Clinical trial results:
Immunogenicity and Safety of a Booster Dose of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Adolescents and Adults

Summary

EudraCT number	2018-001470-18
Trial protocol	Outside EU/EEA
Global end of trial date	19 December 2016

Results information

Result version number	v1 (current)
This version publication date	02 January 2019
First version publication date	02 January 2019

Trial information

Trial identification

Sponsor protocol code	MET56

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02752906
WHO universal trial number (UTN)	U1111-1161-2710

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur Inc.
Sponsor organisation address	1 Discovery Drive, Swiftwater, PA, 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority of the vaccine seroresponse of meningococcal serogroups A, C, Y, and W following the administration of a booster dose of Meningococcal Polysaccharide (Serogroups A, C, Y and W) Tetanus Toxoid (MenACYW) conjugate vaccine compared to those observed following the administration of a booster dose of a Menactra® in subjects who were first vaccinated with 1 dose of a quadrivalent meningococcal vaccine 4 to 10 years before the booster dose.

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 were also available on site in case of any immediate allergic reactions.

Background therapy: -

Evidence for comparator:

Menactra® was used as active treatment control.

Actual start date of recruitment	15 April 2016
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: 810
Worldwide total number of subjects	810
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)	0
Adolescents (12-17 years)	427
Adults (18-64 years)	383

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled in 30 centers in the United States and Puerto Rico from 15 April 2016 to 02 August 2016.

Pre-assignment

Screening details:

A total of 810 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 Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1: MenACYW Conjugate Vaccine

Arm description:

Healthy, meningococcal vaccine-primed adolescents (>= 15 to < 18 years) or adults (>= 18 years) received a single dose of a MenACYW conjugate vaccine.

Arm type	Experimental
Investigational medicinal product name	MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, Y, and W-135) 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: Menactra ®

Arm description:

Healthy, meningococcal- vaccine-primed adolescents (>= 15 to < 18 years) or adults (>= 18 years) received a single dose of Menactra ® vaccine.

Arm type	Active comparator
Investigational medicinal product name	Menactra ® : Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria 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.

Number of subjects in period 1	Group 1: MenACYW Conjugate Vaccine	Group 2: Menactra ®
Started	403	407
Vaccinated	402	407
Completed	396	402
Not completed	7	5
Consent withdrawn by subject	2	2
Lost to follow-up	3	2
Protocol deviation	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Group 1: MenACYW Conjugate Vaccine
Reporting group description:	
Healthy, meningococcal vaccine-primed adolescents (>= 15 to < 18 years) or adults (>= 18 years) received a single dose of a MenACYW conjugate vaccine.	
Reporting group title	Group 2: Menactra ®
Reporting group description:	
Healthy, meningococcal- vaccine-primed adolescents (>= 15 to < 18 years) or adults (>= 18 years) received a single dose of Menactra ® vaccine.	

Reporting group values	Group 1: MenACYW Conjugate Vaccine	Group 2: Menactra ®	Total
Number of subjects	403	407	810
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	20.0	19.9	
standard deviation	± 5.96	± 5.59	-
Gender categorical			
Units: Subjects			
Female	207	200	407
Male	196	207	403

End points

End points reporting groups

Reporting group title	Group 1: MenACYW Conjugate Vaccine
Reporting group description:	
Healthy, meningococcal vaccine-primed adolescents (>= 15 to < 18 years) or adults (>= 18 years) received a single dose of a MenACYW conjugate vaccine.	
Reporting group title	Group 2: Menactra ®
Reporting group description:	
Healthy, meningococcal- vaccine-primed adolescents (>= 15 to < 18 years) or adults (>= 18 years) received a single dose of Menactra ® vaccine.	

Primary: Percentage of Subjects With Seroresponse to Meningococcal Serogroups A, C, Y, and W Following Vaccination With Either MenACYW Conjugate Vaccine or Menactra® Vaccine

End point title	Percentage of Subjects With Seroresponse to Meningococcal Serogroups A, C, Y, and W Following Vaccination With Either MenACYW Conjugate Vaccine or Menactra® Vaccine
End point description:	
The serum bactericidal assay using human complement (hSBA) vaccine seroresponse for serogroups A, C, Y, and W was defined as post-vaccination hSBA titers >= 1:16 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-2 (PPAS2) defined for evaluating the immune response of MenACYW vaccine measured by hSBA assessed at Day 30 after vaccination.	
End point type	Primary
End point timeframe:	
Day 30 (post-vaccination)	

End point values	Group 1: MenACYW Conjugate Vaccine	Group 2: Menactra ®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	384	389		
Units: Percentage of subjects				
number (confidence interval 95%)				
Serogroup A	92.2 (89.0 to 94.7)	87.1 (83.4 to 90.3)		
Serogroup C	97.1 (94.9 to 98.6)	91.8 (88.6 to 94.3)		
Serogroup Y	97.4 (95.3 to 98.7)	95.6 (93.1 to 97.4)		
Serogroup W	98.2 (96.3 to 99.3)	90.7 (87.4 to 93.4)		

Statistical analyses

Statistical analysis title	Serogroup A

Statistical analysis description:

95% confidence interval (CI) of the difference was calculated from the Wilson Score Method without continuity correction. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions was > -10%, the non- inferiority assumption was rejected.

Comparison groups	Group 1: MenACYW Conjugate Vaccine v Group 2: Menactra ®
Number of subjects included in analysis	773
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Percentage Difference
Point estimate	5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.735
upper limit	9.38

Statistical analysis title	Serogroup C

Statistical analysis description:

95% CI of the difference was calculated from the Wilson Score Method without continuity correction. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions was > -10%, the non-inferiority assumption was rejected.

Comparison groups	Group 1: MenACYW Conjugate Vaccine v Group 2: Menactra ®
Number of subjects included in analysis	773
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Percentage Difference
Point estimate	5.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.16
upper limit	8.76

Statistical analysis title	Serogroup Y

Statistical analysis description:

95% CI of the difference was calculated from the Wilson Score Method without continuity correction. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions was > -10%, the non-inferiority assumption was rejected.

Comparison groups	Group 1: MenACYW Conjugate Vaccine v Group 2: Menactra ®
Number of subjects included in analysis	773
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Percentage Difference
Point estimate	1.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.907
upper limit	4.55

Statistical analysis title	Serogroup W

Statistical analysis description:

95% CI of the difference was calculated from the Wilson Score Method without continuity correction. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions was > -10%, the non-inferiority assumption was rejected.

Comparison groups	Group 1: MenACYW Conjugate Vaccine v Group 2: Menactra ®
Number of subjects included in analysis	773
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Percentage Difference
Point estimate	7.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.3
upper limit	10.9

Secondary: Percentage of Subjects With Seroresponse to Meningococcal Serogroups A, C, Y, and W Following Vaccination With Either MenACYW Conjugate Vaccine or Menactra® Vaccine at Day 06 After Vaccination

End point title	Percentage of Subjects With Seroresponse to Meningococcal Serogroups A, C, Y, and W Following Vaccination With Either MenACYW Conjugate Vaccine or Menactra® Vaccine at Day 06 After Vaccination

End point description:

The hSBA vaccine seroresponse for serogroups A, C, Y, and W was defined as post-vaccination hSBA titers >= 1:16 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 (PPAS1) defined for evaluating the immune response of MenACYW vaccine measured by hSBA assessed at Day 06 after vaccination.

End point type	Secondary

End point timeframe:

Day 06 (post-vaccination)

End point values	Group 1: MenACYW Conjugate Vaccine	Group 2: Menactra ®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	62		
Units: Percentage of subjects				

number (confidence interval 95%)				
Serogroup A	72.7 (59.0 to 83.9)	66.1 (53.0 to 77.7)		
Serogroup C	83.6 (71.2 to 92.2)	87.1 (76.1 to 94.3)		
Serogroup Y	90.9 (80.0 to 97.0)	83.9 (72.3 to 92.0)		
Serogroup W	94.5 (84.9 to 98.9)	83.9 (72.3 to 92.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers (GMTs) Against Meningococcal Serogroups A, C, Y, and W Following Vaccination With Either MenACYW Conjugate Vaccine or Menactra® Vaccine

End point title	Geometric Mean Titers (GMTs) Against Meningococcal Serogroups A, C, Y, and W Following Vaccination With Either MenACYW Conjugate Vaccine or Menactra® Vaccine

End point description:

Meningococcal antibody responses against Serogroups A, C, Y, and W were measured by hSBA. Analysis was performed on PPAS2.

End point type	Secondary

End point timeframe:

Day 30 (post-vaccination)

End point values	Group 1: MenACYW Conjugate Vaccine	Group 2: Menactra ®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	384	389		
Units: Ratio				
geometric mean (confidence interval 95%)				
Serogroup A	497 (436 to 568)	296 (256 to 343)		
Serogroup C	2618 (2227 to 3078)	599 (504 to 711)		
Serogroup Y	2070 (1807 to 2371)	811 (699 to 941)		
Serogroup W	1747 (1508 to 2025)	723 (614 to 853)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Solicited Injection Site Reactions or Systemic Reactions Following Vaccination With Either MenACYW Conjugate Vaccine or Menactra® Vaccine

End point title	Number of Subjects With Solicited Injection Site Reactions or Systemic Reactions Following Vaccination With Either MenACYW Conjugate Vaccine or Menactra® Vaccine

End point description:

Solicited injection site reactions: Pain (Grade 1: no interference with activity, Grade 2: some interference with activity, Grade 3: significantly prevent daily activity), erythema and swelling (Grade 1: >=25 mm to <= 50 mm, Grade 2: >=51 to <=100 mm, Grade 3: > 100 mm). Solicited systemic reactions: Fever (Grade 1: >=38.0 degree Celsius (°C) to <=38.4°C, Grade 2: >=38.5°C to <=38.9 °C, Grade 3: >= 39°C), headache, malaise, and myalgia. Number of subjects with any of the Grade 1, 2 or 3 solicited injection-site and systemic reactions were reported. Analysis was performed on Safety Analysis Set which included subjects who have received at least one dose of the study vaccine and have any safety data available. 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 post-vaccination

End point values	Group 1: MenACYW Conjugate Vaccine	Group 2: Menactra ®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	402	407		
Units: Subjects				
number (not applicable)				
Pain- Any Grade (n=398,402)	178	196		
Pain- Grade 1 (n=398,402)	141	154		
Pain- Grade 2 (n=398,402)	33	34		
Pain- Grade 3 (n=398,402)	4	8		
Erythema- Any Grade (n=398,402)	20	6		
Erythema- Grade 1 (n=398,402)	18	5		
Erythema- Grade 2 (n=398,402)	2	1		
Erythema- Grade 3 (n=398,402)	0	0		
Swelling- Any Grade (n=398,402)	16	3		
Swelling- Grade 1 (n=398,402)	13	1		
Swelling- Grade 2 (n=398,402)	3	2		
Swelling- Grade 3 (n=398,402)	0	0		
Fever- Any Grade (n=390,395)	0	2		
Fever- Grade 1 (n=390,395)	0	0		
Fever- Grade 2 (n=390,395)	0	1		
Fever- Grade 3 (n=390,395)	0	1		
Headache- Any Grade (n=398,402)	151	134		
Headache- Grade 1 (n=398,402)	90	73		
Headache- Grade 2 (n=398,402)	52	47		
Headache- Grade 3 (n=398,402)	9	14		
Malaise- Any Grade (n=398,402)	110	108		
Malaise- Grade 1 (n=398,402)	62	64		
Malaise- Grade 2 (n=398,402)	37	30		
Malaise- Grade 3 (n=398,402)	11	14		
Myalgia- Any Grade (n=398,402)	146	156		

Myalgia- Grade 1 (n=398,402)	98	120		
Myalgia- Grade 2 (n=398,402)	40	27		
Myalgia- Grade 3 (n=398,402)	8	9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event (AE) data were collected from Day 0 up to Day 30 post-vaccination. Solicited Reaction (SR) 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 electronic case report form (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	18.0

Reporting groups

Reporting group title	Group 1: MenACYW Conjugate Vaccine

Reporting group description:

Healthy, meningococcal-vaccine naive adolescents (>= 15 to < 18 years) or adults (>= 18 years) received a single dose of a MenACYW conjugate vaccine.

Reporting group title	Group 2: Menactra ®

Reporting group description:

Healthy, meningococcal-vaccine naive adolescents (>= 15 to < 18 years) or adults (>= 18 years) received a single dose of Menactra vaccine.

Serious adverse events	Group 1: MenACYW Conjugate Vaccine	Group 2: Menactra ®	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 402 (1.24%)	4 / 407 (0.98%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Clavicle Fracture			
subjects affected / exposed	1 / 402 (0.25%)	0 / 407 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	0 / 402 (0.00%)	1 / 407 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			

Allergy To Arthropod Sting			
subjects affected / exposed	1 / 402 (0.25%)	0 / 407 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal Perforation			
subjects affected / exposed	0 / 402 (0.00%)	1 / 407 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary Embolism			
subjects affected / exposed	1 / 402 (0.25%)	0 / 407 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 402 (0.25%)	0 / 407 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Major Depression			
subjects affected / exposed	0 / 402 (0.00%)	1 / 407 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal Ideation			
subjects affected / exposed	0 / 402 (0.00%)	1 / 407 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 402 (0.25%)	0 / 407 (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	Group 1: MenACYW Conjugate Vaccine	Group 2: Menactra ®	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	255 / 402 (63.43%)	263 / 407 (64.62%)	
Nervous system disorders			
Headache			
subjects affected / exposed	155 / 402 (38.56%)	137 / 407 (33.66%)	
occurrences (all)	168	152	
General disorders and administration site conditions			
Injection Site Pain			
subjects affected / exposed	178 / 402 (44.28%)	196 / 407 (48.16%)	
occurrences (all)	178	196	
Malaise			
subjects affected / exposed	110 / 402 (27.36%)	108 / 407 (26.54%)	
occurrences (all)	110	108	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	147 / 402 (36.57%)	158 / 407 (38.82%)	
occurrences (all)	148	161	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 January 2016	Following amendments were made: Clarified that subjects could have received only 1 dose of a quadrivalent meningococcal conjugate vaccine; Clarified actions to be taken if a subject came in at the end of the Day 30 visit window but had received antibiotic therapy within the 3 days before the visit.
25 March 2016	Provided the batch number of the investigational product; clarified the vaccination history of potential subjects; updated the presentation of the definition of hSBA vaccine seroresponse after feedback received from the Center for Biologics Evaluation and Research (CBER), US Food and Drug Administration (FDA); clarified the location of the laboratories for hSBA and serum bactericidal assay using baby rabbit complement (rSBA) testing; clarified the higher priority of hSBA sample testing.
29 November 2016	Provided the identity and information for the Coordinating Investigator.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported