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<b>Sponsor:</b> Sanofi Pasteur <b>Drug substance(s):</b> Quadrivalent Meningococcal ACYW Conjugate Vaccine	<b>Study Identifiers:</b> NCT02842866 <b>Study code:</b> MET49
<b>Title of the study:</b> Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Adults Age 56 Years and Older	
<b>Study center(s):</b> This was a multi-center trial conducted at 35 sites in the US and Puerto Rico.	
<b>Study period:</b> Date first subject enrolled: 15/Jul/2016 Date last subject completed: 13/Feb/2017	
<b>Phase of development:</b> III	
<b>Objectives:</b> <b>Primary Objectives:</b> To demonstrate the non-inferiority of the vaccine seroresponse to meningococcal serogroups A, C, Y, and W following the administration of a single dose of MenACYW conjugate vaccine compared to those observed following the administration of a single dose of Menomune® - A/C/Y/W-135. <b>Secondary Objectives:</b> To compare the hSBA antibody geometric mean titers (GMTs) of meningococcal serogroups A, C, Y, and W following the administration of MenACYW conjugate vaccine to those observed following the administration of Menomune® – A/C/Y/W-135.	
<b>Methodology:</b> This was a Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to compare the immunogenicity and safety of MenACYW conjugate vaccine to Menomune® - A/C/Y/W-135 in adults ≥ 56 years of age in the US and Puerto Rico. Approximately 900 healthy adults were randomized in a 1:1 ratio to the following groups: <ul style="list-style-type: none"><li>• Group 1: MenACYW conjugate vaccine</li><li>• Group 2: Menomune® - A/C/Y/W-135</li></ul> Enrollment was stratified by age. For subjects 56 to 64 years of age, 200 subjects were enrolled in both Group 1 and Group 2. For subjects 65 years of age and older, 250 subjects were enrolled in both Group 1 and Group 2. These subjects were further stratified into 2 sub-groups as 65 to 74 years of age and 75 years and older. At least 25% of the 250 subjects were enrolled in each of these age sub-groups. All subjects provided pre-vaccination blood samples for immunogenicity assessment at baseline (Visit [V] 01) and at Day (D) 30 (+14-day window) post-vaccination (V02). Solicited adverse event (AE) information was collected for 7 days after vaccination, unsolicited AE information was collected from V01 to D30 (V02), and serious adverse event (SAE) information was collected from D0 through D180 (+14 days) after vaccination. Medically-attended adverse events (MAAEs) collected from V01 through V02 (as part of the collection of unsolicited AE information) and from V02 through D180 (+14 days) (as MAAEs).	

<p><b>Number of subjects:</b></p> <p>Planned: 900</p> <p>Randomized: 906</p> <p>Vaccinated: 901</p> <p><b>Evaluated:</b></p> <p>Immunogenicity: 864</p> <p>Safety: 901</p>								
<p><b>Diagnosis and criteria for inclusion:</b></p> <p>An individual had to fulfill <i>all</i> of the following criteria in order to be eligible for trial enrollment:</p> <ol style="list-style-type: none"> <li>1) Age <math>\geq</math> 56 years on the day of inclusion</li> <li>2) Informed consent form (ICF) has been signed and dated</li> <li>3) Able to attend all scheduled visits and to comply with all trial procedures</li> </ol>								
<p><b>Study treatments</b></p> <p><b>Investigational product:</b> MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine (Sanofi Pasteur Inc., Swiftwater, PA, USA)</p> <p>Form: Liquid solution</p> <p>Composition:</p> <p>Each 0.5 milliliter (mL) dose of MenACYW conjugate vaccine was formulated in sodium acetate buffered saline solution to contain the following ingredients:</p> <p>Meningococcal capsular polysaccharides:</p> <table style="margin-left: 20px;"> <tr> <td>Serogroup A.....</td> <td>10 micrograms (<math>\mu</math>g)</td> </tr> <tr> <td>Serogroup C.....</td> <td>10 <math>\mu</math>g</td> </tr> <tr> <td>Serogroup Y.....</td> <td>10 <math>\mu</math>g</td> </tr> <tr> <td>Serogroup W.....</td> <td>10 <math>\mu</math>g</td> </tr> </table> <p>Tetanus toxoid protein carrier .....approximately 65 <math>\mu</math>g</p> <p>Route of administration: Intramuscular (IM)</p>	Serogroup A.....	10 micrograms ( $\mu$ g)	Serogroup C.....	10 $\mu$ g	Serogroup Y.....	10 $\mu$ g	Serogroup W.....	10 $\mu$ g
Serogroup A.....	10 micrograms ( $\mu$ g)							
Serogroup C.....	10 $\mu$ g							
Serogroup Y.....	10 $\mu$ g							
Serogroup W.....	10 $\mu$ g							
<p><b>Control product: Menomune® - A, C, Y, W-135:</b> (Meningococcal Polysaccharide Vaccine, Groups A, C, Y, and W-135 Combined) (Sanofi Pasteur Inc., Swiftwater, PA, USA)</p> <p>Form: Lyophilized single-dose vial with 0.6-mL vial of diluent (sterile, pyrogen-free distilled water without preservatives)</p> <p>Composition: After reconstitution with diluent as indicated in the Prescribing Information, each 0.5 mL dose contains 50 <math>\mu</math>g of group-specific polysaccharide antigens from each of Groups A, C, Y, and W-135 in an isotonic sodium chloride solution.</p> <p>Each dose of vaccine also contains 2.5 to 5 milligram (mg) of lactose as a stabilizer.</p> <p>Route: Subcutaneous (SC)</p>								
<p><b>Duration of treatment/participation:</b> The intended duration of each subject's participation in the trial was 180 to 194 days.</p>								
<p><b>Criteria for evaluation:</b></p> <p>Immunogenicity:</p> <p>Primary endpoint: Vaccine seroresponse of meningococcal serogroups A, C, Y, and W measured by serum bactericidal assay using human complement (hSBA) assessed at baseline (D0, before vaccination) and 30 days after vaccination.</p> <p>Secondary endpoint: GMTs against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at 30 days (+14 days) after vaccination with MenACYW conjugate vaccine and Menomune® - A/C/Y/W-135.</p>								

**Statistical methods:**

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). Subjects were analyzed according to the vaccine they actually received.

**Primary Objective:**

Thirty days (D30 [+14 days]) after the administration of MenACYW conjugate vaccine or Menomune® – A/C/Y/W-135, the percentages of subjects who achieve an hSBA vaccine seroresponse\* for meningococcal serogroups A, C, Y, and W in Group 1 are non-inferior to the corresponding percentages in Group 2.

Null hypothesis ( $H_0$ ):  $p_{(G1)} - p_{(G2)} \leq -10\%$

Alternative hypothesis ( $H_1$ ):  $p_{(G1)} - p_{(G2)} > -10\%$

where  $p_{(G1)}$  and  $p_{(G2)}$  are the percentages of subjects who achieved an hSBA vaccine seroresponse in Group 1 and Group 2, respectively.

Each of the serogroups A, C, Y, and W were tested separately. If the lower limit of the 2-sided 95% confidence interval (CI) of the difference between the 2 proportions is  $> -10\%$ , the inferiority assumption was rejected.

For the 4 non-inferiority hypotheses using the seroresponse rates, the CI of the difference in proportions was computed using the Wilson Score method without continuity correction. The overall non-inferiority of this objective would be demonstrated if all 4 individual null hypotheses were rejected.

\* hSBA vaccine seroresponse for serogroups A, C, Y, and W 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.

**Secondary Objective:**

Thirty days (D30 [+14 days]) after the administration of MenACYW conjugate vaccine or Menomune® – A/C/Y/W-135, the hSBA geometric mean titer ratio (GMTR) between Group 1 and Group 2 was calculated and 95% CI was provided.

**Summary:**

**Population characteristics:**

Trial Population

A total of 907 subjects were enrolled in the study. Out of the 907 enrolled subjects, 906 were randomized: 1 enrolled subject (Subjects 004-00006) was not randomized to any of the 2 treatment groups; this subject was not vaccinated and did not provide blood samples.

A total of 901 subjects (99.3%) provided a blood sample and subsequently received a vaccine as randomized (MenACYW conjugate vaccine for Group 1 [448 subjects], and Menomune® – A/C/Y/W-135 for Group 2 [453 subjects]).

A total 896 (98.8%) subjects were present at V02 and completed the trial up to D30 (444 subjects [98.4%] in Group 1 and 452 subjects [99.3%] in Group 2).

Eleven subjects did not complete the study up to D30. This number of subjects includes the Subject 004-00006 who was enrolled but not randomized or vaccinated, and did not complete the trial. This subject could not be assigned to either group. One subject in the Menomune® – A/C/Y/W-135 vaccine group was terminated early from the study between V01 and D30 due to an SAE of worsening of a coronary artery disease (Subject 017-00004 was hospitalized and underwent open heart surgery). The event was considered by the investigator and the sponsor as not related to the vaccine, 7 subjects for non-compliance with the protocol (4 subjects in Group 1 and 2 subjects in Group 2, plus the enrolled but not randomized Subject 004-00006), 2 subjects (both in Group 1) were lost to follow-up, and 1 subject (Group 1) voluntarily withdrew not due to an AE.

There were 2 deaths in the Menomune® – A/C/Y/W-135 vaccine group between V02 and the 6 months follow-up. Subject 035-000009 died due to metastatic lung cancer and was withdrawn from the study. Subject 035-00018 died due to spinal dislocation due to a road traffic accident and was withdrawn from the study. None of these deaths were considered by the investigator and the sponsor as related to the vaccine.

Out of the 906 randomized and vaccinated subjects, 893 (98.6%) were included in the FAS, 196 subjects (21.6%) received the vaccine and a valid post-vaccination rSBA results were obtained and were therefore included in the population defined as rSBA subset, a total of 864 subjects (95.4%) were included in the PPAS, and the SafAS included 901 (99.4%) subjects.

In both Group 1 and Group 2, there were more female than male subjects (259 subjects [57.4%] vs 192 subjects [42.6%] in Group 1, and 261 subjects [57.4%] vs 194 subjects [42.6%] in Group 2).

At enrollment, the mean age of subjects was comparable in both Group 1 and Group 2 ( $66.9 \pm 7.51$  years, and  $67.3 \pm 7.53$  years, respectively), and in the respective age strata ( $60.4 \pm 2.68$  years and  $60.4 \pm 2.48$  years in Groups 1 and 2 respectively for subjects aged 56 to 64 years, and  $72.2 \pm 5.77$  years and  $72.7 \pm 5.47$  years in Groups 1 and 2 respectively for subjects aged  $\geq 65$  years).

In both Group 1 and Group 2, most of the subjects were White (389 subjects [86.3%] in Group 1, and 404 subjects [88.8%] in Group 2).

### ***Immunogenicity***

#### Primary Objective

#### **Non-inferiority of the percentage of subjects achieving hSBA vaccine seroresponse between Group 1 versus Group 2**

The immune response following administration of MenACYW conjugate vaccine was non-inferior to the immune response following administration of Menomune® – A/C/Y/W-135 for all 4 serogroups as measured by hSBA vaccine seroresponse. For each serogroup, the lower limit of the 2-sided 95% CI of the difference was more than -10%.

For all serogroups, the percentages of subjects with an hSBA vaccine seroresponse in Group 1 were higher than the percentages in Group 2 with non-overlapping 95% CIs.

The non-inferiority of MenACYW conjugate vaccine to Menomune® – A/C/Y/W-135 in terms of hSBA vaccine seroresponse at D30 was also demonstrated for all 4 serogroups in the FAS.

#### Complementary Results on Seroprotection

##### *Seroresponse by serostatus*

The seroresponse rates in subjects S- at baseline were higher in Group 1 (ranged from 63.5% [serogroup W] to 82.9% [serogroup Y]) than in Group 2 (ranged from 44.5% [serogroup W] to 53.7% [serogroup C]), with non-overlapping 95% CI. The seroresponse rates in subjects S+ at baseline were also higher in Group 1 (ranged from 49.5% [serogroup Y] to 73.7% serogroup C]) than in Group 2 (ranged from 37.2% [serogroup Y] to 45.9% [serogroup W]) for all serogroups, with non-overlapping 95% CI for serogroups A and C.

##### *Seroresponse by age group*

- Subjects 56 to 64 years of age

In subjects 56 to 64 years of age, results were comparable to those in the whole population. For all serogroups, the percentages of subjects with hSBA vaccine seroresponse at D30 were higher in Group 1 (ranging from 58.9% [serogroup A] to 80.2% [serogroup C]) than in Group 2 (ranging from 44.4% [serogroup A] to 52.9% [serogroup C]). The 95% CIs did not overlap for any of the serogroups, except for serogroup A.

- Subjects  $\geq 65$  years of age

In subjects  $\geq 65$  years of age, results were comparable to those in the whole population. For all serogroups, the percentages of subjects with hSBA vaccine seroresponse at D30 were higher in Group 1 (ranging from 57.7% [serogroup A] to 74.7% [serogroup C]) than in Group 2 (ranging from 40.5% [serogroup Y] to 47.1% [serogroup C]). The 95% CIs did not overlap for any of the serogroups.

- Subjects 56 to 64 years of age vs subjects  $\geq$  65 years of age

After MenACYW conjugate vaccine administration, the percentages of subjects with hSBA vaccine seroresponse at D30 were slightly higher in subjects aged 56 to 64 years than in subjects aged  $\geq$  65 years of age for all serogroups. Similarly, after Menomune<sup>®</sup> – A/C/Y/W-135 administration, the percentages of subjects with hSBA vaccine seroresponse were slightly higher in the subjects aged 56 to 64 years than in subjects aged  $\geq$  65 years of age for all serogroups.

- Subjects aged 65 to 74 years of age

In subjects 65 to 74 years of age, results were comparable to those in the whole population. For all serogroups, the percentages of subjects with hSBA vaccine seroresponse at D30 were higher in Group 1 (ranging from 57.6% [serogroup A] to 73.8% [serogroups C and Y]) than in Group 2 (ranging from 41.7% [serogroup A] to 48.6% [serogroup C]). The 95% CIs did not overlap for any of the serogroups.

- Subjects aged  $\geq$  75 years of age

In subjects  $\geq$  75 years of age, for all serogroups, the percentages of subjects with hSBA vaccine seroresponse at D30 were higher in Group 1 (ranging from 49.3% [serogroup W] to 76.8% [serogroup C]) than in Group 2 (ranging from 34.3% [serogroup Y] to 43.3% [serogroup C]), with no overlapping of the 95% CIs for serogroups C and Y.

#### *Seroresponse by race*

At D30, seroresponse rates in White and Black or African American subjects were higher in Group 1 than in Group 2 for all serogroups, with no 95% CIs overlapping in White subjects. There was an overlap of 95% CIs in Black or African American subjects in all serogroups, except for serogroup C.

#### *Seroresponse by gender*

Similar differences were observed in seroresponse rates in male and female subjects between Group 1 (ranging from 57.1% [serogroup A] to 72.0% [serogroup C] in male subjects and from 59.0% [serogroup A] to 80.9% [serogroup C] in female subjects) and in Group 2 (ranging from 41.9% [serogroup W] to 45.2% [serogroup Y] in male subjects and from 42.0% [serogroup Y] to 54.3% [serogroup C] in female subjects). The 95% CIs did not overlap for any of the serogroups in female subjects, and did not overlap for the serogroups C, Y, and W in male subjects.

#### Secondary Objective

#### **Comparison of hSBA GMTs following MenACYW conjugate vaccine versus Menomune<sup>®</sup> – A/C/Y/W-135 administration**

Thirty days after vaccination, the GMTs were higher in Group 1 than in Group 2 with non-overlapping 95% CIs for all serogroups, ranging from 28.1 (serogroup W) to 101 (serogroup C) in Group 1 and from 15.5 (serogroup W) to 31.4 (serogroup A) in Group 2. The Group 1 / Group 2 GMT ratios ranged from 1.75 to 4.10 for all serogroups.

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