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<b>Sponsor:</b> Sanofi Pasteur <b>Drug substance:</b> Quadrivalent Meningococcal ACYW Conjugate Vaccine	<b>Study Identifiers:</b> U1111-1161-3060, NCT02842853, 2018-001468-48 <b>Study code:</b> MET43
<b>Title of the study:</b> Immune Lot Consistency, Immunogenicity, and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Adolescents and Adults Aged 10 to 55 Years	
<b>Study centers:</b> This was a multi-center trial conducted at approximately 90 sites in the United States (US).	
<b>Study period:</b> Date first subject enrolled: 15/Jul/2016 Date last subject completed: 28/Feb/2017	
<b>Phase of development:</b> III	
<b>Objectives:</b> <b>Primary Objectives:</b> 1) To demonstrate the immune lot consistency of the antibody responses to meningococcal serogroups A, C, Y, and W following the administration of a single dose of MenACYW conjugate vaccine with respect to serum bactericidal assay using human complement (hSBA) geometric mean titers (GMTs) 2) To demonstrate the non-inferiority of the antibody responses to meningococcal serogroups A, C, Y, and W following the administration of a single dose of MenACYW conjugate vaccine (pooled Lots 1 to 3) compared to those observed following the administration of a single dose of Menactra® <b>Secondary Objectives:</b> 1) To demonstrate the non-inferiority of the antibody responses to meningococcal serogroups A, C, Y, and W following the administration of a single dose of MenACYW conjugate vaccine (pooled Lots 1 to 3) compared to those observed following the administration of a single dose of Menactra® in the adult population (18 to 55 years old) 2) To demonstrate the non-inferiority of the antibody responses to meningococcal serogroups A, C, Y, and W following the administration of a single dose of MenACYW conjugate vaccine (pooled Lots 1 to 3) compared to those observed following the administration of a single dose of Menactra® in the adolescent population (10 to 17 years old) 3) To compare the hSBA vaccine seroresponses of meningococcal serogroups A, C, Y, and W for each of 3 lots of MenACYW conjugate vaccine 30 days (+14 days) after vaccination 4) To compare the hSBA antibody GMTs of meningococcal serogroups A, C, Y, and W following the administration of MenACYW conjugate vaccine to those observed following the administration of Menactra®	
<b>Methodology:</b> This was a Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center study to evaluate immune lot consistency of MenACYW conjugate vaccine, evaluate the immune non-inferiority versus Menactra®, and describe the safety and additional immunogenicity of study vaccines in adolescents and adults aged 10 to 55 years in the US. Healthy, meningococcal-vaccine naïve adolescents and adults were randomized in a 3:3:3:2 ratio to the following groups: <ul style="list-style-type: none"><li>• <b>Group 1: MenACYW conjugate vaccine (Lot 1)</b><ul style="list-style-type: none"><li>• Group 1a: 400 subjects 10 to 17 years of age</li><li>• Group 1b: 500 subjects 18 to 55 years of age</li></ul></li></ul>	

- **Group 2: MenACYW conjugate vaccine (Lot 2)**
  - Group 2a: 400 subjects 10 to 17 years of age
  - Group 2b: 500 subjects 18 to 55 years of age
- **Group 3: MenACYW conjugate vaccine (Lot 3)**
  - Group 3a: 400 subjects 10 to 17 years of age
  - Group 3b: 500 subjects 18 to 55 years of age
- **Group 4: Menactra®**
  - Group 4a: 300 subjects 10 to 17 years of age
  - Group 4b: 300 subjects 18 to 55 years of age

All subjects were to provide blood samples for immunogenicity assessment at baseline (pre-vaccination) and at 30 to 44 days post-vaccination. Solicited adverse event (AE) information was collected for 7 days after vaccination, unsolicited AE information was collected from Visit 1 (V01) (Day [D] 0) to V02 (D30 [+14 days]), and serious adverse event (SAE) information was collected from D0 through D180 (+14 days) after vaccination. Medically-attended adverse events (MAAEs) were collected throughout the study from V01 to V02 (as part of the collection of unsolicited AE information) and from V02 through D180 (+14 days) (as MAAEs).

