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Sponsor: Sanofi Pasteur **Drug substance:** Quadrivalent Meningococcal ACYW Conjugate Vaccine	**Study Identifiers:** U1111-1161-2935, NCT02955797, 2016-000749-30 **Study code:** MET51
Title of the study: Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Toddlers 12 to 23 Months of Age	
Study centers: This was a multi-center, multinational trial involving 34 sites over 4 countries.	
Study period: Date first subject enrolled: 24/Feb/2017 Date last subject completed: 26/Oct/2017	
Phase of development: III	

Objectives:

Primary objectives:

1) To demonstrate the non-inferiority of the antibody response to meningococcal serogroups A, C, Y, and W after a single dose of MenACYW conjugate vaccine or Nimenrix® in toddlers who either are meningococcal vaccine naïve or have received monovalent MenC vaccination during infancy
2) To demonstrate the non-inferiority of the antibody response to meningococcal serogroups A, C, Y, and W after a single dose of MenACYW conjugate vaccine or Nimenrix® in meningococcal vaccine naïve toddlers

Secondary objectives:

3) To compare the antibody responses (geometric mean titers [GMTs]) to meningococcal serogroups A, C, Y, and W after a dose of MenACYW conjugate vaccine or Nimenrix® as measured by hSBA in toddlers who either are meningococcal vaccine naïve or have received monovalent MenC vaccination during infancy
4) To compare the antibody responses (GMTs) to meningococcal serogroups A, C, Y, and W after a dose of MenACYW conjugate vaccine or Nimenrix® as measured by hSBA in meningococcal vaccine naïve toddlers
5) To compare the antibody responses (GMTs) to meningococcal serogroups A, C, Y, and W after a dose of MenACYW conjugate vaccine or Nimenrix® as measured by hSBA in toddlers who received monovalent MenC vaccination during infancy

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 single dose of MenACYW conjugate vaccine to a single dose of a licensed quadrivalent meningococcal polysaccharide groups A, C, W-135, and Y conjugate vaccine (MenACWY-Tetanus Toxoid [TT], Nimenrix®) in toddlers (12 to 23 months of age) in the European Union (EU) who were either meningococcal vaccine naïve or had received monovalent MenC vaccination during infancy.

Approximately 918 healthy toddlers aged 12 to 23 months were to be enrolled and randomized as follows depending on their meningococcal vaccine background:

Meningococcal vaccine naïve subjects: 612 subjects were to be randomized in a 1:1 ratio to the following 2 groups:

- Group 1: MenACYW conjugate vaccine (n=306)
- Group 2: Nimenrix® (n=306)

MenC-primed subjects: 306 subjects were to be randomized in a 2:1 ratio to the following 2 groups:

- Group 3: MenACYW conjugate vaccine (n=204)
- Group 4: Nimenrix® (n=102)

Enrollment of MenC-primed subjects was stratified by the type of primed vaccine, MenC-TT (NeisVac-C®) or MenC-CRM (Menjugate®, Meningitec®), considering that at least 25% and a maximum of 50% of subjects were to have been primed with MenC-CRM as described in Table S1:

Table S1: MenC Priming Strategy

Priming	Group 3 MenACYW	Group 4 Nimenrix®
MenC-TT	102 – 152*	51 – 76*
MenC-CRM	52* - 102	26* - 51
Total	204	102

*Sample size corresponding to 25% of subjects primed with MenC-CRM

TT: tetanus toxoid used as carrier protein; CRM: a non-toxic variant of diphtheria toxin used as carrier protein

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 were to be collected for 7 days after vaccination, unsolicited AE information were to be collected from Visit (V) 01 (Day 0) to V02 (Day 30 + 14 days), and serious adverse event (SAE) information, including adverse events of special interest (AESIs), were to be collected throughout the trial.

Number of subjects:

Planned: 918

Randomized: 918

Vaccinated: 914

Evaluated:

Immunogenicity: 886

Safety: 914

Diagnosis and criteria for inclusion:

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

1) Aged 12 to 23 months on the day of the first study visit
2) Subjects received all recommended standard-of-care non-meningococcal vaccinations according to his/her age as per local regulations.
3) Informed consent form (ICF) was signed and dated by the parent/LAR
4) Subject and parent/LAR were able to attend all scheduled visits and to comply with all trial procedures
5) Covered by health insurance if required by local regulations
6) Subjects did not receive any meningococcal vaccine in the second year of life (ie, from 12 months of age).
7) **For Inclusion in Groups 1 and 2:** Subjects did not receive any vaccination against meningococcal disease with either a trial vaccine or a licensed meningococcal vaccine (ie, polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, W, Y, B; or any monovalent or bivalent meningococcal vaccine).
8) **For Inclusion in Groups 3 and 4:** Subjects previously received at least 1 dose of licensed monovalent meningococcal C conjugate (MenC) vaccine during infancy (ie, before 12 months 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 was 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: Nimenrix®: Meningococcal polysaccharide groups A, C, W-135 and Y conjugate vaccine (Pfizer Limited, Sandwich, United Kingdom)

Form: Powder in a vial and solvent, for reconstitution, in a pre-filled syringe

Composition:

Each 0.5 mL dose of Nimenrix® was formulated to contain:

Neisseria meningitidis polysaccharides:

Serogroup A.....5 µg
Serogroup C.....5 µg
Serogroup W-135.....5 µg
Serogroup Y.....5 µg

Tetanus toxoid protein carrier .....44 µg

Excipients:

In the powder: Sucrose, trometamol

In the solvent: Sodium chloride, water for injection

Route of administration: IM

Duration of participation:

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

Criteria for evaluation:

Primary endpoints:

1) Antibody titers ≥ 1:8 against meningococcal serogroups A, C, Y, and W measured by serum bactericidal assay using human complement (hSBA) assessed at 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Nimenrix® in toddlers who either are meningococcal vaccine naïve or have received monovalent MenC vaccination during infancy

2) Antibody titers ≥ 1:8 against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at 30 days (+14 days) after vaccination with MenACYW conjugate vaccine or Nimenrix® in meningococcal vaccine naïve toddlers

Second endpoints:

1) 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 Nimenrix® in toddlers who either are meningococcal vaccine naïve or have received monovalent MenC vaccination during infancy

2) 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 Nimenrix® in meningococcal vaccine naïve toddlers

3) 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 Nimenrix® in toddlers who received monovalent MenC vaccination during infancy

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).

Primary Objectives:

Two co-primary objectives were evaluated.

Co-primary Objective 1: Non-inferiority testing after 1 dose of MenACYW conjugate vaccine or Nimenrix® in toddlers who either are meningococcal vaccine naïve or have received monovalent MenC vaccination during infancy. 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 percentages of subjects who achieved an hSBA titer ≥ 1:8 is > -10%, the inferiority assumption was rejected. For the 4 non-inferiority hypotheses using the response rates, the 95% CI was stratified on the priming status (meningococcal vaccine naïve or primed with monovalent MenC vaccination during infancy) and calculated using the Wald method (normal approximation). Weighted average of the difference over strata was calculated using the Minimal Risk weights with the null variance method. The overall non-inferiority of this objective was demonstrated if all 4 individual null hypotheses were rejected.

The percentages of subjects who achieved an hSBA titer ≥ 1:8 for meningococcal serogroups A, C, Y, and W in toddlers who received MenACYW conjugate vaccine (Groups 1 and 3) are non-inferior to the corresponding percentages in toddlers who received Nimenrix® (Groups 2 and 4) 30 days post administration.

Null hypothesis (H0): p(Men) - p(Nim) ≤ -10%

Alternative hypothesis (H1): p(Men) - p(Nim) > -10%

where p(Men) and p(Nim) are the percentages of subjects who achieved an hSBA titer ≥ 1:8 in the MenACYW conjugate vaccine group and the Nimenrix® group, respectively.

Co-primary Objective 2: Non-inferiority testing after 1 dose of MenACYW conjugate vaccine or Nimenrix® in meningococcal vaccine naïve toddlers. Each of the serogroups A, C, Y, and W was tested separately. If the lower limit of the 2-sided 95% CI of the difference between the 2 percentages of subjects who achieved an hSBA titer ≥ 1:8 is > -10%, the inferiority assumption was rejected. For the 4 non-inferiority hypotheses using the response 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 was demonstrated if all 4 individual null hypotheses were rejected.

Thirty days after the administration of MenACYW conjugate vaccine or Nimenrix®, the percentages of subjects who achieved an hSBA titer ≥ 1:8 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) ≤ -10%

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

where p(G1) and p(G2) are the percentages of subjects who achieved an hSBA titer ≥ 1:8 in Groups 1 and 2, respectively.

Secondary Objectives

No hypotheses were tested. Descriptive statistics are presented.

Secondary Objective 1:

Thirty days after the administration of MenACYW conjugate vaccine or Nimenrix® in toddlers who either were meningococcal vaccine naïve or had received monovalent MenC vaccination during infancy, the hSBA geometric mean titer ratio (GMTR) between MenACYW conjugate vaccine or Nimenrix® was calculated, and 95% CI was provided. The 95% CI of the ratio of post-vaccination GMTs was stratified on the priming vaccination status (meningococcal vaccine naïve or primed with monovalent MenC vaccination) and calculated using an analysis of variance (ANOVA) model of log10-transformed titers.

Secondary Objective 2:

Thirty days after the administration of MenACYW conjugate vaccine or Nimenrix® in meningococcal vaccine naïve toddlers, the hSBA GMTR between MenACYW conjugate vaccine or Nimenrix® was calculated, and 95% CI was provided.

Secondary Objective 3:

Thirty days after the administration of MenACYW conjugate vaccine or Nimenrix® in toddlers who received monovalent MenC vaccination during infancy, the hSBA GMTR between MenACYW conjugate vaccine or Nimenrix® was calculated, and 95% CI was provided.

Summary:

Population characteristics:

Subject Disposition:

A total of 918 subjects were enrolled in this study and randomly allocated to one of the following 4 groups depending on their meningococcal vaccine background: Group 1 (306 subjects) or Group 2 (306 subjects) for meningococcal vaccine naïve subjects, and to Group 3 (203 subjects) or Group 4 (103 subjects) for MenC-primed subjects. All meningococcal vaccine naïve subjects (Groups 1 and 2) were enrolled in Finland (356 [38.8%] subjects) and Germany (256 [27.9%] subjects), and all MenC-primed subjects (Groups 3 and 4) were enrolled in Hungary (145 [15.8%] subjects) and Spain (161 [17.5%] subjects).

In MenC-primed toddlers vaccinated with MenACYW conjugate vaccine (Group 3), 151 (74.4%) and 52 (25.6%) subjects were MenC-TT-and MenC-CRM-primed, respectively. In MenC-primed vaccinated with Nimenrix® (Group 4), 77 (74.8%) and 26 (25.2%) subjects were MenC-TT-and MenC-CRM-primed, respectively; 1 subject with a MenC-TT background was not vaccinated.

There were no early terminations due to an SAE or other AE. A total of 914 (99.6%) subjects received at least 1 dose of study or control vaccine and for whom safety data were available. A total of 910 (99.1%) subjects completed the trial.

Demographics:

There were a total of 482 (52.7%) male subjects and 432 (47.3%) female subjects: the overall ratio of male/female subjects was 1.12. There were more males than females in both subjects vaccinated with MenACYW conjugate vaccine (MenACYW-recipients, Groups 1and 3) and subjects vaccinated with Nimenrix® (Nimenrix®-recipients, Groups 2 and 4).

Subjects' ages were comparable between both MenACYW- and Nimenrix®-recipients. The mean age (± standard deviation [SD]) of the subjects at enrollment was 15.2 ± 3.34 months for subjects vaccinated with MenACYW conjugate vaccine, and 15.6 ± 3.25 months for subjects vaccinated with Nimenrix®. The distribution of racial origin was comparable between both MenACYW- and Nimenrix®-recipients, with the most commonly reported racial origin being White (59.3% overall); however, racial origin information was not reported (ie, was "missing") for 38.6% of the randomized toddlers. Regarding ethnicity, in both MenACYW- and Nimenrix®-recipients, most subjects were not Hispanic or Latino (44.2% overall); however, ethnicity information was not reported (ie, was "missing") for 38.7% of the randomized toddlers. Racial origin and ethnicity were not collected in Finland as per local regulation.

Primary Objectives: Percentages of Subjects Achieving hSBA Antibody Titer ≥ 1:8

Non-Inferiority Hypothesis for Co-Primary Objective 1

Toddlers who either were meningococcal vaccine naïve or had received monovalent MenC vaccination during infancy

The co-primary objective 1 was met. As shown in Table S5, 30 days after vaccination, the lower limit of the 2-sided 95% CI of the overall stratified difference in hSBA response rates (antibody titers ≥ 1:8) between MenACYW- and Nimenrix®-recipients were > -10% for all 4 serogroups. Non-inferiority of immune response, based on percentage of subjects achieving a post-vaccination titer ≥ 1:8 at Day 30 regardless of their meningococcal vaccine background, was demonstrated for MenACYW conjugate vaccine versus Nimenrix® for all serogroups. For serogroup C, the lower bound of the two-sided 95% CI of the overall difference of proportion stratified on the meningococcal vaccine background was greater than 0.

Table S5: Non-inferiority of the hSBA antibody response (percentage of subjects ≥ 1:8) for MenACYW conjugate vaccine (Groups 1 & 3) vs Nimenrix® (Groups 2 & 4) at Day 30 – Per-Protocol Analysis Set

		Groups 1 & 3 MenACYW (N=491)			Groups 2 & 4 Nimenrix (N=395)			MenACYW – Nimenrix		
Serogroup	**Background status**	**n/M**	**(%)**	**95% CI**	**n/M**	**(%)**	**95% CI**	**Stratified difference (%)**	**95% CI**	**Non-inferiority***
A	**Naive**	266/293	90.8	(86.9; 93.8)	264/295	89.5	(85.4; 92.7)	-2.03	(-5.84; 1.78)	Yes
	MenC-Primed	177/197	89.8	(84.8; 93.7)	97/99	98.0	(92.9; 99.8)			
C	**Naive**	291/293	99.3	(97.6; 99.9)	240/295	81.4	(76.4; 85.6)	12.1	(8.16; 16.1)	Yes
	MenC-Primed	194/196	99.0	(96.4; 99.9)	97/99	98.0	(92.9; 99.8)			
Y	**Naive**	273/293	93.2	(89.7; 95.8)	271/296	91.6	(87.8; 94.5)	2.42	(-1.34; 6.19)	Yes
	MenC-Primed	189/197	95.9	(92.2; 98.2)	91/99	91.9	(84.7; 96.4)			
W	**Naive**	245/293	83.6	(78.9; 87.7)	247/296	83.4	(78.7; 87.5)	0.458	(-4.37; 5.28)	Yes
	MenC-Primed	170/196	86.7	(81.2; 91.1)	84/98	85.7	(77.2; 92.0)			

n: Number of subjects with titer ≥ 1:8.
M: Number of subjects with available data for the endpoint; N: number of subjects in per-protocol analysis set.
95% CI of the single percentage calculated from the exact binomial method.
Overall priming status 95% CI calculated using the Wald method (normal approximation).
* Non-inferiority concluded if the lower limit of the two-sided 95% CI of the overall difference of proportion stratified on the priming status is > -10%.
Weighted average of the difference over strata calculated using the Minimal Risk weights with the null variance method.
The overall non-inferiority will be demonstrated if the two-sided 95% CI of the overall difference of proportion stratified on the priming status is > -10% for all 4 serogroups.

Overall, in subjects who were either meningococcal vaccine naïve or MenC-primed combined (ie, based on raw pool, without stratification on priming vaccination status), percentages of subjects with hSBA antibody titers ≥ 1:8 were comparable between both MenACYW- and Nimenrix®-recipients, except for serogroup C. For serogroup C, percentages of subjects with hSBA antibody titers ≥ 1:8 were higher in MenACYW-recipients than Nimenrix®-recipients: 99.2% and 85.5%, respectively.

Non-Inferiority Hypothesis for Co-Primary Objective 2

Meningococcal vaccine naïve

The co-primary objective 2 was met. As shown in Table S6, 30 days after vaccination, the lower limit of the 2-sided 95% CI of the difference in hSBA response rates (antibody titers ≥ 1:8) MenACYW- (Group 1) and Nimenrix®-recipients (Group 2) were > -10% for all 4 serogroups. Non-inferiority of immune response, based on percentage of subjects achieving a post-vaccination titer ≥ 1:8 at Day 30 in meningococcal vaccine naïve toddlers, was demonstrated for MenACYW conjugate vaccine versus Nimenrix® for all serogroups. For serogroup C, the lower bound of the two-sided 95% CI of the overall difference of proportion stratified on the meningococcal vaccine priming status was greater than 0.

Table S6: Non-inferiority of the hSBA antibody response (percentage of subjects ≥ 1:8) in meningococcal vaccine naïve toddlers (Group 1 vs Group 2) at Day 30 – Per-Protocol Analysis Set

	MenACYW Group 1 (N=293)			Nimenrix Group 2 (N=296)			Group 1 – Group 2		
Serogroup	**n/M**	**(%)**	**(95% CI)**	**n/M**	**(%)**	**(95% CI)**	**Difference (%)**	**95% CI**	**Non-inferiority**
A	266/293	90.8	(86.9; 93.8)	264/295	89.5	(85.4; 92.7)	1.3	(-3.60; 6.20)	Yes
C	291/293	99.3	(97.6; 99.9)	240/295	81.4	(76.4; 85.6)	18.0	(13.6; 22.8)	Yes
Y	273/293	93.2	(89.7; 95.8)	271/296	91.6	(87.8; 94.5)	1.6	(-2.76; 6.03)	Yes
W	245/293	83.6	(78.9; 87.7)	247/296	83.4	(78.7; 87.5)	0.2	(-5.85; 6.18)	Yes

n: Number of subjects with titer ≥ 1:8.
M: Number of subjects with available data for the endpoint.
N: number of subjects in per-protocol analysis set.
95% CI of the single percentage calculated from the exact binomial method.
95% CI of the difference calculated from the Wilson Score method without continuity correction.
The overall non-inferiority will be demonstrated if the lower limit of the 2-sided 95% CI of the difference is > -10% for all 4 serogroups.

Secondary Objectives

Secondary Objective 1: Comparison of hSBA GMTs following MenACYW conjugate vaccine (Groups 1 & 3) vs Nimenrix® (Groups 2 & 4) at Day 30

Toddlers who either were meningococcal vaccine naïve or had received monovalent MenC vaccination during infancy

The GMTRs (stratified on priming vaccination background) were 7.59, 1.28, and 1.32 for serogroups C, Y and W, respectively, with the lower bound of the 95% CI greater than 1.0; and the GMTR (stratified on priming vaccination background) was 0.819 for serogroup A, with the upper bound of the 95% CI lower than 1.0.

Secondary Objective 2: Comparison of hSBA GMTs following MenACYW conjugate vaccine (Group 1) vs Nimenrix® (Group 2) at Day 30

Meningococcal vaccine naïve toddlers

The GMTRs were 1.03 and 1.18 (with the lower bound of the 95% CI below 1.0) for serogroups A and Y, respectively, and 16.5 and 1.34 (with the lower bound of the 95% CI greater than 1.0) for serogroups C and W, respectively.

Secondary Objective 3: Comparison of hSBA GMTs following MenACYW conjugate vaccine (Group 3) vs Nimenrix® (Group 4) at Day 30

Toddlers who received monovalent MenC vaccination during infancy

The GMTRs were 0.496 (with the upper bound of the 95% CI lower than 1.0) for serogroup A, 1.34 and 1.29 (with the lower bound of the 95% CI below 1.0) for serogroups C and W, respectively, and 1.53 (with the lower bound of the 95% CI greater than 1.0) for serogroup Y.

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