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Sponsor: Sanofi Pasteur **Drug substance:** Quadrivalent Meningococcal ACYW Conjugate Vaccine	**Study Identifiers:** U1111-1161-2710, NCT02752906, 2018-001470-18 **Study code:** MET56
Title of the study: Immunogenicity and Safety of a Booster Dose of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Adolescents and Adults	
Study centers: This was a multi-center trial involving 30 trial centers in the United States and Puerto Rico.	
Study period: Date first subject enrolled: 15/Apr/2016 Date last subject completed: 19/Dec/2016 (6-month follow up)	
Phase of development: III	

Objectives:

Primary objective:

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 MenACYW conjugate vaccine compared to those observed following the administration of a booster dose of Menactra® in subjects who were first vaccinated with 1 dose of a quadrivalent meningococcal conjugate vaccine 4 to 10 years before the booster dose.

Secondary objectives:

1) To evaluate the vaccine seroresponse of meningococcal serogroups A, C, Y, and W measured using hSBA in serum specimens collected 6 days (± 1 day) after vaccination in a subset of 120 subjects

2) To evaluate the antibody responses (geometric mean titers [GMTs]) to serogroups A, C, Y, and W measured using hSBA on D0 (pre-vaccination) and D30 (+ 14 days) after vaccination

Methodology:

This was a Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to compare the immunogenicity and describe the safety of a booster dose of MenACYW conjugate vaccine compared to Menactra® in quadrivalent meningococcal conjugate vaccine-primed adolescents and adults aged at least 15 years in the US and Puerto Rico. A total of 810 healthy adolescents and adults who had received 1 dose of a quadrivalent meningococcal conjugate vaccine 4 to 10 years previously were randomized in a 1:1 ratio to the following groups:

- Group 1: MenACYW conjugate vaccine
- Group 2: Menactra®

The first 120 subjects enrolled in the study and randomized 1:1 to each of the 2 study groups (i.e., 60 subjects randomized to Group 1 and 60 subjects randomized to Group 2) comprised a subset from which an additional blood sample was to be obtained on Day (D) 6 (±1 day) post-vaccination. This subset had 3 visits in total.

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 D0 to D30 (+14 days), and serious adverse event (SAE) information was to be collected from D0 through D180 after vaccination. Medically-attended adverse events (MAAEs) were to be collected from D30 through D180 (+14 days).

Number of subjects:	Planned: 800 Randomized: 810 Vaccinated:809
Evaluated:	
	Immunogenicity: 773
	Safety: 809

Diagnosis and criteria for inclusion:

An individual had to fulfill all of the following criteria in order to be eligible for trial enrollment:

1) Aged ≥ 15 years on the day of inclusion

2) Subject has documented record of having received 1 dose of a quadrivalent meningococcal conjugate vaccine 4 to 10 years prior to study vaccination*

3) **Subject aged 15 to < 18 years†:** assent form signed and dated by the subject and informed consent form (ICF) signed and dated by the parent or guardian

Subject aged ≥ 18 years†: ICF signed and dated by the subject

4) **Subjects aged 15 to < 18 years†:** both the subject and parent / guardian are able to attend all scheduled visits and to comply with all trial procedures

Subjects aged ≥ 18 years†: able to attend all scheduled visits and to comply with all trial procedures

* "4 years" means from the first day of the 4th anniversary of the last vaccination; "10 years" means up until the day before the 11th anniversary of the last vaccination

† or legal age of majority, if different from 18 years of age

Study treatments

Investigational product: MenACYW conjugate vaccine: 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 milliliter (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

Tetanus toxoid protein carrier ..... approximately 65 µg

Route of administration: Intramuscular (IM)

Control product: Menactra® Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine (Sanofi Pasteur Inc., Swiftwater, PA, USA)

Form: Solution for injection

Composition:

Each 0.5 mL dose of Menactra® is formulated in sodium phosphate buffered isotonic sodium chloride solution to contain the following components:

Serogroup A.....4 µg
Serogroup C.....4 µg
Serogroup Y.....4 µg
Serogroup W-135.....4 µg

Diphtheria toxoid protein carrier ---------- approximately 48 µg

Route of administration: IM

Duration of participation: The duration of each subject's participation in the trial was to last approximately 6 months.

Criteria for evaluation:

Primary endpoint:

Vaccine seroresponse against 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 (+14 days) after vaccination

Secondary endpoints:

1) Vaccine seroresponse against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at 6 days post-vaccination in a subset of 120 subjects

2) GMTs against meningococcal serogroups A, C, Y, and W measured by hSBA before and 30 days after vaccination with MenACYW conjugate vaccine or Menactra®

Statistical methods:

Primary objectives:

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

Null hypothesis (H0): $p(G1) - p(G2) \leq -10\%$

Alternative hypothesis (H1): $p(G1) - p(G2) > -10\%$

where p(G1) and p(G2) are the percentages of subjects who achieve an hSBA 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. The overall non-inferiority of this objective was 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 ≥ 1:16.
- For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer.

All immunogenicity analyses were performed on the Per-Protocol Analysis Sets (PPAS1 for D06 and PPAS2 for D30). Additional immunogenicity analyses were performed for exploratory purposes on the Full Analysis Set (FAS) according to the randomization group. All safety analyses were performed on the Safety Analysis Set (SafAS).

Secondary Objectives:

- Six days after the administration of MenACYW conjugate vaccine or Menactra®, the difference of hSBA vaccine seroresponse rates between Group 1 and Group 2 was calculated and 95% CI is provided.
- Thirty days after the administration of MenACYW conjugate vaccine or Menactra®, the hSBA geometric mean titer ratio (GMTR) between Group 1 and Group 2 was calculated, and 95% CI is provided.

Summary

Population characteristics:

Subject Disposition:

A total of 810 subjects were enrolled in this study and randomly allocated to Group 1 (403 subjects) or Group 2 (407 subjects). A total of 798 subjects (98.5%) completed the trial: 98.3% (396/403) of Group 1 subjects and 98.8% (402/407) of Group 2 subjects. There were no early terminations due to an SAE or AE. A total of 790 subjects (97.5%) performed the safety follow-up after the last visit: 97.0% (391/403) of Group 1 subjects and 98.0% (399/407) of Group 2 subjects.

Demographics:

The distribution of males and females was comparable between both groups. There were a total of 402 male subjects (49.7%) and 407 female subjects (50.3%) in the SafAS. The overall ratio of male/female subjects was 0.99: the ratio was 0.94 in Group 1 and 1.04 in Group 2.

Subjects' ages were comparable between both groups. The mean age of the subjects at enrollment was 20.0 ± 5.78 years.

The distribution of racial origin was comparable between both groups. Most subjects in the study were White (84.3%), followed by Black (10.5%), Mixed origin (3.1%), and Asian (1.7%). Racial origin information was missing for 0.1% of subjects. The majority of subjects (83.3%) were not Hispanic or Latino.

Immunogenicity results:

Primary Objective: Non-Inferiority of MenACYW Conjugate Vaccine to Menactra(R) When Used as a Booster

The immune response to MenACYW conjugate vaccine was non-inferior to the immune response to Menactra® 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%.

Primary Objective, comparison of the percentages of subjects achieving hSBA vaccine seroresponse at D30 between Group 1 and Group 2 – PPAS2

	Group 1 – Group 2 P1 - P2		
Serogroup	**Difference (%)**	**2-sided 95% CI for Difference**	**Non-inferior***
A	5.0	(0.735; 9.38)	Yes
C	5.4	(2.16; 8.76)	Yes
Y	1.8	(-0.907; 4.55)	Yes
W	7.4	(4.30; 10.9)	Yes

*If the lower limit of the 2-sided 95% CI of the difference is more than -10% for each serogroup, the inferiority hypothesis is rejected.

Secondary Objective 1: hSBA Vaccine Seroresponse at D06

At D06, the differences of the percentages of subjects achieving hSBA vaccine seroresponse between Group 1 and Group 2 for serogroups A, Y, and W were > 0 (6.6%, 7.0%, and 10.7%, respectively). For serogroup C, the difference of the percentages of subjects achieving hSBA vaccine seroresponse between Group 1 and Group 2 was < 0 (-3.5%).

Secondary Objective 2: Antibody Responses (GMTs) at D30 At D30, the Group 1 / Group 2 GMT ratios ranged from 1.68 to 4.37 for all serogroups.
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