Clinical trial results:
A Phase II Study of the Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Healthy Adolescents

Summary

EudraCT number	2016-001963-35
Trial protocol	Outside EU/EEA
Global end of trial date	02 October 2015

Results information

Result version number	v1 (current)
This version publication date	05 January 2019
First version publication date	05 January 2019

Trial information

Trial identification

Sponsor protocol code	MET50

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02199691
WHO universal trial number (UTN)	U1111-1143-8537
Other trial identifiers	BB-IND: 14171

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur Inc.
Sponsor organisation address	1 Discovery Drive, Swiftwater, United States, 18370
Public contact	Trial Transparency Team, Sanofi Pasteur , Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi Pasteur , Contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001930-PIP01-16
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 May 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the antibody responses to the antigens present in Meningococcal Polysaccharide (Serogroups A, C, Y and W) Tetanus Toxoid (MenACYW) conjugate vaccine when MenACYW conjugate vaccine was given alone compared to those when MENVEO vaccine was given alone.

Protection of trial subjects:

Vaccinations were performed by qualified and trained study personnel. Subjects with allergy to any of the vaccine components were not vaccinated. After vaccination, subjects were also kept under clinical observation for 30 minutes to ensure their safety. Appropriate medical equipment was also available on site in case of any immediate allergic reactions.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 July 2014
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: 1715
Worldwide total number of subjects	1715
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)	1356
Adolescents (12-17 years)	359
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled in 40 centers in the Unites States (US) from 22 July 2014 to 25 February 2015.

Pre-assignment

Screening details:

A total of 1715 subjects who met all of the inclusion criteria and none of the exclusion criteria were enrolled and randomized in the study.

Period 1

Period 1 title	Overall trial (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 1: MenACYW Conjugate Vaccine

Arm description:

Healthy, meningococcal-vaccine naïve subjects aged 10 to 17 years received a single dose of MenACYW conjugate vaccine.

Arm type	Experimental
Investigational medicinal product name	MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, single dose on Day 0.

Arm title	Group 2: MENVEO® Vaccine

Arm description:

Healthy, meningococcal-vaccine naive subjects aged 10 to 17 years received a single dose of MENVEO® vaccine.

Arm type	Active comparator
Investigational medicinal product name	MENVEO®: Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM197 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:

0.5 mL, intramuscular, single dose on Day 0.

Arm title	Group 3: MenACYW conjugate vaccine+Tdap+HPV

Arm description:

Healthy, meningococcal-vaccine naïve subjects aged 10 to 17 years received a single dose of the MenACYW conjugate vaccine, Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap), and 3 doses of Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant (HPV). HPV Dose 2 and Dose 3 were given 2 and 6 months, respectively, after Dose 1 given on Day 0.

Arm type	Experimental

Investigational medicinal product name	MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, single dose on Day 0.

Investigational medicinal product name	Tdap: Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed
Investigational medicinal product code	
Other name	Adacel®
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, single dose on Day 0.

Investigational medicinal product name	HPV: Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant
Investigational medicinal product code	
Other name	GARDASIL®
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, single dose each on Day 0, Day 60, and Day 180.

Arm title	Group 4: Tdap+HPV

Arm description:

Healthy, meningococcal-vaccine naïve subjects aged 10 to 17 years received a single dose of Tdap and 3 doses of HPV. HPV Dose 2 and Dose 3 were given 2 and 6 months, respectively, after Dose 1 given on Day 0.

Arm type	Active comparator
Investigational medicinal product name	Tdap: Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed
Investigational medicinal product code	
Other name	Adacel®
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, single dose on Day 0.

Investigational medicinal product name	HPV: Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant
Investigational medicinal product code	
Other name	GARDASIL®
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL, intramuscular, single dose each on Day 0, Day 60, and Day 180.

Number of subjects in period 1	Group 1: MenACYW Conjugate Vaccine	Group 2: MENVEO® Vaccine	Group 3: MenACYW conjugate vaccine+Tdap+HPV
Started	505	507	403
Completed	495	500	376
Not completed	10	7	27
Consent withdrawn by subject	5	3	12
Lost to follow-up	2	1	9
Protocol deviation	3	3	6

Number of subjects in period 1	Group 4: Tdap+HPV
Started	300
Completed	270
Not completed	30
Consent withdrawn by subject	13
Lost to follow-up	10
Protocol deviation	7

Baseline characteristics

Reporting groups	
Reporting group title	Group 1: MenACYW Conjugate Vaccine
Reporting group description:	
Healthy, meningococcal-vaccine naïve subjects aged 10 to 17 years received a single dose of MenACYW conjugate vaccine.	
Reporting group title	Group 2: MENVEO® Vaccine
Reporting group description:	
Healthy, meningococcal-vaccine naive subjects aged 10 to 17 years received a single dose of MENVEO® vaccine.	
Reporting group title	Group 3: MenACYW conjugate vaccine+Tdap+HPV
Reporting group description:	
Healthy, meningococcal-vaccine naïve subjects aged 10 to 17 years received a single dose of the MenACYW conjugate vaccine, Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap), and 3 doses of Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant (HPV). HPV Dose 2 and Dose 3 were given 2 and 6 months, respectively, after Dose 1 given on Day 0.	
Reporting group title	Group 4: Tdap+HPV
Reporting group description:	
Healthy, meningococcal-vaccine naïve subjects aged 10 to 17 years received a single dose of Tdap and 3 doses of HPV. HPV Dose 2 and Dose 3 were given 2 and 6 months, respectively, after Dose 1 given on Day 0.	

Reporting group values	Group 1: MenACYW Conjugate Vaccine	Group 2: MENVEO® Vaccine	Group 3: MenACYW conjugate vaccine+Tdap+HPV
Number of subjects	505	507	403
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	405	396	320
Adolescents (12-17 years)	100	111	83
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	11.4	11.4	11.3
standard deviation	± 1.39	± 1.39	± 1.06
Gender categorical Units: Subjects			
Female	259	232	197
Male	246	275	206

Reporting group values	Group 4: Tdap+HPV	Total	
Number of subjects	300	1715	

Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	235	1356	
Adolescents (12-17 years)	65	359	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	11.4		
standard deviation	± 1.41	-	
Gender categorical Units: Subjects			
Female	144	832	
Male	156	883	

End points

End points reporting groups

Reporting group title	Group 1: MenACYW Conjugate Vaccine
Reporting group description:	
Healthy, meningococcal-vaccine naïve subjects aged 10 to 17 years received a single dose of MenACYW conjugate vaccine.	
Reporting group title	Group 2: MENVEO® Vaccine
Reporting group description:	
Healthy, meningococcal-vaccine naive subjects aged 10 to 17 years received a single dose of MENVEO® vaccine.	
Reporting group title	Group 3: MenACYW conjugate vaccine+Tdap+HPV
Reporting group description:	
Healthy, meningococcal-vaccine naïve subjects aged 10 to 17 years received a single dose of the MenACYW conjugate vaccine, Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap), and 3 doses of Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant (HPV). HPV Dose 2 and Dose 3 were given 2 and 6 months, respectively, after Dose 1 given on Day 0.	
Reporting group title	Group 4: Tdap+HPV
Reporting group description:	
Healthy, meningococcal-vaccine naïve subjects aged 10 to 17 years received a single dose of Tdap and 3 doses of HPV. HPV Dose 2 and Dose 3 were given 2 and 6 months, respectively, after Dose 1 given on Day 0.	

Primary: Percentages of Subjects Achieving Serum Bactericidal Assay Using Human Complement (hSBA) Vaccine Seroresponse for Meningococcal Serogroups A, C, Y, and W Following Vaccination With Either MenACYW Conjugate Vaccine or MENVEO® Vaccine

End point title	Percentages of Subjects Achieving Serum Bactericidal Assay Using Human Complement (hSBA) Vaccine Seroresponse for Meningococcal Serogroups A, C, Y, and W Following Vaccination With Either MenACYW Conjugate Vaccine or MENVEO® Vaccine[1]

End point description:

Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA. The hSBA vaccine seroresponse for serogroups A, C, Y, and W was defined as post-vaccination hSBA titers >= 1:8 for subjects with pre-vaccination hSBA titers < 1:8 or at least a 4-fold increase in hSBA titers from pre- to post-vaccination for subjects with pre-vaccination hSBA titers >= 1:8. Analysis was performed on Per-Protocol Analysis Set-1 (PPAS-1) defined for accessing the ACYW and the Tdap immune response data for all subjects after they had received vaccination(s) at Visit 1 (Day 0) and completed blood sampling (BL) at Visit 2 (Day 30). Here 'n' signifies number of subjects with available data for specified category, for each arm respectively.

End point type	Primary

End point timeframe:

Day 30 (post-vaccination)

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: The statistical comparison was planned to be analysed for the reported arms only.

End point values	Group 1: MenACYW Conjugate Vaccine	Group 2: MENVEO® Vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	463	464		
Units: Percentage of subjects				
number (confidence interval 95%)				
Serogroup A (n= 463, 464)	75.6 (71.4 to 79.4)	66.4 (61.9 to 70.7)		
Serogroup C (n= 462, 463)	97.2 (95.2 to 98.5)	72.6 (68.3 to 76.6)		
Serogroup Y (n= 462, 464)	97.0 (95.0 to 98.3)	80.8 (76.9 to 84.3)		
Serogroup W (n= 463, 464)	86.2 (82.7 to 89.2)	66.6 (62.1 to 70.9)		

Statistical analyses

Statistical analysis title	Serogroup A
Comparison groups	Group 1: MenACYW Conjugate Vaccine v Group 2: MENVEO® Vaccine
Number of subjects included in analysis	927
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Percentage Difference
Point estimate	9.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.4
upper limit	15

Notes:

[2] - 95% confidence interval (CI) of the difference was calculated from the Wilson Score Method without continuity correction. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference between the 2 percentages was > -10%.

Statistical analysis title	Serogroup C

Statistical analysis description:

Actual number of subjects analyzed = 925

Comparison groups	Group 1: MenACYW Conjugate Vaccine v Group 2: MENVEO® Vaccine
Number of subjects included in analysis	927
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Percentage Difference
Point estimate	24.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.3
upper limit	29

Notes:

[3] - 95% CI of the difference was calculated from the Wilson Score Method without continuity correction. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference between the 2 percentages was > -10%.

Statistical analysis title	Serogroup Y

Statistical analysis description:

Actual number of subjects analyzed = 926

Comparison groups	Group 1: MenACYW Conjugate Vaccine v Group 2: MENVEO® Vaccine
Number of subjects included in analysis	927
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	Percentage Difference
Point estimate	16.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.3
upper limit	20.2

Notes:

[4] - 95% CI of the difference was calculated from the Wilson Score Method without continuity correction. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference between the 2 percentages was > -10%.

Statistical analysis title	Serogroup W
Comparison groups	Group 1: MenACYW Conjugate Vaccine v Group 2: MENVEO® Vaccine
Number of subjects included in analysis	927
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	Percentage Difference
Point estimate	19.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.2
upper limit	24.8

Notes:

[5] - 95% CI of the difference was calculated from the Wilson Score Method without continuity correction. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference between the 2 percentages was > -10%.

Secondary: Percentages of Subjects Achieving hSBA Vaccine Seroresponse for Meningococcal Serogroups A, C, Y, and W Following Vaccination With Either MenACYW Conjugate Vaccine or MenACYW Conjugate Vaccine Given with Tdap and HPV Vaccines

End point title	Percentages of Subjects Achieving hSBA Vaccine Seroresponse for Meningococcal Serogroups A, C, Y, and W Following Vaccination With Either MenACYW Conjugate Vaccine or MenACYW Conjugate Vaccine Given with Tdap and HPV Vaccines[6]

End point description:

Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA. The hSBA vaccine seroresponse for serogroups A, C, Y, and W was defined as post-vaccination hSBA titers >= 1:8 for subjects with pre-vaccination hSBA titers < 1:8 or at least a 4-fold increase in hSBA titers from pre- to post-vaccination for subjects with pre-vaccination hSBA titers >= 1:8. Analysis was performed on PPAS-

1. Here 'n' signifies number of subjects with available data for specified category, for each arm respectively.

End point type	Secondary

End point timeframe:

Day 30 (post-vaccination)

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: The statistical comparison was planned to be analysed for the reported arms only.

End point values	Group 1: MenACYW Conjugate Vaccine	Group 3: MenACYW conjugate vaccine+Tdap+HPV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	463	360		
Units: Percentage of subjects				
number (not applicable)				
Serogroup A (n= 463, 360)	75.6	80.6		
Serogroup C (n= 462, 360)	97.2	97.2		
Serogroup Y (n= 462, 360)	97.0	95.6		
Serogroup W (n= 463, 360)	86.2	83.9		

Statistical analyses

Statistical analysis title	Serogroup A
Comparison groups	Group 1: MenACYW Conjugate Vaccine v Group 3: MenACYW conjugate vaccine+Tdap+HPV
Number of subjects included in analysis	823
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Parameter estimate	Percentage Difference
Point estimate	5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	10.5

Notes:

[7] - 95% CI of the difference was calculated from the Wilson Score Method without continuity correction. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference between the 2 percentages was > -10%.

Statistical analysis title	Serogroup C

Statistical analysis description:

Actual number of subjects analyzed = 822.

Comparison groups	Group 1: MenACYW Conjugate Vaccine v Group 3: MenACYW conjugate vaccine+Tdap+HPV

Number of subjects included in analysis	823
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Parameter estimate	Percentage Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	2.4

Notes:

[8] - 95% CI of the difference was calculated from the Wilson Score Method without continuity correction. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference between the 2 percentages was > -10%.

Statistical analysis title	Serogroup Y

Statistical analysis description:

Actual number of subjects analyzed = 822.

Comparison groups	Group 1: MenACYW Conjugate Vaccine v Group 3: MenACYW conjugate vaccine+Tdap+HPV
Number of subjects included in analysis	823
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
Parameter estimate	Percentage Difference
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	1.2

Notes:

[9] - 95% CI of the difference was calculated from the Wilson Score Method without continuity correction. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference between the 2 percentages was > -10%.

Statistical analysis title	Serogroup W
Comparison groups	Group 1: MenACYW Conjugate Vaccine v Group 3: MenACYW conjugate vaccine+Tdap+HPV
Number of subjects included in analysis	823
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
Parameter estimate	Percentage Difference
Point estimate	-2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	2.6

Notes:

[10] - 95% CI of the difference was calculated from the Wilson Score Method without continuity correction. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference between the 2 percentages was > -10%.

Secondary: Geometric Mean Concentrations (GMCs) of PT, FHA, PRN, and FIM Antibodies Following Vaccination with Either MenACYW Conjugate Vaccine Given

With Tdap and HPV Vaccines or Tdap and HPV Vaccines	
End point title	Geometric Mean Concentrations (GMCs) of PT, FHA, PRN, and FIM Antibodies Following Vaccination with Either MenACYW Conjugate Vaccine Given With Tdap and HPV Vaccines or Tdap and HPV Vaccines[11]

End point description:

Anti-Pertussis toxoid (PT), Filamentous hemagglutinin (FHA), Pertactin (PRN), and Fimbriae types 2 and 3 (FIM) antibodies were measured by enzyme-linked immunosorbent assay (ELISA). Analysis was performed on PPAS-1. Here 'n' signifies number of subjects with available data for specified category, for each arm respectively.

End point type	Secondary

End point timeframe:

Day 30 (post-vaccination)

Notes:

[11] - 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: The statistical comparison was planned to be analysed for the reported arms only.

End point values	Group 3: MenACYW conjugate vaccine+Tdap+HPV	Group 4: Tdap+HPV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	360	263		
Units: ELISA units (EU)/mL				
geometric mean (confidence interval 95%)				
PT (n= 339, 258)	37.5 (33.8 to 41.7)	44.4 (39.5 to 49.9)		
FHA (n= 358, 263)	180 (168 to 194)	242 (218 to 268)		
PRN (n= 360, 263)	200 (177 to 225)	265 (231 to 304)		
FIM (n= 350, 262)	339 (285 to 403)	499 (414 to 601)		

Statistical analyses

Statistical analysis title	PT: Geometric Mean Ratio

Statistical analysis description:

Actual number of subjects analyzed = 597

Comparison groups	Group 3: MenACYW conjugate vaccine+Tdap+HPV v Group 4: Tdap+HPV
Number of subjects included in analysis	623
Analysis specification	Pre-specified
Analysis type	non-inferiority[12]
Parameter estimate	Geometric Mean Ratio
Point estimate	0.845

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.722
upper limit	0.99

Notes:

[12] - 95% CI of the difference was calculated from the Wilson Score Method without continuity correction. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the ratio was >2/3.

Statistical analysis title	FHA: Geometric Mean Ratio

Statistical analysis description:

Actual number of subjects analyzed = 621

Comparison groups	Group 3: MenACYW conjugate vaccine+Tdap+HPV v Group 4: Tdap+HPV
Number of subjects included in analysis	623
Analysis specification	Pre-specified
Analysis type	non-inferiority[13]
Parameter estimate	Geometric Mean Ratio
Point estimate	0.746
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.661
upper limit	0.842

Notes:

[13] - 95% CI of the difference was calculated from the Wilson Score Method without continuity correction. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the ratio was >2/3.

Statistical analysis title	PRN: Geometric Mean Ratio
Comparison groups	Group 3: MenACYW conjugate vaccine+Tdap+HPV v Group 4: Tdap+HPV
Number of subjects included in analysis	623
Analysis specification	Pre-specified
Analysis type	non-inferiority[14]
Parameter estimate	Geometric Mean Ratio
Point estimate	0.753
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.627
upper limit	0.903

Notes:

[14] - 95% CI of the difference was calculated from the Wilson Score Method without continuity correction. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the ratio was >2/3.

Statistical analysis title	FIM: Geometric Mean Ratio

Statistical analysis description:

Actual number of subjects analyzed = 612

Comparison groups	Group 3: MenACYW conjugate vaccine+Tdap+HPV v Group 4: Tdap+HPV

Number of subjects included in analysis	623
Analysis specification	Pre-specified
Analysis type	non-inferiority[15]
Parameter estimate	Geometric Mean Ratio
Point estimate	0.679
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.525
upper limit	0.878

Notes:

[15] - 95% CI of the difference was calculated from the Wilson Score Method without continuity correction. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the ratio was >2/3.

Secondary: Percentage of Subjects Achieving Anti-Tetanus and Anti-Diphtheria Concentrations >= 1.0 International Unit (IU)/mL Following Vaccination With Either MenACYW Conjugate Vaccine Given With Tdap and HPV Vaccines or Tdap and HPV Vaccines

End point title	Percentage of Subjects Achieving Anti-Tetanus and Anti-Diphtheria Concentrations >= 1.0 International Unit (IU)/mL Following Vaccination With Either MenACYW Conjugate Vaccine Given With Tdap and HPV Vaccines or Tdap and HPV Vaccines[16]

End point description:

Anti-Diphtheria antibodies were measured by a toxin neutralization test. Anti-Tetanus antibodies were measured by ELISA. Analysis was performed on PPAS-1. Here 'n' signifies number of subjects with available data for specified category, for each arm respectively.

End point type	Secondary

End point timeframe:

Day 30 (post-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: The statistical comparison was planned to be analysed for the reported arms only.

End point values	Group 3: MenACYW conjugate vaccine+Tdap+HPV	Group 4: Tdap+HPV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	360	263		
Units: percentage of subjects				
number (confidence interval 95%)				
Diphtheria (n =360, 263)	97.8 (95.7 to 99.0)	98.9 (96.7 to 99.8)		
Tetanus (n=360, 262)	99.7 (98.5 to 100.0)	99.6 (97.9 to 100.0)		

Statistical analyses

Statistical analysis title	Serogroup Diphtheria
Comparison groups	Group 3: MenACYW conjugate vaccine+Tdap+HPV v Group 4: Tdap+HPV
Number of subjects included in analysis	623
Analysis specification	Pre-specified
Analysis type	non-inferiority[17]
Parameter estimate	Percentage Difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	1.3

Notes:

[17] - 95% CI of the difference was calculated from the Wilson Score Method without continuity correction. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference between the 2 percentages was >-10%.

Statistical analysis title	Serogroup Tetanus

Statistical analysis description:

Actual number of subjects analyzed = 622

Comparison groups	Group 3: MenACYW conjugate vaccine+Tdap+HPV v Group 4: Tdap+HPV
Number of subjects included in analysis	623
Analysis specification	Pre-specified
Analysis type	non-inferiority[18]
Parameter estimate	Percentage Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	1.9

Notes:

[18] - 95% CI of the difference was calculated from the Wilson Score Method without continuity correction. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference between the 2 percentages was >-10%.

Secondary: Percentage of Subjects Achieving Seroconversion for Anti-HPV6, HPV11, HPV16, and HPV18 Antibodies Following Vaccination With Either MenACYW Conjugate Vaccine Given With Tdap and HPV Vaccines or Tdap and HPV Vaccines

End point title	Percentage of Subjects Achieving Seroconversion for Anti-HPV6, HPV11, HPV16, and HPV18 Antibodies Following Vaccination With Either MenACYW Conjugate Vaccine Given With Tdap and HPV Vaccines or Tdap and HPV Vaccines[19]

End point description:

Anti-HPV 6, 11, 16, and 18 antibodies were measured using a competitive Luminex immunoassay. Seroconversion was defined as changing serostatus from seronegative to seropositive. Cutoff values for HPV seropositivity were >= 20 milli-Merck units per milliliter (mMU/mL) for types 6 and 16, >= 16 mMU/mL for type 11, and >= 24mMU/mL for type 18. Analysis was performed on Per-Protocol Analysis Set-2 (PPAS-2) defined for accessing the HPV immune response data for subjects in Group 3 and in Group 4 after they had received the third HPV vaccination at Visit 4 and complete blood sample at Visit 5 (BL3 [Day 210]).

End point type	Secondary

End point timeframe:

Day 210 (post-vaccination)

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: The statistical comparison was planned to be analysed for the reported arms only.

End point values	Group 3: MenACYW conjugate vaccine+Tdap+HPV	Group 4: Tdap+HPV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	242	164		
Units: Percentage of subjects				
number (confidence interval 95%)				
HPV Type 6	97.5 (94.7 to 99.1)	95.7 (91.4 to 98.3)		
HPV Type 11	99.6 (97.7 to 100.0)	98.8 (95.7 to 99.9)		
HPV Type 16	99.2 (97.0 to 99.9)	98.8 (95.7 to 99.9)		
HPV Type 18	99.2 (97.0 to 99.9)	98.8 (95.7 to 99.9)		

Statistical analyses

Statistical analysis title	HPV Type 6
Comparison groups	Group 3: MenACYW conjugate vaccine+Tdap+HPV v Group 4: Tdap+HPV
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	non-inferiority[20]
Parameter estimate	Percentage Difference
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	6.3

Notes:

[20] - 95% CI of the difference was calculated from the Wilson Score Method without continuity correction. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference between the 2 percentages was >-10%.

Statistical analysis title	HPV Type 11
Comparison groups	Group 3: MenACYW conjugate vaccine+Tdap+HPV v Group 4: Tdap+HPV
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	non-inferiority[21]
Parameter estimate	Percentage Difference
Point estimate	0.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	3.9

Notes:

[21] - 95% CI of the difference was calculated from the Wilson Score Method without continuity correction. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference between the 2 percentages was >-10%.

Statistical analysis title	HPV Type 16
Comparison groups	Group 3: MenACYW conjugate vaccine+Tdap+HPV v Group 4: Tdap+HPV
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	non-inferiority[22]
Parameter estimate	Percentage Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	3.6

Notes:

[22] - 95% CI of the difference was calculated from the Wilson Score Method without continuity correction. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference between the 2 percentages was >-10%.

Statistical analysis title	HPV Type 18
Comparison groups	Group 3: MenACYW conjugate vaccine+Tdap+HPV v Group 4: Tdap+HPV
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	non-inferiority[23]
Parameter estimate	Percentage Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	3.6

Notes:

[23] - 95% CI of the difference was calculated from the Wilson Score Method without continuity correction. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference between the 2 percentages was >-10%.

Secondary: Percentage of Subjects Reporting Solicited Injection Site Reactions (Pain, Erythema, Swelling) Following Vaccination at Day 0: Group 1 and Group 2

End point title	Percentage of Subjects Reporting Solicited Injection Site Reactions (Pain, Erythema, Swelling) Following Vaccination at Day 0: Group 1 and Group 2[24]

End point description:

A solicited reaction was an Adverse Event (AE) that was prelisted in the electronic Case Report Form (eCRF) and considered to be related to vaccination. Solicited injection site reactions: Pain, Erythema, Swelling. Percentages of subjects with at least one solicited injection site reactions were reported. Analysis was performed on safety analysis set defined as those subjects who had received at least one dose of the trial vaccine(s) and had any safety data available. All subjects had their safety data analysed

according to the vaccine(s) they actually received. Here 'n' signifies number of subjects with available data for specified category, for each arm respectively.

End point type	Secondary

End point timeframe:

Within 7 days after vaccines injections at Day 0

Notes:

[24] - 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: Arms applicable for this endpoint are reported.

End point values	Group 1: MenACYW Conjugate Vaccine	Group 2: MENVEO® Vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	503	501		
Units: percentage of subjects				
number (not applicable)				
MenACYW/MENVEO: Pain (n=496, 492)	45.2	42.5		
MenACYW/MENVEO: Erythema (n=496, 491)	5.0	7.5		
MenACYW/MENVEO: Swelling (n=496, 491)	5.4	6.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reporting Solicited Injection Site Reactions (Pain, Erythema, Swelling) Following Vaccination at Day 0: Group 3

End point title	Percentage of Subjects Reporting Solicited Injection Site Reactions (Pain, Erythema, Swelling) Following Vaccination at Day 0: Group 3[25]

End point description:

A solicited reaction was an AE that was prelisted in the eCRF and considered to be related to vaccination. Solicited injection site reactions: Pain, Erythema, Swelling. Percentages of subjects with at least one solicited injection site reactions were reported. Analysis was performed on safety analysis set. Here, subjects analysed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

Within 7 days after vaccines injections at Day 0

Notes:

[25] - 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: Only arm applicable for this endpoint is reported.

End point values	Group 3: MenACYW conjugate vaccine+Tdap+ HPV			
Subject group type	Reporting group			
Number of subjects analysed	388			
Units: percentage of subjects				
number (not applicable)				
MenACYW/MENVEO: Pain	47.2			
MenACYW/MENVEO: Erythema	3.9			
MenACYW/MENVEO: Swelling	4.4			
Tdap: Pain	73.7			
Tdap: Erythema	7.2			
Tdap: Swelling	6.2			
HPV: Pain	74.2			
HPV: Erythema	8.0			
HPV: Swelling	6.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reporting Solicited Injection Site Reactions (Pain, Erythema, Swelling) Following Vaccination at Day 0: Group 4

End point title	Percentage of Subjects Reporting Solicited Injection Site Reactions (Pain, Erythema, Swelling) Following Vaccination at Day 0: Group 4[26]

End point description:

A solicited reaction was an AE that was prelisted in the eCRF and considered to be related to vaccination. Solicited injection site reactions: Pain, Erythema, Swelling. Percentages of subjects with at least one solicited injection site reactions were reported. Analysis was performed on safety analysis set. Here, subjects analysed = subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Within 7 days after vaccines injections at Day 0

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only arm applicable for this endpoint is reported.

End point values	Group 4: Tdap+HPV			
Subject group type	Reporting group			
Number of subjects analysed	289			
Units: percentage of subjects				
number (not applicable)				
Tdap: Pain	73.0			
Tdap: Erythema	4.8			
Tdap: Swelling	6.9			
HPV: Pain	69.6			
HPV: Erythema	5.5			

HPV: Swelling	8.0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE data were collected from Day 0 up to Day 30 post-vaccination. Solicited Reaction (SR) data were collected from Day 0 up to Day 7 post-vaccination.

Adverse event reporting additional description:

A SR was an AE that was prelisted (i.e.,solicited) in the eCRF and considered to be related to vaccination (adverse drug reaction). An unsolicited AE was an observed AE that did not fulfill the conditions prelisted in the eCRF (i.e.,solicited) in terms of symptom and/or onset post-vaccination. Safety Analysis Set.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Group 1 MenACYW

Reporting group description:

Healthy, meningococcal-vaccine naïve subjects aged 10 to 17 years received a single dose of MenACYW conjugate vaccine.

Reporting group title	Group 2: MENVEO® Vaccine

Reporting group description:

Healthy, meningococcal-vaccine naive subjects aged 10 to 17 years received a single dose of MENVEO® vaccine.

Reporting group title	Group 3: MenACYW conjugate vaccine+Tdap+HPV

Reporting group description:

Healthy, meningococcal-vaccine naïve subjects aged 10 to 17 years received a single dose of the MenACYW conjugate vaccine, Tdap, and 3 doses of HPV. HPV Dose 2 and Dose 3 were given 2 and 6 months, respectively, after Dose 1 given on Day 0.

Reporting group title	Group 4: Tdap+HPV

Reporting group description:

Healthy, meningococcal-vaccine naïve subjects aged 10 to 17 years received a single dose of Tdap and 3 doses of HPV. HPV Dose 2 and Dose 3 were given 2 and 6 months, respectively, after Dose 1 given on Day 0.

Serious adverse events	Group 1 MenACYW	Group 2: MENVEO® Vaccine	Group 3: MenACYW conjugate vaccine+Tdap+HPV
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 503 (0.80%)	4 / 501 (0.80%)	4 / 392 (1.02%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 503 (0.20%)	0 / 501 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Mucosal Inflammation			
subjects affected / exposed	1 / 503 (0.20%)	0 / 501 (0.00%)	0 / 392 (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			
Faecaloma			
subjects affected / exposed	1 / 503 (0.20%)	0 / 501 (0.00%)	0 / 392 (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
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 503 (0.00%)	0 / 501 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Erythema Multiforme			
subjects affected / exposed	0 / 503 (0.00%)	1 / 501 (0.20%)	0 / 392 (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			
Abnormal Behaviour			
subjects affected / exposed	0 / 503 (0.00%)	1 / 501 (0.20%)	0 / 392 (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
Major Depression			
subjects affected / exposed	0 / 503 (0.00%)	1 / 501 (0.20%)	0 / 392 (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
Suicidal Ideation			
subjects affected / exposed	0 / 503 (0.00%)	0 / 501 (0.00%)	1 / 392 (0.26%)
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			
Hypothyroidism			

subjects affected / exposed	0 / 503 (0.00%)	0 / 501 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 503 (0.00%)	1 / 501 (0.20%)	0 / 392 (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
Staphylococcal Scalded Skin Syndrome			
subjects affected / exposed	0 / 503 (0.00%)	0 / 501 (0.00%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Type 1 Diabetes Mellitus			
subjects affected / exposed	1 / 503 (0.20%)	0 / 501 (0.00%)	0 / 392 (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

