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Sponsor: Sanofi Pasteur **Drug substance:** Quadrivalent Meningococcal ACYW Conjugate Vaccine	**Study Identifiers:** U1111-1143-8537, NCT02199691, 2016-001963-35 **Study code:** MET50
Title of the study: A Phase II Study of the Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Healthy Adolescents	
Study centers: This was a multi-center trial involving 40 trial centers in the US.	
Study period: Date first subject enrolled: 22/Jul/2014 Date last subject completed: 02/Oct/2015	
Phase of development: II	
Objectives: **Primary objectives:** To evaluate the antibody responses to the antigens present in MenACYW conjugate vaccine when MenACYW conjugate vaccine is given alone compared to those when MENVEO® is given alone. **Secondary objectives:** 1) To evaluate the antibody responses to the antigens present in MenACYW conjugate vaccine, when MenACYW conjugate vaccine is given concomitantly with Tdap and HPV vaccines, compared to those when it is given alone 2) To evaluate the antibody responses to the antigens present in Tdap vaccine, when Tdap vaccine is given concomitantly with MenACYW conjugate vaccine and HPV vaccine, compared to those when Tdap vaccine is given with HPV vaccine only 3) To evaluate the antibody responses to the antigens present in HPV vaccine after the 3-dose series, when the first dose of HPV vaccine is given concomitantly with MenACYW conjugate vaccine and Tdap vaccine, compared to those when the first dose of HPV vaccine is given with Tdap vaccine only	
Methodology: A Phase II, open-label (the laboratory technicians were blinded to group assignment), randomized, parallel-group, controlled, multi-center study to evaluate the immunogenicity and safety profile of a single dose of MenACYW conjugate vaccine when given alone compared to that of the licensed vaccine MENVEO® and when MenACYW conjugate vaccine was given concomitantly with Adacel® (Tetanus, diphtheria, acellular pertussis [Tdap] vaccine) and GARDASIL® (human papilloma virus [HPV] vaccine) in healthy, meningococcal vaccine-naïve adolescents 10 to 17 years of age in the US. Subjects were randomized to one of 4 groups to receive: Group 1 - MenACYW conjugate vaccine Group 2 - MENVEO® Group 3 - MenACYW conjugate vaccine, Tdap, and HPV* vaccines Group 4 - Tdap and HPV* vaccines * First dose of HPV vaccine was given on D0; HPV Dose 2 and Dose 3 were given 2 and 6 months, respectively, after Dose 1.	

A preliminary analysis was conducted on the first 40% of all subjects enrolled in the study. Endpoints assessed included meningococcal hSBA, tetanus, diphtheria, and pertussis immunogenicity, as well as safety data for the period between Visit 1 and Visit 2. This analysis was descriptive in nature and did not contain any hypothesis testing; thus, no statistical adjustment was needed.

This final analysis on 100% of the study population was performed at the end of the study after all subjects had completed their scheduled visits and long-term safety follow-up.

Number of subjects: Planned: 1700

Randomized: 1715

Vaccinated: 1692

Evaluated:

Immunogenicity: 1550

Safety: 1692

Diagnosis and criteria for inclusion:

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

1) Aged 10 to 17 years on the day of inclusion
2) Informed consent form has been signed and dated by the parent(s) or another legally acceptable representative
3) Assent form has been signed and dated by the subject
4) Subject and parent legally acceptable representative are able to attend all scheduled visits and comply with all trial procedures

Study treatments:

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

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 W135 ---------- 10 µg

Tetanus toxoid protein carrier ---------- approximately 65 µg

Route of administration: Intramuscular (IM)

Control product: MENVEO®: Meningococcal (Groups A, C, Y and W 135) Oligosaccharide Diphtheria CRM197Conjugate Vaccine (Novartis Vaccines and Diagnostics S.r.l., Sovicille, Italy)

Form: Lyophilized powder and liquid components are combined to produce a Solution for IM Injection

Composition:

Each 0.5 mL dose of vaccine contain the following active ingredients:

MenA oligosaccharide ---------- 10 µg

MenC oligosaccharide ---------- 5 µg

MenY oligosaccharide ---------- 5 µg

MenW-135 oligosaccharide ---------- 5 µg

CRM197 protein ---------- 32.7 to 64.1 µg

Other ingredients per 5 mL dose: residual formaldehyde $\leqslant$ 0.30 µg.

Route of administration: IM

Other products:

Vaccine 1: Adacel® (Tdap): Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Sanofi Pasteur Limited, Toronto Ontario Canada)

Form: Suspension

Composition:

Each 0.5 mL dose of vaccine contains the following active ingredients:

Tetanus toxoid ---------- 5 flocculation units (Lf)
Diphtheria toxoid ---------- 2 Lf
Acellular pertussis antigens
Detoxified pertussis toxin (PT) ---------- 2.5 µg
Filamentous hemagglutinin (FHA) ---------- 5 µg
Pertactin (PRN) ---------- 3 µg
Fimbriae types 2 and 3 (FIM) ---------- 5 µg

Other ingredients per 0.5 mL dose include aluminum phosphate, formaldehyde, glutaraldehyde and 2-phenoxyethanol.

Route of administration: IM

Vaccine 2: GARDASIL® (HPV): Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant (Merck & Co., Inc., Whitehouse Station, NJ, USA)

Form: Suspension

Composition:

Each 0.5 mL dose contains approximately:

HPV 6 L1 protein ---------- 20 µg
HPV 11 L1 protein ---------- 40 µg
HPV 16 L1 protein ---------- 40 µg
HPV 18 L1 protein ---------- 20 µg

Other ingredients per 0.5 mL dose include aluminum, sodium chloride, L-histidine, polysorbate 80, sodium borate, yeast protein, and Water for injection

Route of administration: IM

Duration of treatment/participation: The duration of each subject's participation in the trial was 180 to 210 days.

Criteria for evaluation:

Primary endpoint:

Antibody titers against meningococcal serogroups A, C, Y, and W measured by serum bactericidal assay using human complement (hSBA) for Group 1 and Group 2 at Day (D) 0 (before vaccination) and 30 days post vaccination

Secondary endpoints:

- Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA for Group 1 and Group 3 at D0 (before vaccination[s]) and 30 days post vaccination(s)
- Anti-pertussis antibody concentrations (pertussis toxoid [PT], filamentous hemagglutinin [FHA], pertactin [PRN], fimbriae types 2 and 3 [FIM]) for Group 3 and Group 4 at 30 days post vaccinations
- Anti-tetanus and anti-diphtheria antibody concentrations for Group 3 and Group 4 at 30 days post vaccinations
- Anti-HPV antibody titers (types 6, 11, 16, and 18) for Group 3 and Group 4 at D0 and 30 days after the third dose of HPV vaccine

Statistical methods:

All immunogenicity analyses were performed on the Per-Protocol Analysis Set (PPAS). All safety analyses were performed on the Safety Analysis Set (SafAS).

For Primary Objective:

Thirty days after the administration of MenACYW conjugate vaccine or MENVEO®, 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 (H0): p(men, G1) - p(men, G2) ≤ -10%

Alternative hypothesis (H1): p(men, G1) - p(men, G2) > -10%

where p(men, G1) and p(men, G2) are the percentages of subjects who achieve 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 was > -10%, the inferiority assumption was rejected.

*hSBA vaccine seroresponse for serogroups A, C, Y, and W is defined as post-vaccination hSBA titers ≥ 1:8 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.

Secondary Objectives

<u>For Secondary Objective 1:</u>

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

Null hypothesis (H0): p(men, G3) - p(men, G1) ≤ -10%

Alternative hypothesis (H1): p(men, G3) - p(men, G1) > -10%

where p(men, G1) and p(men, G3) are the percentages of subjects in Group 1 and Group 3, respectively, who achieve an hSBA vaccine seroresponse. 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.

<u>For Secondary Objective 2:</u>

Non-inferiority of Pertussis Antigens

- Thirty days after receiving Tdap vaccine, the geometric mean concentrations (GMCs) of antibodies against the pertussis antigens (PT, FHA, PRN, and FIM) in Group 3 are non-inferior to the GMCs in Group 4.

Null hypothesis (H0): GMC(pert, G3) / GMC(pert, G4) ≤ 2/3
Alternative hypothesis (H1): GMC(pert, G3) / GMC(pert, G4) > 2/3

where GMC(pert, G3) and GMC(pert, G4) are the GMCs of antibodies against the pertussis antigens (PT, FHA, PRN, and FIM) in Group 3 and Group 4, respectively. Each of the antigens of PT, FHA, PRN, and FIM were tested separately. If the lower limit of the 2-sided 95% CI of the ratio of the GMCs from the 2 groups was > 2/3 for each antigen, the inferiority assumption was rejected.

Non-inferiority of Tetanus/Diphtheria Antigens

- Thirty days after the administration of Tdap vaccine, the percentages of subjects who achieve ≥ 1.0 IU/mL in anti-tetanus (or anti-diphtheria) antibody concentrations in Group 3 are non-inferior to those in Group 4.

Null hypothesis (H0): p(G3) - p(G4) ≤ -10%

Alternative hypothesis (H1): p(G3) - p(G4) > -10%

where p(G3) and p(G4) are the percentages of subjects in Group 3 and Group 4, respectively, who achieve an anti-tetanus antibody concentration ≥ 1.0 IU/mL (or an anti-diphtheria antibody concentration ≥ 1.0 IU/mL). Tetanus and diphtheria 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.

<u>For Secondary Objective 3:</u>

Non-inferiority of HPV in terms of Geometric Mean Titers (GMTs)

- Thirty days after receiving the third dose of HPV vaccine, GMTs of antibodies against the HPV antigens (types 6, 11, 16, and 18) in Group 3 are non-inferior to the GMTs in Group 4.

Null hypothesis (H0): GMT(hpv, G3) / GMT(hpv, G4) ≤ 2/3

Alternative hypothesis (H1): GMT(hpv, G3) / GMT(hpv, G4) > 2/3

where GMT(hpv, G3) and GMT(hpv, G4) are the GMTs of antibodies against the HPV antigens (types 6, 11, 16, and 18) in Group 3 and Group 4, respectively. Each of the antigens of HPV types 6, 11, 16 and 18 was tested separately. If the lower limit of the 2-sided 95% CI of the ratio of the GMTs from the 2 groups is > 2/3 for each antigen, the inferiority assumption was rejected.

Non-inferiority of HPV in terms of percentage of subjects with seroconversion

- Thirty days after receiving the third dose of HPV vaccine, the percentages of subjects who achieve a HPV seroconversion* for HPV types 6, 11, 16, and 18 in Group 3 are non-inferior to the corresponding percentages in Group 4.

Null hypothesis (H_0): $p_{(hpv, G3)} - p_{(hpv, G4)} \leq -10\%$
Alternative hypothesis (H_1): $p_{(hpv, G3)} - p_{(hpv, G4)} > -10\%$

where $p_{(hpv, G3)}$ and $p_{(hpv, G4)}$ are the percentages of subjects who achieve a HPV seroconversion in Group 3 and Group 4, respectively. Each of the HPV types 6, 11, 16, and 18 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.

*HPV seroconversion was defined as changing serostatus from seronegative to seropositive. Cutoff values for HPV seropositivity were ≥20 milli-Merck units/milliliter (mMU/mL) for types 6 and 16, ≥ 16 mMU/mL for type 11, and ≥ 24mMU/mL for type 18

Summary:

Population characteristics:

<u>Subject Disposition:</u>

A total of 1715 subjects were enrolled in this study and randomly allocated to Group 1 (505 subjects), Group 2 (507 subjects), Group 3 (403 subjects), and Group 4 (300 subjects).

Four subjects were randomized to Group 2 (MENVEO®) but received Group 1 vaccination (MenACYW conjugate vaccine) and were analyzed for safety as Group 1; 1 subject was randomized to Group 3 (MenACYW conjugate vaccine+Tdap+HPV) but received Group 2 vaccination and was analyzed for safety as Group 2; 1 subject was randomized to Group 4 (Tdap+HPV) but received Group 3 vaccinations and was analyzed for safety as Group 3.

A total of 1641 subjects (95.7%) completed the trial: 98.0% of Group 1 subjects, 98.6% of Group 2, 93.3% of Group 3 subjects, and 90.0% of Group 4 subjects.

Reasons for Withdrawal:

A total of 74 subjects (4.3%) did not complete the trial: 10 (2.0%) in Group 1, 7 (1.4%) in Group 2, 27 (6.7%) in Group 3, and 30 (10.0%) in Group 4.

The most frequently reported reasons for discontinuation were: voluntary withdrawal not due to an adverse event, lost to follow-up, and non-compliance with the protocol. There were no early terminations due to an SAE or other AE.

Demographics:

The distribution of males and females was comparable across the 4 treatment groups. A total of 871 male subjects (51.5%) and 821 female subjects (48.5%) were in the SafAS. The overall ratio of male:female was 1.06.

Overall, the ages were comparable across the 4 treatment groups; the mean age of the subjects at enrollment was 11.4 years ± 1.33.

The distribution of racial origin was comparable across the 4 treatment groups. Most subjects in the study were White (88.5%), followed by Black (5.0%), Mixed origin (4.8%), Native Hawaiian or other Pacific Islander (0.6%), American Indian or Alaska Native (0.5%), and Asian (0.4%). Racial origin information was Missing for 0.1% of subjects. The majority of subjects (80.4%) were not Hispanic or Latino.

Immunogenicity results:

Primary Objective:

MenACYW conjugate vaccine was non-inferior to MENVEO® as measured by the hSBA vaccine seroresponse*. For each serogroup, the lower limit of the 2-sided 95% CI of the difference was more than -10%. The percentages of subjects with an hSBA vaccine seroresponse were higher in Group 1 than in Group 2 for all serogroups: 75.6% (350/463) in Group 1 and 66.4% (308/464) in Group 2 for serogroup A; 97.2% (449/462) in Group 1 and 72.6% (336/463) in Group 2 for serogroup C; 97.0% (448/462) in Group 1 and 80.8% (375/464) in Group 2 for serogroup Y; and 86.2% (399/463) in Group 1 and 66.6% (309/464) in Group 2 for serogroup W.

*hSBA vaccine seroresponse for serogroups A, C, Y, and W is defined as post-vaccination hSBA titers ≥ 1:8 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.

Secondary Objective 1:

MenACYW conjugate vaccine administered concomitantly with Tdap and HPV vaccines was non-inferior when compared to MenACYW conjugate vaccine administered alone. For each serogroup, the lower limit of the 2-sided 95% CI of the difference was more than -10%. The percentages of subjects with an hSBA vaccine seroresponse were comparable between both vaccination groups for all serogroups: 75.6% (350/463) in Group 1 and 80.6% (290/360)) in Group 3 for serogroup A; 97.2% (449/462) in Group 1 and 97.2% (350/360) in Group 3 for serogroup C; 97.0% (448/462) in Group 1 and 95.6% (344/360 in Group 3 for serogroup Y; and 86.2% (399/463) in Group 1 and 83.9% (302/360) in Group 3 for serogroup W.

Secondary Objective 2:

Non-Inferiority of Pertussis Antigens

The non-inferiority of Tdap vaccine administered concomitantly with MenACYW conjugate vaccine and HPV vaccine compared to Tdap vaccine administered with HPV vaccine alone was met for the PT antigen but not the FHA, PRN, and FIM antigens The lower limit of the 2-sided 95% CI of the ratio had to be more than 2/3 (0.667) for the objective to have been met. The lower limits for FHA and PRN were close to the cut-off (0.661 and 0.627, respectively) while the lower limit for FIM was 0.525.

At baseline, the GMCs for PT, FHA, PRN, and FIM were comparable in both study groups

Non-Inferiority of Tetanus and Diphtheria Antigens

The anti-tetanus and anti-diphtheria responses of the Tdap vaccine administered concomitantly with MenACYW conjugate vaccine and HPV vaccine versus Tdap vaccine administered concomitantly with HPV vaccine alone were non-inferior as measured by the percentage of subjects who achieved ≥ 1.0 IU/mL anti-tetanus or anti-diphtheria antibody concentrations. The lower limit of the 2-sided 95% CI of the ratio was more than -10%.

At Visit 2, the percentages of subjects with anti-diphtheria antibody concentration ≥ 1.0 IU/mL were 97.8% (352/360) and 98.9% (260/263) in Group 3 and Group 4, respectively. The percentages of subjects with anti-tetanus antibody concentration ≥ 1.0 IU/mL were 99.7% (359/360) and 99.6% (261/262) in Group 3 and Group 4, respectively

Secondary Objective 3:

Non-inferiority of HPV Antigens

The non-inferiority of HPV vaccine after the 3-dose series when the first dose was administered concomitantly with MenACYW conjugate vaccine and Tdap vaccine compared to when the first dose of HPV vaccine was administered with Tdap vaccine alone was demonstrated for the PPAS2. Thirty days after receiving the 3rd dose of the HPV vaccine, the GMTs of antibodies against the HPV antigens 6, 11, 16, and 18 in Group 3 were non-inferior to the GMTs in Group 4. The lower limit of the 2-sided 95% CI of the ratio of the GMTs from the 2 groups was > 2/3 (0.667) for each antigen.

Thirty days after receiving the 3rd dose of the HPV vaccine, the percentages of subjects who achieved an HPV seroconversion for HPV types 6, 11, 16, and 18 in Group 3 were non-inferior to the corresponding percentages of subjects who achieved HPV seroconversion for HPV types 6, 11, 16, and 18 in Group 4. The percentages of subjects achieving seroconversion for anti-HPV6, HPV11, HPV16, and HPV18 antibody titer were 97.5% (236/242), 99.6% (241/242), 99.2% (240/242), and 99.2% (240/242), respectively in Group 3, and were 95.7% (157/164), 98.8% (162/164), 98.8% (162/164), and 98.8% (162/164), respectively in Group 4. Immune non-inferiority was demonstrated as the lower limit of the 2-sided 95% CI of the difference between the 2 proportions was > -10%.

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