population, subjects were to be included in the group they were assigned to during randomization.

Subject analysis set title	MITT Population- MenACWY
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

The MITT population included all subjects in the enrolled population who received all the relevant doses of vaccine, and provided at least 1 evaluable serum sample after baseline. For purposes of analysis of this population, subjects were to be included in the group they were assigned to during randomization.

Subject analysis set title	Per Protocol (PP) Population - Tdap
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Subject analysis set type	Per protocol
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Subject analysis set description:

The PP population included all subjects in the MITT immunogenicity population who: ◦ correctly received all the relevant doses of vaccine; ◦ provided evaluable serum samples at the relevant time points; and ◦ had no major protocol deviation as defined prior to study unblinding.

Subject analysis set title	Safety Population
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Subject analysis set type	Safety analysis
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Subject analysis set description:

All subjects who had received at least 1 study vaccine and had postbaseline safety data were included in the safety analysis.

Subject analysis set title	Per Protocol (PP) Population- MenACWY
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Subject analysis set type	Per protocol
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Subject analysis set description:

The PP population included all subjects in the MITT immunogenicity population who: ◦ correctly received all the relevant doses of vaccine; ◦ provided evaluable serum samples at the relevant time points; and ◦

Primary: 1. Percentages of Subjects With Anti-diphtheria and Anti-tetanus Antibody Concentrations ≥ 1.0 IU/mL When Tdap is Administered Concomitantly With HPV and MenACWY-CRM Vaccine Compared to Tdap Given Concomitantly With HPV and Placebo

End point title	1. Percentages of Subjects With Anti-diphtheria and Anti-tetanus Antibody Concentrations ≥ 1.0 IU/mL When Tdap is Administered Concomitantly With HPV and MenACWY-CRM Vaccine Compared to Tdap Given Concomitantly With HPV and Placebo
End point description:	The percentages of subjects with anti-diphtheria and anti-tetanus antibody concentrations ≥ 1.0 IU/mL (as measured by ELISA) following concomitant administration of Tdap with HPV and MenACWY-CRM vaccine as compared to concomitant administration of Tdap with HPV and placebo. Analysis was done on the Tdap per protocol population, i.e., all subjects who received all the relevant doses of vaccine correctly, and provided evaluable serum samples at the relevant time points, and had no major protocol violation as defined prior to unblinding.
End point type	Primary
End point timeframe:	1 month post Tdap vaccination

End point values	MenACWY-CRM+Tdap+HPV	Placebo+Tdap+HPV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	376	382		
Units: percentages of subjects				
number (confidence interval 95%)				
Day 1 (diphtheria) (N=375, 380)	5 (3 to 8)	3 (2 to 5)		
One month post dose (diphtheria)	95 (93 to 97)	82 (78 to 86)		
Day 1 (tetanus) (N=375, 380)	28 (24 to 33)	28 (23 to 32)		
One month post dose (tetanus)	99 (97 to 100)	98 (97 to 99)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	Non-inferiority of anti-diphtheria immune response following concomitant administration of Tdap with HPV and MenACWY-CRM as compared to concomitant administration of Tdap with HPV and placebo
Comparison groups	MenACWY-CRM+Tdap+HPV v Placebo+Tdap+HPV
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
Parameter estimate	Vaccine group difference
Point estimate	13

Confidence interval	
level	95 %
sides	2-sided
lower limit	9
upper limit	17

Notes:

[1] - The immune response to diphtheria toxin for the MenACWY-CRM+Tdap+HPV group was considered non-inferior to that of the Placebo+Tdap+HPV group if the lower limit of the two-sided 95% CI of the difference in seroprotection rates [(MenACWYCRM+Tdap+HPV) minus (Placebo+Tdap + HPV)] was greater than -10%, at 1 month after Tdap vaccination

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

Non-inferiority of anti-tetanus immune response following concomitant administration of Tdap with HPV and MenACWY-CRM as compared to concomitant administration of Tdap with HPV and placebo.

Comparison groups	MenACWY-CRM+Tdap+HPV v Placebo+Tdap+HPV
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
Parameter estimate	Vaccine group difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	2

Notes:

[2] - The immune response to tetanus toxin for the MenACWY-CRM+Tdap+HPV group was considered non-inferior to that of Placebo+Tdap+HPV group if the lower limit of the two-sided 95% CI of the difference in seroprotection rates [(MenACWY-CRM+ Tdap+HPV) minus (Placebo+Tdap + HPV)] was greater than -10%, at 1 month after Tdap vaccination.

Primary: 2. Geometric Mean Concentrations of Antibodies Against Pertussis Antigens After Concomitant Administration of Tdap With HPV and MenACWY-CRM Compared to Concomitant Administration of Tdap With HPV and Placebo

End point title	2. Geometric Mean Concentrations of Antibodies Against Pertussis Antigens After Concomitant Administration of Tdap With HPV and MenACWY-CRM Compared to Concomitant Administration of Tdap With HPV and Placebo
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End point description:

The geometric mean concentrations (GMCs) of antibodies against pertussis antigens (Pertussis Toxin (PT), Filamentous Hemagglutinin (FHA) and Pertactin (PRN), as measured by ELISA, following concomitant administration of Tdap with HPV and MenACWY-CRM as compared to concomitant administration of Tdap with HPV and placebo.

Analysis was done on the Tdap per protocol population, i.e., all subjects who received all the relevant doses of vaccine correctly, and provided evaluable serum samples at the relevant time points, and had no major protocol violation as defined prior to unblinding.

End point type	Primary
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End point timeframe:

1 month post Tdap vaccination

End point values	MenACWY-CRM+Tdap+HPV	Placebo+Tdap+HPV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	376	382		
Units: Concentration of antibodies				
geometric mean (confidence interval 95%)				
PT (Day 1) (N= 375, 380)	4.77 (4.11 to 5.53)	4.16 (3.59 to 4.82)		
PT (One month post dose)	44 (40 to 48)	44 (40 to 48)		
FHA (Day 1) (N= 375, 380)	24 (21 to 27)	21 (18 to 23)		
FHA (One month post dose)	202 (187 to 218)	240 (222 to 259)		
PRN (Day 1) (N= 375, 380)	20 (18 to 23)	21 (18 to 24)		
PRN (One month post dose)	330 (300 to 363)	403 (367 to 443)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Non-inferiority of anti-PT immune response following concomitant administration of Tdap with HPV and MenACWY-CRM as compared to concomitant administration of Tdap with HPV and placebo.	
Comparison groups	MenACWY-CRM+Tdap+HPV v Placebo+Tdap+HPV
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[3]
Parameter estimate	Vaccine group ratio of GMCs
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.14

Notes:

[3] - The immune response to PT antigen for the MenACWY-CRM+Tdap+HPV group was considered non-inferior to that of the Placebo+Tdap+HPV group if the lower limit of the two-sided 95% CI of the ratio of the GMCs of the MenACWY-CRM +Tdap+HPV group to the Placebo+Tdap + HPV group was greater than 0.5, at 1 month after Tdap vaccination.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Non-inferiority of anti-FHA immune response following concomitant administration of Tdap with HPV and MenACWY-CRM as compared to concomitant administration of Tdap with HPV and placebo.	
Comparison groups	MenACWY-CRM+Tdap+HPV v Placebo+Tdap+HPV

Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[4]
Parameter estimate	Vaccine group ratio of GMCs
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	0.93

Notes:

[4] - The immune response to FHA antigen for the MenACWY-CRM+Tdap+HPV group was considered non-inferior to that of

Placebo+Tdap+HPV group if the lower limit of the 95% CI of the difference [(MenACWY-CRM +Tdap+HPV) minus (Placebo+Tdap + HPV)] was greater than 0.5, at 1 month after Tdap vaccination.

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Non-inferiority of anti-PRN immune response following concomitant administration of Tdap with HPV and MenACWY-CRM as compared to concomitant administration of Tdap with HPV and placebo.	
Comparison groups	MenACWY-CRM+Tdap+HPV v Placebo+Tdap+HPV
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[5]
Parameter estimate	Vaccine group ratio of GMCs
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	0.93

Notes:

[5] - The immune response to PRN antigen for the MenACWY-CRM+Tdap+HPV group was considered non-inferior to that of

Placebo+Tdap+HPV group if the lower limit of the 95% CI of the difference [(MenACWY-CRM+Tdap+HPV) minus (Placebo+Tdap + HPV)] was greater than 0.5, at 1 month after vaccination.

Secondary: 3. Geometric Mean of Human Serum Bactericidal Assay (hSBA) Titers Against N. meningitidis when MenACWY-CRM is Concomitantly Administered With Tdap and HPV

End point title	3. Geometric Mean of Human Serum Bactericidal Assay (hSBA) Titers Against N. meningitidis when MenACWY-CRM is Concomitantly Administered With Tdap and HPV
End point description:	
The Geometric Mean of hSBA Titers Against N meningitidis Serogroups A, C, W, and Y were determined at 1 Month After MenACWY or Placebo Vaccination.	
End point type	Secondary
End point timeframe:	
1 month post MenACWY-CRM vaccination or Placebo Vaccination	

End point values	MenACWY-CRM+Tdap+HPV	Placebo+Tdap+HPV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	371	99		
Units: Geometric mean of hSBA titers				
geometric mean (confidence interval 95%)				
Men A	35 (29 to 42)	2.13 (1.97 to 2.31)		
Men C (N=370, 97)	59 (48 to 73)	3.92 (3.3 to 4.66)		
Men W (N=369, 96)	61 (53 to 69)	12 (9.26 to 17)		
Men Y (N=369, 97)	48 (40 to 58)	3.54 (2.9 to 4.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: 4. Number of Subjects With Solicited Local and Systemic Adverse Events When Tdap and HPV Are Concomitantly Administered With MenACWY-CRM Compared to When Tdap and HPV Are Concomitantly Administered With Placebo

End point title	4. Number of Subjects With Solicited Local and Systemic Adverse Events When Tdap and HPV Are Concomitantly Administered With MenACWY-CRM Compared to When Tdap and HPV Are Concomitantly Administered With Placebo
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End point description:

The number of subjects reporting solicited local and systemic reactions following concomitant administration of MenACWY-CRM vaccine, Tdap and HPV vaccine as compared to concomitant administration of placebo with Tdap and HPV.

Analysis was done on the safety population.

End point type	Secondary
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End point timeframe:

Day 1-7 after any vaccination

End point values	MenACWY-CRM+Tdap+HPV	Placebo+Tdap+HPV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	389	385		
Units: Subjects				
Local	209	164		
Injection site pain	158	134		
Injection site erythema	65	25		
Injection site induration	61	37		
Systemic	205	179		
Chills	60	50		
Nausea	54	39		
Malaise	57	44		
Myalgia	115	101		

Arthralgia	35	43		
Headache	113	95		
Rash	4	7		
Fever $\geq 38^{\circ}\text{C}$	9	8		
Other	88	80		
Stayed home due to reaction	25	33		
Analgesic / Antipyretic medication used	74	65		

Statistical analyses

No statistical analyses for this end point

Secondary: 5. Number of Subjects With Unsolicited Adverse Events When Tdap and HPV Are Concomitantly Administered With MenACWY-CRM Compared to When Tdap and HPV Are Concomitantly Administered With Placebo

End point title	5. Number of Subjects With Unsolicited Adverse Events When Tdap and HPV Are Concomitantly Administered With MenACWY-CRM Compared to When Tdap and HPV Are Concomitantly Administered With Placebo
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End point description:

The number of subjects reporting any unsolicited adverse reactions (AEs) when Tdap and HPV are concomitantly administered with MenACWY-CRM as compared to when Tdap and HPV vaccine are concomitantly administered with placebo.

Note: A total of 2 MenACWY-CRM+Tdap+HPV subjects reported AEs leading to premature withdrawal - one subject due to treatment emergent AEs and another subject prior to study vaccination on day 1. Analysis was done on the safety population.

End point type	Secondary
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End point timeframe:

Throughout the study (Day 1 to Day 211)

End point values	MenACWY-CRM+Tdap+HPV	Placebo+Tdap+HPV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	396	397		
Units: Subjects				
Any AEs	201	197		
At least possibly related AEs	17	14		
Serious AEs	4	3		
AEs leading to Premature Withdrawal	2	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From day 1 through day 211

Adverse event reporting additional description:

Serious adverse events (SAEs) were collected from Day 1 through Day 211.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	MenACWY-CRM+Tdap+HPV
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Reporting group description:

Subjects received one dose of Tdap, MenACWY-CRM, and HPV concomitantly on day 1. A second and third dose of HPV was administered at 2 and 6 months, respectively, after the first dose.

Reporting group title	Placebo+Tdap+HPV
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Reporting group description:

Subjects received one dose of Tdap, placebo, and HPV concomitantly on day 1. A second and third dose of HPV was administered at 2 and 6 months, respectively, after the first dose.

Serious adverse events	MenACWY-CRM+Tdap+HPV	Placebo+Tdap+HPV	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 396 (1.01%)	3 / 397 (0.76%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 396 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	1 / 396 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	1 / 396 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	0 / 396 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aggression			
subjects affected / exposed	1 / 396 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 396 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 396 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Peritonsillar abscess			
subjects affected / exposed	0 / 396 (0.00%)	1 / 397 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 396 (0.25%)	0 / 397 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	MenACWY- CRM+Tdap+HPV	Placebo+Tdap+HPV	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	289 / 396 (72.98%)	251 / 397 (63.22%)	
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	128 / 396 (32.32%)	106 / 397 (26.70%)	
occurrences (all)	165	146	
General disorders and administration site conditions			
Chills			
alternative assessment type: Systematic			
subjects affected / exposed	66 / 396 (16.67%)	51 / 397 (12.85%)	
occurrences (all)	78	62	
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed	80 / 396 (20.20%)	30 / 397 (7.56%)	
occurrences (all)	93	34	
Injection site induration			
alternative assessment type: Systematic			
subjects affected / exposed	70 / 396 (17.68%)	43 / 397 (10.83%)	
occurrences (all)	75	47	
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed	196 / 396 (49.49%)	167 / 397 (42.07%)	
occurrences (all)	236	207	
Malaise			
alternative assessment type: Systematic			
subjects affected / exposed	59 / 396 (14.90%)	46 / 397 (11.59%)	
occurrences (all)	72	55	
Gastrointestinal disorders			
Nausea			
alternative assessment type: Systematic			
subjects affected / exposed	59 / 396 (14.90%)	43 / 397 (10.83%)	
occurrences (all)	73	57	
Musculoskeletal and connective tissue disorders			

Arthralgia alternative assessment type: Systematic subjects affected / exposed occurrences (all)	40 / 396 (10.10%) 49	49 / 397 (12.34%) 56	
Myalgia alternative assessment type: Systematic subjects affected / exposed occurrences (all)	118 / 396 (29.80%) 136	112 / 397 (28.21%) 125	
Infections and infestations Pharyngitis subjects affected / exposed occurrences (all)	22 / 396 (5.56%) 23	21 / 397 (5.29%) 25	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2011	Amendment No. 1. The amendment included clarifications and revisions primarily related to operational aspects of the protocol.
19 July 2011	Amendment No. 2. The rationale for the amendment was the requirement to switch from MenACWY prefilled syringe and vial presentation to a vial-vial presentation, as well as to require that all female subjects have a negative urine pregnancy test before enrollment, instead of only female subjects of child bearing potential.
20 December 2012	Amendment No. 3. The third amendment dated 20 JUN 2013, was due to delays associated with testing of immune response to HPV types at an external laboratory. The protocol was revised to include a stepwise analysis for the 2 coprimary objectives as follows. A final analysis including all safety data and immunogenicity data for the first primary and secondary objectives would be conducted on cleaned data. The results of this analysis would be presented in the clinical study report, including individual listings and unblinded data. The immunogenicity analysis for the second primary objective (assessment of immune response against HPV antigens) would be performed as soon as serological results become available. The HPV results would be presented in an addendum to the clinical study report. This change was communicated to and accepted by regulatory authorities in the US and Italy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported