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<p>Sponsor: Sanofi Pasteur</p> <p>Drug substance: Quadrivalent Meningococcal ACYW Conjugate Vaccine</p>	<p>Study Identifiers: U1111-1161-2625, NCT03077438, 2018-001471-20</p> <p>Study code: MET35</p>
<p>Title of the study: Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine Administered in Healthy Children 2 to 9 Years of Age</p>	
<p>Study centers: This was a multi-center trial involving 36 Investigators in 36 trial centers in the United States (US) and Puerto Rico.</p>	
<p>Study period:</p> <p>Date first subject enrolled: 17/Feb/2017</p> <p>Date last subject completed: 10/Oct/2017</p>	
<p>Phase of development: III</p>	
<p>Objectives:</p> <p>Primary Objective:</p> <p>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 that observed following the administration of a single dose of MENVEO® in children aged 2 to 9 years.</p> <p>Secondary Objectives:</p> <ol style="list-style-type: none"> 1) To compare the serum bactericidal assay using human complement (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 MENVEO® in children 2 to 9 years of age 2) To evaluate the hSBA antibody GMTs of meningococcal serogroups A, C, Y, and W following the administration of MenACYW conjugate vaccine and those observed following the administration of MENVEO® in children 2 to 5 years of age, and in children 6 to 9 years of age, respectively 3) To evaluate the hSBA vaccine seroresponse to meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) post-vaccination in children 2 to 5 years of age, and in children 6 to 9 years of age, respectively 	
<p>Methodology:</p> <p>This was a Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to evaluate the immunogenicity and describe the safety of MenACYW conjugate vaccine compared to MENVEO® in healthy children 2 to 9 years of age in the US and Puerto Rico.</p> <p>Approximately 1000 healthy, meningococcal-vaccine naïve children aged 2 to 9 years were randomized in a 1:1 ratio to the following two groups:</p> <ul style="list-style-type: none"> • Group 1: MenACYW conjugate vaccine • Group 2: MENVEO® 	

Enrollment was stratified by age: 250 children 2 to 5 years old and 250 children 6 to 9 years old, respectively, were to be enrolled in each group.

All subjects were to provide blood samples (BLs) for immunogenicity assessment at baseline (pre-vaccination) and at 30 to 44 days after vaccination. Solicited adverse event (AE) information was collected for 7 days after vaccination; unsolicited AE information was collected from Visit (V) 01 (Day [D] 0) to V02 (D30 [+14 days]), and serious adverse event (SAE) information (including adverse events of special interest [AESIs]) was collected throughout the study period from D0 through D180 (+14 days) after vaccination. Medically-attended adverse events (MAAEs) were to be collected from V01 through V02 (as part of the collection of unsolicited AE information) and from V02 through D180 (+14 days) (as MAAEs).

Number of subjects: Planned: 1000
 Randomized: 1000
 Vaccinated: 1000

Evaluated:
 Immunogenicity: 918
 Safety: 992

Diagnosis and criteria for inclusion:

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

- 1) Aged 2 to 9 years on the day of inclusion
- 2) Assent form has been signed and dated by the subject (as required by local regulations) and informed consent form (ICF) has been signed and dated by the parent(s) or guardian
- 3) Subject and parent / guardian are 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 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:

Form: Lyophilized powder and liquid components were combined to produce a solution for IM injection

Composition: Each 0.5 mL dose of vaccine contained 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 0.5 mL dose: residual formaldehyde ≤ 0.30 µg

Route of administration: IM

Duration of participation: The planned duration of each subject's participation in the trial was approximately 180 to 194 days.

Criteria for evaluation:

Primary endpoint:

Vaccine seroresponse against meningococcal serogroups A, C, Y, and W measured by serum bactericidal assays using human complement (hSBA) assessed at baseline (D0, before vaccination) and 30 days (+14 days) after vaccination.

Secondary endpoints:

- GMTs against meningococcal serogroups A, C, Y, and W measured by hSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or MENVEO®
- Vaccine seroresponse against meningococcal serogroups A, C, Y, and W measured by hSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or MENVEO®

Statistical methods:

Statistical methods for the primary objective:

Thirty days (D30 [+14 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): $p(G1) - p(G2) \leq -10\%$
- Alternative hypothesis (H1): $p(G1) - p(G2) > -10\%$

where $p_{(G1)}$ and $p_{(G2)}$ are the percentages of subjects who achieve an hSBA 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.

*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

The overall non-inferiority of this objective was demonstrated if all 4 individual null hypotheses were rejected.

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). All safety analyses were performed on the safety analysis set (SafAS).

Statistical methods for secondary objectives:

- 1) Thirty days (D30 [+14 days]) after the administration of MenACYW conjugate vaccine or MENVEO®, the hSBA geometric mean titer ratio (GMTR) between Group 1 and Group 2 was calculated and 95% CI were provided.
- 2) Thirty days (D30 [+14 days]) after the administration of MenACYW conjugate vaccine or MENVEO®, the hSBA GMTR between Group 1a and Group 2a, and between Group 1b and Group 2b was to be calculated and 95% CI were provided, respectively.
- 3) Thirty days (D30 [+14 days]) after the administration of MenACYW conjugate vaccine or MENVEO®, the difference of hSBA vaccine seroresponse* rates between Group 1a and Group 2a, and between Group 1b, and Group 2b were calculated and 95% CI were provided, respectively.

* 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 had to be \geq 1:16
- For a subject with a pre-vaccination titer \geq 1:8, the post-vaccination titer had to be at least 4-fold greater than the pre-vaccination titer

Summary:

Population characteristics:

Subject Disposition

A total of 1000 subjects were enrolled in this study and randomly allocated to Group 1 (499 subjects) or Group 2 (501 subjects). A total of 974 subjects (97.4%) completed the trial: 487 subjects (97.6%) in Group 1 and 487 subjects (97.2%) in Group 2. There were no early terminations due to an SAE or other AE. A total of 969 subjects (96.9%) performed the safety follow-up after the last visit: 483 subjects (96.8%) in Group 1 and 486 subjects (97.0%) in Group 2.

Demographics

There were a total of 516 (52.0%) male subjects and 476 (48.0%) female subjects: the overall ratio of male/female subjects was 1.08. There were more males than females in both groups (male/female ratio was 1.04 in Group 1 and 1.13 in Group 2).

Subjects' ages were comparable between both groups. The mean age (\pm standard deviation [SD]) of the subjects at enrollment was 6.0 ± 2.34 years for all randomized subjects, 4.0 ± 1.20 years for the subset of subjects aged 2 to 5 years, and 8.0 ± 1.16 years for the subset of subjects aged 6 to 9 years.

The distribution of racial origin was comparable between both groups. Most subjects in the study were White (81.9%), followed by Black or African American (12.7%) and Mixed origin (4.2%). Racial origin information was missing for 0.3% of subjects. The majority of subjects (76.8%) were not Hispanic or Latino.

Immunogenicity Results

Primary Objective: Meningococcal hSBA Vaccine Seroresponse

The immune response following administration of MenACYW conjugate vaccine was non-inferior to the immune response following administration of MENVEO® 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 greater than -10%.

Table S4: Non-inferiority of the percentage of subjects achieving hSBA vaccine seroresponse at D30 between Group 1 and Group 2 - Per-Protocol Analysis Set

Serogroup	Group 1 MenACYW (N=458)			Group 2 MENVEO (N=460)			Group 1 - Group 2		Non-inferiority
	n/M	Seroresponse rate (%)	95% CI	n/M	Seroresponse rate (%)	95% CI	Difference (%)	95% CI	
A	252/455	55.4	(50.7; 60.0)	219/458	47.8	(43.2; 52.5)	7.6	(1.1, 14.0)	Yes
C	436/458	95.2	(92.8; 97.0)	219/458	47.8	(43.2; 52.5)	47.4	(42.2, 52.2)	Yes
Y	419/458	91.5	(88.5; 93.9)	364/459	79.3	(75.3; 82.9)	12.2	(7.7, 16.7)	Yes
W	361/458	78.8	(74.8; 82.5)	294/459	64.1	(59.5; 68.4)	14.8	(8.9, 20.5)	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 PPAS

hSBA vaccine seroresponse: 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.

95% CI of the single proportion 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 was > -10% for all four serogroups

Secondary Objective 1: hSBA GMTs at D30

At D30, for serogroup A, the GMT in Group 1 (24.8) was slightly numerically higher than in Group 2 (22.6) with overlapping 95% CIs. The GMTR for serogroup A was 1.09, with the lower limit of the 2-sided 95% CI of the GMTR lower than 1.0.

At D30, for serogroups C, Y and W, the GMTs were higher in Group 1 (238, 68.8, and 37.5, respectively) than in Group 2 (17.0, 43.5, and 26.2, respectively) with non-overlapping 95% CIs. The GMTRs for serogroups C, Y and W were 14.0, 1.58, and 1.43, respectively, and the lower limits of the 2-sided 95% CIs of the GMTRs were all greater than 1.0.

Secondary Objective 2: hSBA GMTs at D30 by Age Group

At D30, the Group 1 / Group 2 GMTRs ranged from 1.14 to 17.4 in subjects aged 2 to 5 years and from 1.06 to 11.5 in subjects aged 6 to 9 years for all serogroups.

In subjects aged 2 to 5 years, at D30, the GMTs in Group 1 were numerically higher than in Group 2 for serogroups A and Y (21.6 and 49.8 in Group 1 and 18.9 and 36.1 in Group 2, respectively) with overlapping 95% CIs, and the GMTRs for serogroups A and Y were 1.14 and 1.38, respectively. The GMTs were higher in Group 1 than in Group 2 for serogroups C and W (208 and 28.8 in Group 1 and 11.9 and 20.1 in Group 2, respectively) with non-overlapping 95% CIs; and the GMTRs for serogroups C and W were 17.4 and 1.43, respectively.

In subjects aged 6 to 9 years, at D30, the GMTs were numerically higher in Group 1 (28.4) than in Group 2 (26.8) for serogroup A with overlapping 95% CIs, and the GMTR was 1.06. The GMTs were higher in Group 1 than in Group 2 with non-overlapping 95% CIs for serogroups C, Y, and W ranging from 48.9 to 272 in Group 1 and from 23.7 to 51.8 in Group 2, and GMTRs ranging from 1.45 to 11.5.

Secondary Objective 3: hSBA Vaccine Seroreponse at D30 by Age Group

At D30, for subjects aged 2 to 5 years and subjects aged 6 to 9 years, the percentage of subjects achieving hSBA vaccine seroreponse in Group 1 was numerically higher than that in Group 2, in all serogroups. The differences of the percentages of subjects achieving hSBA vaccine seroreponse between Group 1 and Group 2 in subjects aged 2 to 5 years ranged from 7.6% to 51.1% across all serogroups, and in subjects aged 6 to 9 years ranged from 7.7% to 44.0% across all serogroups.

In subjects aged 2 to 5 years, at D30, the percentages of subjects with an hSBA vaccine seroreponse ranged from 52.4% (119/227) to 94.3% (216/229) in Group 1 and from 43.2% (96/222) to 77.0% (171/222) in Group 2. The differences of the seroreponse rates between Group 1 and Group 2 ranged from 7.6% to 51.1%.

In subjects aged 6 to 9 years, at D30, the percentages of subjects with an hSBA vaccine seroreponse ranged from 58.3% (133/228) to 94.8% (217/229) in Group 1 and from 50.6% (120/237) to 81.4% (193/237) in Group 2. The differences of the seroreponse rates between Group 1 and Group 2 ranged from 7.7% to 44.0%.

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