Serious adverse events	Group 4: Tdap+HPV		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 296 (1.35%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 296 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Mucosal Inflammation			
subjects affected / exposed	0 / 296 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Faecaloma			

subjects affected / exposed	0 / 296 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 296 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Erythema Multiforme			
subjects affected / exposed	0 / 296 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Abnormal Behaviour			
subjects affected / exposed	0 / 296 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Major Depression			
subjects affected / exposed	0 / 296 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicidal Ideation			
subjects affected / exposed	1 / 296 (0.34%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 296 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			

subjects affected / exposed	2 / 296 (0.68%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Staphylococcal Scalded Skin Syndrome			
subjects affected / exposed	1 / 296 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Type 1 Diabetes Mellitus			
subjects affected / exposed	0 / 296 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Group 1 MenACYW	Group 2: MENVEO® Vaccine	Group 3: MenACYW conjugate vaccine+Tdap+HPV
Total subjects affected by non-serious adverse events			
subjects affected / exposed	331 / 503 (65.81%)	338 / 501 (67.47%)	348 / 392 (88.78%)
Nervous system disorders			
Headache			
subjects affected / exposed	155 / 503 (30.82%)	159 / 501 (31.74%)	137 / 392 (34.95%)
occurrences (all)	166	169	145
General disorders and administration site conditions			
Injection Site Erythema			
subjects affected / exposed	25 / 503 (4.97%)	37 / 501 (7.39%)	44 / 392 (11.22%)
occurrences (all)	25	37	74
Injection Site Pain			
subjects affected / exposed	224 / 503 (44.53%)	209 / 501 (41.72%)	327 / 392 (83.42%)
occurrences (all)	224	209	759
Injection Site Swelling			
subjects affected / exposed	27 / 503 (5.37%)	32 / 501 (6.39%)	42 / 392 (10.71%)
occurrences (all)	27	32	67
Malaise			

subjects affected / exposed	130 / 503 (25.84%)	131 / 501 (26.15%)	113 / 392 (28.83%)
occurrences (all)	130	131	113
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	175 / 503 (34.79%)	174 / 501 (34.73%)	239 / 392 (60.97%)
occurrences (all)	175	174	239
Infections and infestations			
Pharyngitis			
subjects affected / exposed	15 / 503 (2.98%)	32 / 501 (6.39%)	22 / 392 (5.61%)
occurrences (all)	15	34	22
Upper Respiratory Tract Infection			
subjects affected / exposed	24 / 503 (4.77%)	30 / 501 (5.99%)	27 / 392 (6.89%)
occurrences (all)	27	33	31

Non-serious adverse events	Group 4: Tdap+HPV		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	263 / 296 (88.85%)		
Nervous system disorders			
Headache			
subjects affected / exposed	87 / 296 (29.39%)		
occurrences (all)	90		
General disorders and administration site conditions			
Injection Site Erythema			
subjects affected / exposed	24 / 296 (8.11%)		
occurrences (all)	30		
Injection Site Pain			
subjects affected / exposed	234 / 296 (79.05%)		
occurrences (all)	412		
Injection Site Swelling			
subjects affected / exposed	32 / 296 (10.81%)		
occurrences (all)	43		
Malaise			
subjects affected / exposed	81 / 296 (27.36%)		
occurrences (all)	81		
Musculoskeletal and connective tissue disorders			

Myalgia subjects affected / exposed occurrences (all)	161 / 296 (54.39%) 161		
Infections and infestations Pharyngitis subjects affected / exposed occurrences (all) Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	 14 / 296 (4.73%) 16 12 / 296 (4.05%) 13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 September 2014	Following amendments were made: Clarified the collection dates of safety data, the timing of the third dose of HPV and additional vaccinations during the study period, and that parents (not subjects) would be interviewed concerning safety data; updated batch numbers for the vaccines and clarified how each vaccine would be supplied; clarified the presentation of the antibody concentrations or titers, the procedure to follow if the site staff were unable to obtain the first blood draw, and the timelines for Visits 3, 4, and 5; added the collection of concomitant medications during the review of the memory aid, clarified the follow-up of early terminated subjects, clarified that site staff will verify the subject's number on the label prior to drawing blood, improved the clarity of the text regarding serious adverse events (SAE), clarified the definition (and timing of collection) of the medically-attended adverse events of special interest (MAAESIs) and the definition of the second per-protocol analysis set; and also clarified that an interim analyses will be conducted on data collected up to Visit 2 and that subjects and/or the parent may receive a stipend for participation in the study.
17 February 2015	Added a preliminary analysis to the study plan; clarified follow-up and visit timing for 6 month follow-up and Visit 5, the reporting and collection of MAAESIs and SAEs, and the definition of any unplanned contact of a physician's office; corrected the window (and days) for Visit 3 and Visit 4 to comply with Advisory Committee on Immunization Practices recommendations for the HPV vaccination schedule; updated the trial calendar; updated the description of the HPV assay; prioritized HPV testing; added Celsius scale temperature ranges; and amended the interim analysis section.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported