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Sponsor: Sanofi Pasteur **Drug substance:** Quadrivalent Meningococcal ACYW Conjugate Vaccine	**Study Identifiers:** U1111-1127-6804, NCT01732627 **Study code:** MET44
Title of the study: Immunogenicity and Safety of a Quadrivalent Meningococcal Conjugate Vaccine Administered in Subjects 56 Years of Age and Older.	
Study centers: This was a multi-center trial conducted at 12 sites in the US.	
Study period: Date first subject enrolled: 12/Nov/2012 Date last subject completed: 17/Jan/2013	
Phase of development: II	

Objectives:

Immunogenicity:

To describe the antibody responses to meningococcal serogroups A, C, Y, and W135, measured by serum bactericidal assay using human complement (hSBA) and baby rabbit complement (rSBA), induced by a single dose of MenACYW conjugate vaccine or Menomune® − A/C/Y/W-135 in subjects 56 years of age and older.

Safety:

To describe the safety profile of a single dose of MenACYW conjugate vaccine or Menomune® − A/C/Y/W-135 in subjects 56 years of age and older.

Methodology:

This was a Phase II, randomized, open-label (the laboratory technicians were blinded to group assignment), multi-center study in adults aged ≥ 56 years in the US, to receive either MenACYW conjugate vaccine or Menomune® − A/C/Y/W-135. Subjects were enrolled using an interactive voice response system (IVRS) to ensure the proper number of subjects was enrolled in each group.

Subjects aged 56 years and older on the day of enrollment were randomized to receive MenACYW conjugate vaccine (Group 1) or Menomune® − A/C/Y/W-135 (Group 2) in a 2:1 ratio, and stratified according to age into 2 subsets 56 to 64 and ≥ 65 years as follows:

- Group 1: Received MenACYW conjugate vaccine (n=200)
    - Group 1a: 100 subjects 56 to 64 years of age
    - Group 1b: 100 subjects ≥ 65 years of age
- Group 2: Received Menomune® − A/C/Y/W-135 (n=100)
    - Group 2a: 50 subjects 56 to 64 years of age
    - Group 2b: 50 subjects ≥ 65 years of age

All subjects were to receive a single dose of vaccine, and were to provide blood samples for immunogenicity assessment at Day (D) 0 baseline, pre-vaccination and at D30 (+14 day window) post-vaccination. Safety data were collected from D0 to D30 (+14 day window).

Number of subjects/patients: Planned: 300

Randomized: 301

Vaccinated: 301

Evaluated:

Immunogenicity: 301

Safety: 299

Diagnosis and criteria for inclusion:

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

1) Group 1a and Group 2a: Aged 56 to 64 years on the day of inclusion; Group 1b and Group 2b: Aged ≥ 65 years on the day of inclusion

2) Informed consent form has been signed and dated

3) Able to attend all scheduled visits and to comply with all trial procedures

Study treatments

Investigational product: MenACYW conjugate vaccine: Meningococcal Polysaccharide (Serogroups A, C, Y, and W135) Tetanus Toxoid Conjugate Vaccine

Form: Liquid solution

Composition: Each 0.5 mL dose of MenACYW conjugate vaccine was formulated in sodium acetate buffered saline solution to contain 10 µg each of serogroups A, C, Y, and W135 meningococcal capsular polysaccharide, conjugated to a total of approximately 65 µg of tetanus toxoid protein.

Route of administration: Intramuscular

Control Product: Menomune® − A, C, Y, W-135: Meningococcal Polysaccharide Vaccine, Groups A, C, Y, and W-135 Combined (Sanofi Pasteur Inc., Swiftwater, PA, USA)

Form: Lyophilized single dose vial with 0.6-mL vial of diluent

Composition: After reconstitution with diluent as indicated in the Prescribing Information (PI), each 0.5 mL dose contains 50 µg of group-specific polysaccharide antigens from each of the serogroups A, C, Y, and W135 in an isotonic sodium chloride solution.

Route of administration: Subcutaneous

Duration of participation: The duration of each subject's participation in the trial was 30 to 44 days.

Criteria for Evaluation:

Immunogenicity:

The endpoints for the evaluation of immunogenicity were:

- Functional antibodies to the meningococcal serogroups (A, C, Y, and W135) measured by hSBA and rSBA at D0 and D30 in all subjects

Safety:

The following endpoints were used for all subjects for the evaluation of safety:

1) Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after vaccination
2) Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and electronic Case Report Form [CRF]) injection site reactions occurring up to 7 days after vaccination
3) Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRF) systemic reactions occurring up to 7 days after vaccination
4) Occurrence, nature (MedDRA preferred term), time to onset, duration, intensity, action taken, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the study, of unsolicited AEs up to 30 days after vaccination
5) Occurrence, nature (MedDRA preferred term), time to onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the serious adverse event (SAE) led to early termination from the study, of SAEs throughout the trial

Statistical methods:

All analyses were descriptive; no hypotheses were tested.

In general, categorical variables were summarized and presented by frequency counts, proportion percentages and confidence intervals (CIs). For the main parameters, 95% CIs of point estimates were calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for proportions. For geometric mean titers (GMTs), 95% CIs of point estimates were calculated using normal approximation assuming they are log-normally distributed.

Summary

Population characteristics:

Disposition of Participants

A total of 301 subjects were enrolled in this study. The subjects were randomly allocated to Group 1 or Group 2 with a 2:1 ratio (201 in Group 1 and 100 in Group 2), and stratified according to age into 2 subsets (101 in Group 1a, 100 in Group 1b, 50 in Group 2a, and 50 in Group 2b).

All 301 subjects provided a blood sample at Visit 1, and received a vaccine as randomized (MenACYW conjugate vaccine for Group 1, and Menomune® − A/C/Y/W-135 for Group 2).

All subjects but 1 in Group 1a completed the study: One subject voluntarily withdrew from the study. The reported reason for early termination was "voluntary withdrawal not due to an AE".

A total of 2 subjects did not provide a blood sample at Visit 2 in Group 1a: one subject withdrew from the study and one subject because of difficult venipuncture.

Demographic and Baseline Characteristics

In both Group 1 and Group 2, there were slightly more female subjects (60.8% [121/199] and 55.0% [55/100], respectively) than male subjects (39.2% [78/199] and 45.0% [45/100], respectively). The same tendency was observed in the subsets, with the exception of Group 2b where there were equal numbers of female and male subjects (50.0% [25/50]).

At enrollment, the mean age of subjects was similar in both Group 1 and Group 2 (66.1 ± 7.13 years, and 65.8 ± 6.58 years, respectively), and in the respective subsets (60.3 ± 2.52 years in Group 1a, 60.8 ± 2.59 years in Group 2a, 71.9 ± 5.28 years in Group 1b, and 70.8 ± 5.45 years in Group 2b).

In both Group 1 and Group 2, most of the subjects were white (94.5% [188/199] in Group 1, and 97.0% [97/100] in Group 2).

Immunogenicity:

Antibody Responses to Serogroups A, C, Y, and W135 Measured by Serum Bactericidal Assay using Human Complement (hSBA)

At baseline, the proportions of subjects with hSBA titers ≥ 1:8 were comparable for all serogroups between Group 1 (MenACYW conjugate vaccine group) and Group 2 (Menomune® − A/C/Y/W-135 group); there was a higher percentage of subjects with titers ≥ 1:8 for serogroup A than for the other serogroups in both vaccination groups: 76.4% (149/195) in Group 1 and 79.8% (75/94) in Group 2 for serogroup A; 17.4% (34/195) in Group 1 and 10.6% (10/94) in Group 2 for serogroup C; 13.3% (26/195) in Group 1 and 24.5% (23/94) in Group 2 for serogroup Y; 13.3% (26/195) in Group 1 and 8.5% (8/94) in Group 2 for serogroup W135.

At D30, the proportion of subjects with hSBA titers ≥ 1:8 against serogroups C, Y, and W135 was markedly increased from baseline. The proportion of subjects with hSBA titers ≥ 1:8 against serogroup A at D30 was higher than the one against serogroups C, Y, and W135. The proportions of subjects with hSBA titers ≥ 1:8 obtained after MenACYW conjugate vaccine administration for serogroups A and C were comparable to, or for serogroups Y and W135 higher than, those obtained after Menomune® − A/C/Y/W-135 administration: 93.8% (183/195) in Group 1 and 85.1% (80/94) in Group 2 for serogroup A; 74.9% (146/195) in Group 1 and 62.8% (59/94) in Group 2 for serogroup C; 80.5% (157/195) in Group 1 and 59.6% (56/94) in Group 2 for serogroup Y; 79.5% (155/195) in Group 1 and 60.6% (57/94) in Group 2 for serogroup W135.

Overall, results were similar or did not show a consistent trend in the subset of subjects 56 to 64 years of age compared to those in the subset ≥ 65 years of age within the vaccination groups (those who received MenACYW conjugate vaccine or Menomune® − A/C/Y/W-135).

Vaccine hSBA Seroresponse

Seroresponse using hSBA Baseline Cutoff Titers of 1:8

A higher hSBA vaccine seroresponse was observed in Group 1 than in Group 2 for serogroups A, Y, and W135: 65.1% (127/195) in Group 1 and 46.8% (44/94) in Group 2 for serogroup A; 75.4% (147/195) in Group 1 and 48.9% (46/94) in Group 2 for serogroup Y; and 74.4% (145/195) in Group 1 and 55.3% (52/94) in Group 2 for serogroup W135. The hSBA vaccine seroresponse was comparable between both vaccination groups for serogroup C: 70.8% (138/195) in Group 1 and 59.6% (56/94) in Group 2.

In the subset of subjects 56 to 64 years of age, comparable or higher hSBA vaccine seroresponses were observed after MenACYW conjugate vaccine administration (Group 1a) than after Menomune® − A/C/Y/W-135 administration (Group 2a) for all serogroups.

In the subset of subjects ≥ 65 years of age, comparable or higher hSBA vaccine seroresponses were observed after MenACYW conjugate vaccine administration (Group 1b) than after Menomune® − A/C/Y/W-135 administration (Group 2b) for all serogroups.

Within each vaccination group, vaccine responses were comparable between the younger age subset (subjects 56 to 64 years of age) and the older one (subjects ≥ 65 years of age).

hSBA Geometric Mean Titers (GMTs)

At baseline, the hSBA GMTs for all serogroups were comparable between Group 1 and Group 2: 9.73 in Group 1 and 10.4 in Group 2 for serogroup A; 3.32 in Group 1 and 2.87 in Group 2 for serogroup C; 3.02 in Group 1 and 3.53 in Group 2 for serogroup Y; and 2.83 in both vaccination groups for serogroup W135. At D30, the hSBA GMTs were markedly increased from baseline for all serogroups in both vaccination groups. The hSBA GMTs after MenACYW conjugate vaccine administration for serogroups A and W135 were comparable to, or for serogroups C and Y higher than, those after Menomune® − A/C/Y/W-135 administration: 51.0 in Group 1 and 31.8 in Group 2 for serogroup A; 48.3 in Group 1 and 18.5 in Group 2 for serogroup C; 41.9 in Group 1 and 16.6 in Group 2 for serogroup Y; and 29.0 in Group 1 and 17.1 in Group 2 for serogroup W135.

In the subset of subjects 56 to 64 years of age, the hSBA GMTs before and after MenACYW conjugate vaccine administration (Group 1a) were comparable for all serogroups to those before and after Menomune® − A/C/Y/W-135 administration (Group 2a).

In the subset of subjects ≥ 65 years of age, the hSBA GMTs after MenACYW conjugate vaccine administration (Group 1b) for serogroups A and W135 were comparable to, or for serogroups C and Y higher than, those after Menomune® − A/C/Y/W-135 administration (Group 2b).

Within each vaccination group, hSBA GMTs were comparable between the younger age subset (subjects 56 to 64 years of age) and the older one (subjects ≥ 65 years of age).

Antibody Responses to Serogroups A, C, Y, and W135 Measured by Serum Bactericidal Assay using Baby Rabbit Complement (rSBA)

At baseline, the proportions of subjects with rSBA titers ≥ 1:8 were comparable between Group 1 and Group 2 for all serogroups. At D30, the proportions of subjects with rSBA titers ≥ 1:8 were markedly increased from baseline for all serogroups and reached 87.2 to 98.4%. The proportions of subjects with rSBA titers ≥ 1:8 were comparable for all serogroups between those obtained after MenACYW conjugate vaccine administration and those obtained after Menomune® − A/C/Y/W-135 administration.

Similar trend was observed when results were compared by age within the vaccination groups and across groups.

Vaccine rSBA Seroresponse

Seroresponse using rSBA Baseline Cutoff Titers of 1:8

The rSBA vaccine seroresponses obtained after MenACYW conjugate vaccine administration were comparable for all serogroups to those obtained after Menomune® − A/C/Y/W-135 administration.

Similar trend was observed when results were compared by age within the vaccination groups and across groups.

rSBA Geometric Mean Titers (GMTs)

At baseline, the rSBA GMTs for all serogroups were comparable between Group 1 and Group 2. At D30, the rSBA GMTs were markedly increased from baseline for all serogroups. The rSBA GMTs after MenACYW conjugate vaccine administration for serogroups A and W135 were comparable to, or for serogroups C and Y, higher than, those after Menomune® − A/C/Y/W-135 administration.

When results were compared by age, rSBA GMTs were comparable within the vaccination groups and across groups except for serogroup C where rSBA GMTs after MenACYW conjugate vaccine administration were higher than those after Menomune® − A/C/Y/W-135 administration in subjects ≥ 65 years of age.

Safety results：

Solicited Reactions between Day 0 and Day 7

Overall, the percentages of subjects reporting at least one solicited reaction were comparable between both vaccination groups (MenACYW conjugate vaccine [Group 1] and Menomune® − A/C/Y/W-135 [Group 2] recipients): 57.8% (115/119) and 53.0% (53/100), respectively. Most solicited reactions were of Grade 1 or Grade 2 intensity. The percentages of subjects reporting at least one solicited reaction were generally higher in the subset of subjects 56 to 64 years of age than in the subset ≥ 65 years of age.

Solicited Injection Site Reactions: 35.7% (71/199) in Group 1 and 35.0% (35/100) in Group 2 reported solicited injection site reactions. The percentages of subjects reporting at least one solicited injection site reaction (pain, erythema or swelling) were comparable between both vaccination groups. However, the percentages of subjects reporting injection site erythema and injection site swelling were numerically higher in Group 1 than in Group 2. Injection site erythema was reported by 11.6% (23/199) of subjects in Group 1, and by 5.0% (5/100) of subjects in Group 2. Injection site swelling was reported by 7.6% (15/198) of subjects in Group 1, and by 2.0% (2/100) of subjects in Group 2. The most commonly reported solicited injection site reaction was pain, reported by 30.7% (61/199) of subjects in Group 1, and by 32.0% (32/100) of subjects in Group 2. The percentages of subjects reporting at least one solicited injection site reaction were generally higher in the subset of subjects 56 to 64 years of age than in the subset ⩾ 65 years of age in Group 1 but were comparable in Group 2. Most solicited injection site reactions were of Grade 1 or Grade 2 intensity, started between D0 and D3 and lasted 1 to 3 days.

Solicited Systemic Reactions: In Group 1, 46.7% (93/199) reported solicited systemic reactions, and 41.0% (41/100) in Group 2. The percentages of subjects reporting at least one solicited systemic reaction (fever, headache, malaise or myalgia) were comparable between both vaccination groups. The most frequently reported solicited systemic reaction was myalgia in Group 1, reported by 35.2% (70/199) of subjects in Group 1, and by 26.0% (26/100) of subjects in Group 2, and headache in Group 2, reported by 23.6% (47/199) of subjects in Group 1, and by 28.0% (28/100) of subjects in Group 2. Fever had a very low reporting rate, being reported by 1.5% (3/197) of subjects in Group 1, and by 1.0% (1/99) of subjects in Group 2. The percentages of subjects reporting at least one solicited systemic reaction were generally higher in the subset of subjects 56 to 64 years of age than in the subset ⩾ 65 years of age in Group 1 but were comparable in Group 2. Most solicited systemic reactions were of Grade 1 or Grade 2 intensity, started between D0 and D3 and lasted 1 to 3 days.

Unsolicited Adverse Events between Day 0 and Day 30

The percentages of subjects reporting at least one unsolicited AE were comparable between Group 1 and Group 2: 20.6% (41/199) and 17.0% (17/100), respectively.

Immediate Unsolicited Adverse Events: There were no immediate unsolicited AEs or ARs reported for any subject in the study.

Unsolicited Adverse Events: The percentage of subjects reporting at least one unsolicited AE in Group 1 was comparable to that in Group 2. The most commonly reported unsolicited AEs in Group 1 were in the Infections and Infestations SOC (6.0% [12/199]) followed by General Disorders and Administration Site Conditions (5.0%[10/199]), Respiratory, Thoracic and Mediastinal Disorders (4.5% [9/199]) and Gastrointestinal Disorders (4.5% [9/199]). The most commonly reported unsolicited AEs in Group 2 were in the Infections and Infestations SOC (7.0% [7/100]) followed by Respiratory, Thoracic and Mediastinal Disorders (5.0% [5/100]) and Musculoskeletal and Connective Tissue Disorders (4.0% [4/100]). Injection site pruritus (3.0% [6/199]), upper respiratory tract infection (2.5% [5/199]), cough (2.0% [4/199]) and diarrhea (2.0% [4/199]) were the most commonly reported unsolicited AEs by preferred term in Group 1. Upper respiratory tract infection, cough, headache, and neck pain (2.0% [2/100] each) were the most commonly reported events by preferred term in Group 2. The percentages of subjects reporting at least one unsolicited AE in the subset of subjects 56 to 64 years of age were comparable to those in the subset ≥ 65 years of age. Most unsolicited AEs were of Grade 1 or Grade 2 intensity.

Unsolicited Adverse Reactions: Overall, the percentages of subjects reporting at least one unsolicited AR were low in both groups, but more frequently reported in Group 1 than in Group 2 (6.5% [13/199] of subjects in Group 1 and 2.0% [2/100] of subjects in Group 2). The percentages of subjects reporting at least one unsolicited AR in the subset of subjects 56 to 64 years of age were comparable to those in the subset ≥ 65 years of age. Most unsolicited ARs were of Grade 1 or Grade 2 intensity.

Deaths, other Serious Adverse Events, and other Significant Adverse Events

There were no deaths, SAEs or AEs that led to study discontinuation reported during the study.

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