**Number of subjects:**           Planned: 3300  
   Randomized: 3344  
   Vaccinated: 3344

**Evaluated:**  
   Immunogenicity: 3101  
   Safety: 3311

**Diagnosis and criteria for inclusion:**

A potential subject had to meet all of the following criteria to be considered for trial enrollment:

- 1) Aged 10 to 55 years on the day of inclusion
- 2) Informed consent form (ICF) has been signed and dated by the subject (aged 18 to 55 years) or assent form has been signed and dated by the subject and ICF has been signed and dated by the parent(s) or guardian (for subjects aged 10 to < 18 years)
- 3) Subject (≥18 years) or subject (10 to < 18 years) and parent / guardian are able to attend all scheduled visits and to comply with all trial procedures

**Study treatments**

**Investigational product:** Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine (Sanofi Pasteur Inc., Swiftwater, PA, USA)

Form: Liquid Solution

Composition: Each 0.5 milliliters (mL) dose of MenACYW conjugate vaccine is formulated in sodium acetate buffered saline solution to contain the following ingredients:

Meningococcal capsular polysaccharides:

- Serogroup A ----- 10 micrograms (µg)
- Serogroup C ----- 10 µg
- Serogroup Y ----- 10 µg
- Serogroup W ----- 10 µg

<p>Tetanus toxoid protein carrier ----- approximately 65 µg</p> <p>Route of administration: Intramuscular (IM)</p>
<p><b>Control product:</b> Menactra®: Meningococcal (Groups A, C, Y, and W 135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine (Sanofi Pasteur Inc., Swiftwater, PA, USA) Solution for injection</p> <p>Form: Solution for injection</p> <p>Composition: Each 0.5 mL dose of vaccine is formulated in sodium phosphate buffered isotonic sodium chloride solution to contain the following ingredients:</p> <p>Serogroup A ----- 4 µg</p> <p>Serogroup C ----- 4 µg</p> <p>Serogroup Y ----- 4 µg</p> <p>Serogroup W 135 ----- 4 µg</p> <p>Diphtheria toxoid protein carrier ----- approximately 48 µg</p> <p>Route of administration: IM</p>
<p><b>Duration of treatment/participation:</b> The duration of each subject's participation in the trial was approximately 6 months.</p>
<p><b>Criteria for evaluation:</b></p> <p><b>Immunogenicity:</b></p> <p>Primary endpoints:</p> <ol style="list-style-type: none"> <li>1) Geometric mean titer ratios (GMTRs) of antibodies against meningococcal serogroups A, C, Y, and W measured by hSBA 30 days (+14 days) after vaccination between lots for immune lot consistency</li> <li>2) Vaccine seroresponse of meningococcal serogroups A, C, Y, and W measured by hSBA assessed at baseline (D0, before vaccination) and 30 days (+14 days) after vaccination for immune non-inferiority between MenACYW conjugate vaccine and Menactra® (Groups 1 - 3 pooled versus Group 4)</li> </ol> <p>Secondary endpoints:</p> <ol style="list-style-type: none"> <li>3) Vaccine seroresponse of meningococcal serogroups A, C, Y, and W measured by hSBA assessed at baseline (D0, before vaccination) and 30 days (+14 days) after vaccination for immune non-inferiority between MenACYW conjugate vaccine and Menactra® adult study participants (Groups 1b, 2b, and 3b pooled versus Group 4b)</li> <li>4) Vaccine seroresponse of meningococcal serogroups A, C, Y, and W measured by hSBA assessed at baseline (D0, before vaccination) and 30 days (+14 days) after vaccination for immune non-inferiority between MenACYW conjugate vaccine and Menactra® adolescent study participants (Groups 1a, 2a, and 3a pooled versus Group 4a)</li> <li>5) Vaccine seroresponse of meningococcal serogroups A, C, Y, and W measured by hSBA 30 days (+14 days) following the administration of MenACYW conjugate vaccine (Groups 1, 2, and 3)</li> <li>6) GMTRs of antibodies against meningococcal serogroups A, C, Y, and W measured by hSBA for the groups that received MenACYW conjugate vaccine (Groups 1 - 3 pooled) and Menactra® (Group 4)</li> </ol>
<p><b>Statistical methods:</b></p> <p>All immunogenicity analyses were performed on the Per-Protocol Analysis Set (PPAS). Additional immunogenicity analyses were performed for exploratory purposes on the Full Analysis Set (FAS) according to randomization group. All safety analyses were performed on the Safety Analysis Set (SafAS).</p> <p><u>For Primary Objective 1:</u></p> <p><i>Equivalence of 3 MenACYW conjugate vaccine lots in terms of GMTs</i></p>

Thirty days after the administration of the MenACYW conjugate vaccine, GMTs of antibodies against meningococcal serogroups A, C, Y, and W in Groups 1, 2, and 3 are equivalent.

Null hypothesis ( $H_0$ ):  $GMT_{(G_i)} / GMT_{(G_j)} \leq 1/2$  or  $GMT_{(G_i)} / GMT_{(G_j)} \geq 2$  for any  $i \neq j$

Alternative hypothesis ( $H_1$ ):  $1/2 < GMT_{(G_i)} / GMT_{(G_j)} < 2$  for all  $i \neq j$

$GMT_{(G_i)}$  and  $GMT_{(G_j)}$  are the GMTs of antibodies against the meningococcal serogroups A, C, Y, and W for the  $i$ th and  $j$ th lots, respectively.

Each of the antigens of A, C, Y, and W serogroups was planned to be tested separately. If the 2-sided 95% confidence interval (CI) of the ratio of the GMTs is  $> 1/2$  and  $< 2$  for each antigen, the non-equivalence assumption was planned to be rejected.

#### For Primary Objective 2:

*Non-inferiority of MenACYW conjugate vaccine compared to Menactra® in terms of hSBA vaccine seroresponse*

Thirty days after the administration of MenACYW conjugate vaccine or Menactra®, the percentages of subjects who achieve an hSBA vaccine seroresponse for meningococcal serogroups A, C, Y, and W in Groups 1, 2, and 3 combined are non-inferior to the corresponding percentages in Group 4.

Null hypothesis ( $H_0$ ):  $p_{(G123)} - p_{(G4)} \leq -10\%$

Alternative hypothesis ( $H_1$ ):  $p_{(G123)} - p_{(G4)} > -10\%$

where  $p_{(G123)}$  and  $p_{(G4)}$  are the percentages of subjects who achieve an hSBA vaccine seroresponse in Groups 1 - 3 pooled and Group 4, respectively.

Each of the serogroups A, C, Y, and W was tested separately. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions is  $> -10\%$ , the inferiority assumption was rejected. The overall non-inferiority of this objective was demonstrated if all 4 individual null hypotheses were rejected

#### Secondary Objective 1:

*Non-inferiority of MenACYW conjugate vaccine compared to Menactra® in terms of hSBA vaccine seroresponse in the adult population (18 to 55 years old)*

Thirty days after the administration of MenACYW conjugate vaccine or Menactra®, the percentages of subjects who achieved an hSBA vaccine seroresponse\* for meningococcal serogroups A, C, Y, and W in Groups 1b, 2b, and 3b combined were non-inferior to the corresponding percentages in Group 4b.

Null hypothesis ( $H_0$ ):  $p_{(G123)} - p_{(G4)} \leq -10\%$

Alternative hypothesis ( $H_1$ ):  $p_{(G123)} - p_{(G4)} > -10\%$

where  $p_{(G123)}$  and  $p_{(G4)}$  were the percentages of subjects who achieved an hSBA vaccine seroresponse in Groups 1b, 2b, and 3b pooled and Group 4b, respectively. Each of the serogroups A, C, Y, and W were tested separately. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions was  $> -10\%$ , the inferiority assumption was rejected.

\* hSBA vaccine seroresponse for serogroups A, C, Y, and W was defined as:

- For a subject with a pre-vaccination titer  $< 1:8$ , the post-vaccination titer must have been  $\geq 1:16$ .
- For a subject with a pre-vaccination titer  $\geq 1:8$ , the post-vaccination titer must have been at least 4-fold greater than the pre-vaccination titer.

#### Secondary Objective 2

*Non-inferiority of MenACYW conjugate vaccine compared to Menactra® in terms of hSBA vaccine seroresponse in the adolescent population (10 to 17 years old)*

Thirty days after the administration of MenACYW conjugate vaccine or Menactra®, the percentages of subjects who achieved an hSBA vaccine seroresponse\* for meningococcal serogroups A, C, Y, and W in Groups 1a, 2a, and 3a combined were non-inferior to the corresponding percentages in Group 4a

Null hypothesis (H0):  $p(G123) - p(G4) \leq -10\%$

Alternative hypothesis (H1):  $p(G123) - p(G4) > -10\%$

where  $p(G123)$  and  $p(G4)$  were the percentages of subjects who achieved an hSBA vaccine seroresponse in Groups 1a, 2a, and 3a pooled and Group 4a, respectively. Each of the serogroups A, C, Y, and W were tested separately. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions was  $> -10\%$ , the inferiority assumption was rejected.

### **Secondary Objective 3**

*Comparison of 3 MenACYW conjugate vaccine lots in terms of hSBA vaccine seroresponse*

The difference in percentages of subjects who achieved an hSBA vaccine seroresponse\* 30 days after the administration of MenACYW conjugate vaccine for meningococcal serogroups A, C, Y, and W in Groups 1, 2, and 3 was calculated for each comparison and 95% CI was provided.

\* hSBA vaccine seroresponse for serogroups A, C, Y, and W was defined as:

- For a subject with a pre-vaccination titer  $< 1:8$ , the post-vaccination titer must have been  $\geq 1:16$ .
- For a subject with a pre-vaccination titer  $\geq 1:8$ , the post-vaccination titer must have been at least 4-fold greater than the pre-vaccination titer.

### **Secondary Objective 4**

*Comparison of MenACYW conjugate vaccine to Menactra® in terms of hSBA GMTs*

The ratio of GMTs of meningococcal serogroups A, C, Y, and W between the MenACYW conjugate vaccine Groups 1- 3 pooled (Lots 1, 2, and 3 combined) and the Menactra® Group 4, 30 days after the administration of vaccine was calculated and 95% CI was provided.

### **Summary:**

#### **Population characteristics:**

##### Subject Disposition:

A total of 3344 subjects were enrolled in this study and randomly allocated to Group 1 (902 subjects), Group 2 (895 subjects), Group 3 (906 subjects) or Group 4 (641 subjects). A total of 3242 out of 3344 subjects (96.9%) completed the study: 97.5% (879/902) of Group 1 subjects, 96.2% (861/895) of Group 2 subjects, 97.7% (885/906) of Group 3 subjects, and 96.3% (617/641) of Group 4 subjects. There were no early terminations due to an SAE or AE. A total of 3183 out of 3344 subjects (95.2%) performed the 6-month safety follow-up after the last visit: 94.8% (855/902) of Group 1 subjects, 94.6% (847/895) of Group 2 subjects, 96.4% (873/906) of Group 3 subjects, and 94.9% (608/641) of Group 4 subjects.

##### Demographics:

In the SafAS, 42.5% (1407/3311) of subjects were male and 57.5% (1904/3311) of subjects were female: the overall ratio of male/female subjects was 0.74. There were fewer males than females across the 4 groups (male/female ratio was 0.69 in Group 1, 0.68 in Group 2, 0.83 in Group 3, and 0.79 in Group 4).

Subjects' ages were comparable across the 4 groups. The mean age of the subjects at enrollment was 27.1 years with a standard deviation (SD) of 15.6 years.

The distribution of racial origin was comparable across the 4 groups. Most subjects in the study were White (74.4% [2462/3311]), followed by Black or African American (19.4% [643/3311]), and Mixed origin (3.3% [109/3311]). Racial origin information was missing for 0.2% (5/3311) of subjects. The majority of subjects (78.5% [2598/3311]) were not Hispanic or Latino.

#### **Immunogenicity Results:**

##### Primary Objective 1:

*Equivalence of 3 MenACYW conjugate vaccine lots in terms of GMTs*

Immune equivalence was demonstrated across the 3 lots in that the 2-sided 95% CI of the ratio of the GMTs was between  $> 1/2$  and  $< 2$  for each pair of lots and each serogroup.

**Table S4: Primary Objective 1, Equivalence of hSBA GMT against meningococcal serogroups A, C, Y, and W among 3 lots (Groups 1-3) 30 days after vaccination - PPAS**

Sero group	MenACYW									GMT ratio						Lot consistency
	Lot 1 (N=843)			Lot 2 (N=820)			Lot 3 (N=845)			Lot 1/Lot 2		Lot 2/Lot 3		Lot 1/Lot 3		
	M	GM (95% T CI)		M	GM (95% T CI)		M	GM (95% T CI)		(95% Ratio CI)		Ratio (95% CI)		(95% Ratio CI)		
A	843	84.9 (75.8; 95.1)		819	96.5 (86.4; 108)		843	97.9 (87.7; 109)		0.880 (0.751; 1.03)		0.985 (0.843; 1.15)		0.867 (0.740; 1.02)	Yes	
C	841	326 (286; 372)		820	305 (267; 349)		845	352 (307; 405)		1.07 (0.888; 1.29)		0.866 (0.714; 1.05)		0.927 (0.766; 1.12)	Yes	
Y	843	213 (191; 238)		820	210 (188; 234)		844	218 (194; 246)		1.02 (0.869; 1.19)		0.961 (0.816; 1.13)		0.975 (0.829; 1.15)	Yes	
W	843	84.5 (75.1; 95.1)		820	81.6 (72.7; 91.5)		844	87.2 (77.2; 98.5)		1.04 (0.878; 1.22)		0.936 (0.791; 1.11)		0.970 (0.818; 1.15)	Yes	

Abbreviations: CI, confidence interval

M: Number of subjects with available data for the endpoint.

N: number of subjects in PPAS

Overall lot consistency among the 3 lots was demonstrated if, for each pair of lots and each antigen, the 2-sided 95% CI for the ratio of GMTs lies between 1/2 and 2.

**Primary Objective 2:**

Non-inferiority of MenACYW conjugate vaccine compared to Menactra® in terms of hSBA vaccine seroresponse

Non-inferiority of immune response was demonstrated between MenACYW conjugate vaccine and Menactra® based on percentage of subjects achieving hSBA vaccine seroresponse. For each serogroup, the lower limit of the 2-sided 95% CI of the difference was > -10%.

The percentage of subjects with an hSBA vaccine seroresponse was numerically higher in Groups 1-3 pooled than in Group 4 for all serogroups: ranging from 73.8% (1846/2503) to 91.4% (2290/2505) in Groups 1-3 pooled and from 47.9% (284/593) to 73.4% (435/593) in Group 4.

**Table S5: Primary Objective 2, Non-inferiority of hSBA vaccine seroresponse rate for MenACYW conjugate vaccine (Groups 1-3 pooled) versus Menactra® (Group 4) - PPAS**

Serogroup	Group 1-3 pooled (N=2508) Seroresponse			Group 4 (N=593) Seroresponse			Groups 1-3 pooled - Group 4		Non-inferiority
	n/M	Rate (%)	95% CI	n/M	Rate (%)	95% CI	Difference (%)	95% CI	
A	1846/2503	73.8	(72.0; 75.5)	324/593	54.6	(50.5; 58.7)	19.1	(14.8; 23.5)	Yes
C	2222/2503	88.8	(87.5; 90.0)	284/593	47.9	(43.8; 52.0)	40.9	(36.7; 45.0)	Yes
Y	2290/2505	91.4	(90.3; 92.5)	435/593	73.4	(69.6; 76.9)	18.1	(14.5; 21.9)	Yes
W	2011/2505	80.3	(78.7; 81.8)	363/593	61.2	(57.2; 65.2)	19.1	(14.9; 23.3)	Yes

n: Number of subjects who achieve an hSBA vaccine seroresponse.

M: Number of subjects with available data for the endpoint.

N: number of subjects in per-protocol analysis set

hSBA vaccine seroresponse is defined as: for a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must be  $\geq$  1:16; for a subject with a pre-vaccination titer  $\geq$  1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer.

95% CI of the single percentage calculated from the exact binomial method.

95% CI of the difference calculated from the Wilson Score method without continuity correction.

The overall non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference is > -10% for all 4 serogroups.

#### Secondary Objective 1:

*Non-inferiority of MenACYW conjugate vaccine compared to Menactra® in terms of hSBA vaccine seroresponse in the adult population (18 to 55 years old)*

In subjects aged 18 to 55 years, non-inferiority of immune response was demonstrated between MenACYW conjugate vaccine and Menactra® based on percentage of subjects achieving hSBA vaccine seroresponse. For each serogroup, the lower limit of the 2-sided 95% CI of the difference was > -10%.

The percentage of subjects aged 18 to 55 years with an hSBA vaccine seroresponse was numerically higher in Groups 1b-3b pooled than in Group 4b for all serogroups: ranging from 73.5% (1034/1406) to 88.1% (1241/1408) in Groups 1b-3b pooled and from 42.3% (124/293) to 60.8% (178/293) in Group 4b.

#### Secondary Objective 2:

*Non-inferiority of MenACYW conjugate vaccine compared to Menactra® in terms of hSBA vaccine seroresponse in the adolescent population (10 to 17 years old)*

In subjects aged 10 to 17 years, non-inferiority of immune response was demonstrated between MenACYW conjugate vaccine and Menactra® based on percentage of subjects achieving hSBA vaccine seroresponse. For each serogroup, the lower limit of the 2-sided 95% CI of the difference was > -10%.

The percentage of subjects aged 10 to 17 years with an hSBA vaccine seroresponse was numerically higher in Groups 1a-3a pooled than in Group 4a for all serogroups: ranging from 74.0% (812/1097) to 95.6% (1049/1097) in Groups 1a-3a pooled and from 53.3% (160/300) to 85.7% (257/300) in Group 4a.

#### Secondary Objective 3:

*Comparison of 3 MenACYW conjugate vaccine lots in terms of hSBA vaccine seroresponse*

The difference in the rate of subjects achieving hSBA vaccine seroresponse for Lot 1 – Lot 2 was -5.4% for serogroup A, 1.3% for serogroup C, 0.5% for serogroup Y, and 0.8% for serogroup W; Lot 2 -Lot 3 was 2.9% for serogroup A, 2.4% for serogroup C, 2.0% for serogroup Y, and 2.0% for serogroup W and Lot 1 – Lot 3 was -2.5% for serogroup A, 3.7% for serogroup C, 2.5% for serogroup Y, and 2.8% for serogroup W., The lower limit of the 2-sided 95% CI of the difference was > -10%.

The percentage of subjects with an hSBA vaccine seroresponse was numerically higher in Lot 1 than in Lot 3 for serogroup C and comparable for all the other serogroups. The percentage of subjects achieving an hSBA vaccine seroresponse was numerically higher in Lot 2 compared to Lot 1 for serogroup A and comparable for all the other serogroups. Lot 2 and Lot 3 were comparable for all serogroups.

#### Secondary Objective 4:

*Comparison of MenACYW conjugate vaccine to Menactra® in terms of hSBA GMTs*

At D30, the Groups 1-3 pooled / Group 4 GMTRs ranged from 1.90 to 8.05 for all serogroups (1.93 for serogroup A, 8.05 for serogroup C, 3.22 for serogroup Y, and 1.90 for serogroup W) with lower limit of the 95% CIs greater than 1.



At D30, the GMTs were higher in Groups 1-3 pooled than in Group 4 for all serogroups, ranging from 84.4 to 328 in Groups 1-3 pooled and from 40.7 to 66.4 in Group 4.

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